CHAPTER

4

Neurophysiology, Neurotransmitters, and the Nervous System

All behavior is under the control of the nervous system, and the effect of behaviorally active drugs can ultimately be traced to a direct or an indirect action on some aspect of the functioning of the nervous system. It is therefore necessary to have at least a rudimentary grasp of the normal functioning of the nervous system to understand the behavioral effects of drugs.

THE NEURON

Like all other tissues in the body, the nervous system is made up of cells. The two main types of cells are *neurons* and *glial cells* (or *glia*), which exist in the brain in roughly equal proportions of about 100 billion each. Neurons are excitable cells that analyze and transmit information. They are responsible for receiving sensory information from outside the body, for integrating and storing information, and for controlling the action of the muscles and glands—in other words, for everything that we see and understand as behavior. Glia support neurons. For much of the past century, it was thought that glia simply fulfilled a structural role, gluing neurons in place (*glia* is Latin for glue). But we now know that glia also play a protective role, helping to maintain efficient cell communication by shielding neurons from microorganisms and chemicals in the blood as well as from other neurons with which messages may become scrambled. They fulfill a metabolic role, supplying neurons with oxygen and nutrients and removing waste. And they play a maintenance role, destroying dead neurons. Glia are also active, reciprocal communicators within the nervous system. They form circuits; contain special receptor sites that are sensitive to chemicals released by neurons; and, in turn, influence communication between neurons by supplying chemical transmitters, limiting the dispersion of these chemicals, and getting rid of these chemicals when they are no longer needed. With these remarkable discoveries, glia have become the focus of intense investigation.

Nerve cells come in many shapes and sizes and contain a number of identifiable parts. A typical nerve cell is shown in Figure 4-1. The cell is covered by a *membrane* and is filled with a fluid called *cytoplasm*. All nerve cells have a *cell body* or *soma*, which is the largest part of the cell and contains structures vital to the cell's life processes, as well as the cell's *nucleus*. The nucleus contains *chromosomes*, long strands of *deoxyribonucleic acid* (*DNA*) in which distinct segments, called *genes*, code for the production of specific *proteins*. A protein is a chain

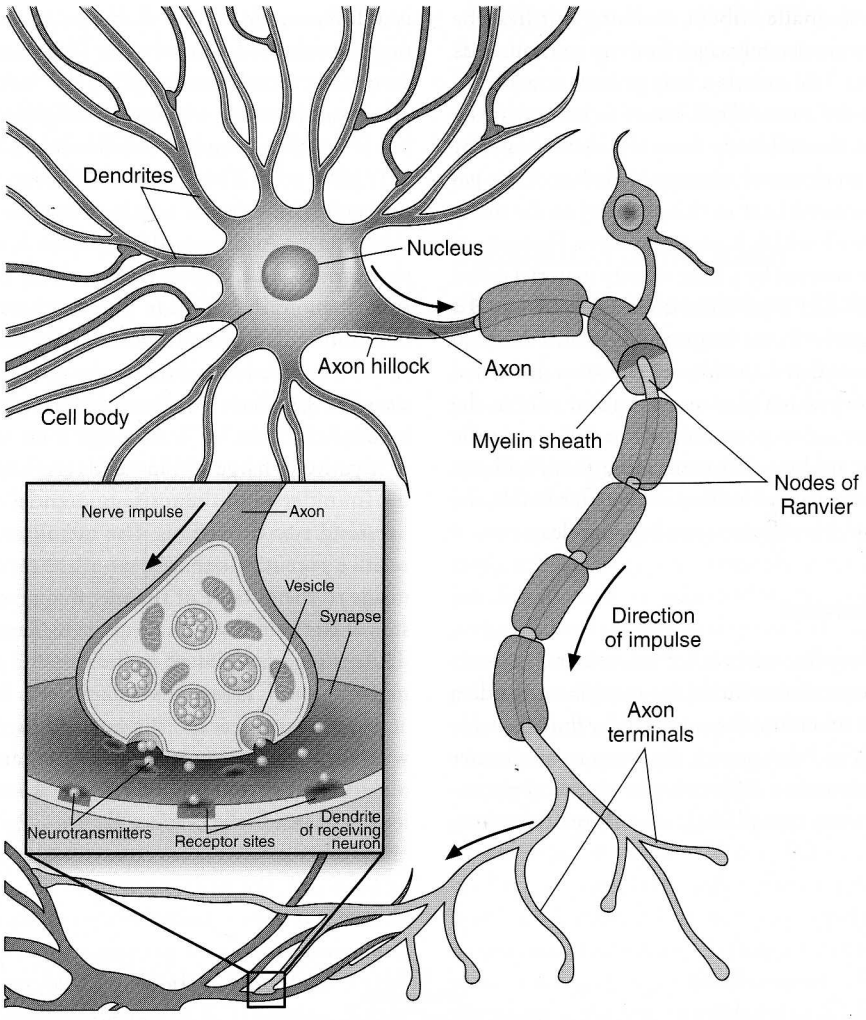


FIGURE 4-1 A prototypical nerve cell. Note that the neuron receives input at its dendrites and cell body through synapses from several other nerve cells. In turn, it synapses onto other nerve cells. The molecules of transmitter normally stored in vesicles in the axon terminals are released into the synaptic cleft in response to the arrival of an action potential. The transmitter molecules diffuse across the synapse and occupy receptor sites on the dendrites and/or cell body of the postsynaptic neuron. These events cause changes in the excitability of the postsynaptic cell membrane, making it either easier (excitation) or more difficult (inhibition) to fire. (Adapted from *Society for Neuroscience Brain Facts,* 2008, p. 7, reprinted with permission.)

of fairly simple building-block molecules called *amino acids*. There are only 22 standard amino acids that link together in varying sequences to create all of the proteins in our body. Eight of these are not produced by the body in sufficient quantities and must be ingested in food. Proteins can be hundreds of amino acids long, but these chains do not form in a straight line. Rather, they fold up into very complex three-dimensional shapes, which allows them to have the sophisticated mechanical properties they need to perform functions such as cell communication, growth, and repair; biochemical reactions; immune system functions; and many more.

Arising from the cell body are several structures. At one end are projections called *dendrites*, which divide

into smaller and smaller fibers, reaching out like the roots of a tree to receive messages from up to thousands of other neurons. The *axon* is a long process attached to the cell body at the *axon hillock*, which is located at the opposite end of the cell body from the dendrites. The axon transmits an electrical message (called an *action potential*, to be discussed later in this chapter) to the many other neurons with which it communicates. Sections of the axon may be covered by a layer of fatty material called the *myelin sheath*. The myelin sheath is an extension of a special type of glial cell that wraps and insulates the axon in sections. Uninsulated sections of the axon are called *Nodes of Ranvier*, which play an important role in the conduction of an action potential, as you will see. At the end of the axon are branches containing small bulbous structures called *terminal buttons* or *axon terminals*, the importance of which will also soon become clear.

Resting Potential

If we take two very fine wires called *microelectrodes*, insert one into the intracellular fluid (the cytoplasm inside a neuron) and the other into the extracellular fluid (outside the membrane), and then attach the wires to a *voltmeter* (a device that measures differences in electrical potential energy between two places), we will see that there is a difference in electrical charge; the inside is slightly negative relative to the outside. This potential difference across the membrane is called the *resting potential* or *membrane potential*, which varies slightly from cell to cell but is usually around −70 millivolts (mV; one millivolt is 1/1,000 volt). This potential difference results from an uneven distribution of ions between the inside and outside of a cell. As discussed in Chapter 1, *ions* are particles that possess an electrical charge, either positive or negative. The ions described in Chapter 1 were usually large drug molecules; those responsible for the resting potential of a cell are ionized molecules of the elements potassium (K^+), sodium (Na^+), and chlorine (which, as an ion, is called chloride, Cl^-), although some larger molecules of negatively charged amino acids (A^-) are also involved.

To understand the resting potential, we need to understand two things: (a) The membrane potential is a relative potential—that is, we are always comparing the inside to the outside of the membrane; and (b) the outside of the membrane is always considered equal to zero. The resting potential exists because the ratio of negative to positive ions is higher inside the cell. Both passive and active processes create this uneven distribution of ions whereby higher concentrations of Na^+ and Cl^- ions exist outside the cell and higher concentrations of K^+ and A^- ions exist inside the cell (see Figure 4-2).

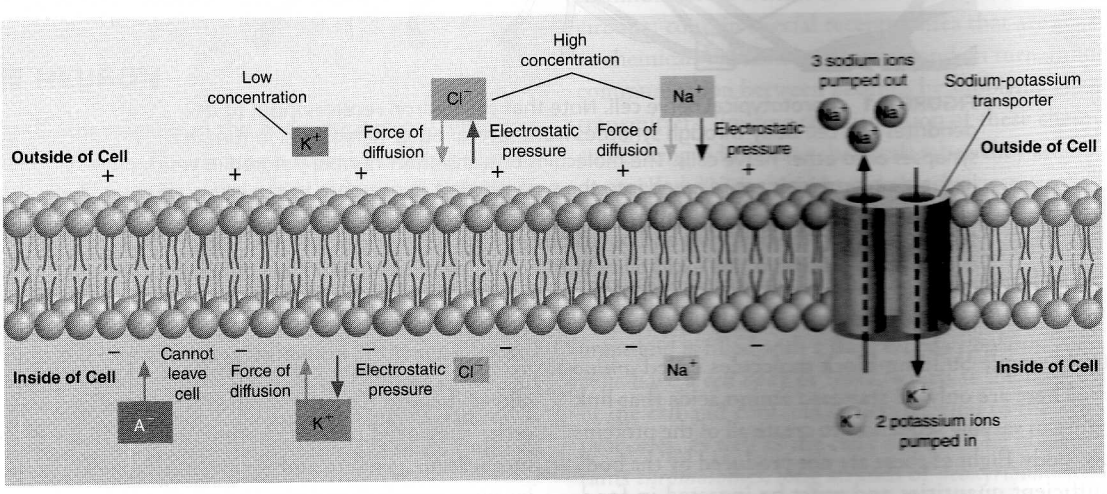


FIGURE 4-2 Passive and active forces produce differential ion distribution across the cell membrane to create the cell's resting potential. The relative size of each box represents the abundance of that ion inside versus outside the cell. An ion pump actively moves potassium ions (K^+) into the cell and sodium ions (Na^+) out of the cell. (Adapted from Carlson, 2011, figs. 2.15 & 2.16, pp. 40, 41, reprinted with permission.)

The first passive process is simple *diffusion*, the tendency for a substance to move down its *concentration gradient*, from an area of higher concentration to an area of lower concentration. Diffusion would force Na^+ and Cl^- ions into the cell and K^+ and A^- ions out of the cell.

The second passive process is *electrostatic charge*, the tendency for similar electrical charges to repel each other and for opposite electrical charges to attract each other. Positive ions (K^+ and Na^+) are repelled by the net positive charge outside the membrane and attracted to the negative charge inside. The reverse is true for negative ions (Cl^- and A^-).

The third passive process involves the *differential permeability* of the cell membrane to particular ions. As we saw in Chapter 1, the cell membrane consists of a lipid bilayer with large proteins embedded in it (see Figure 1-6). In neurons, these large protein molecules serve special functions that make the cells excitable and capable of conveying, storing, and integrating information. These actions are accomplished by the flow of ions across the membrane. The only way ions can move into and out of the cell is through thousands of these specialized protein channels called *ionophores* or *ion channels*. These proteins are often a target of behaviorally active drugs.

Nongated ion channels are always open but are specialized so that only certain ions are permitted to pass through, and then only at a particular rate and with varying ease. K^+ and Cl^- ions cross the cell membrane by easily passing through these channels, but tend to maintain their relative concentrations inside and outside the cell (respectively) because the forces of diffusion and electrostatic charge offset each other, either fully (in the case of Cl^-) or partly (in the case of K^+; there is a slightly greater tendency for K^+ ions to leave the cell). A^- ions are too large to cross the cell membrane and therefore remain trapped inside the cell. Na^+ is forced into the cell, both by diffusion and by electrostatic charge. Why, then, are Na^+ ions more highly concentrated outside the cell? The answer lies in the fourth process at play.

The fourth process is an active one, involving *transporters* or *ion pumps* spanning the cell membrane. These specialized protein molecules selectively move ions from one side of a membrane to another. *Sodium–potassium pumps* transport three Na^+ ions out of the cell for every two K^+ ions they move in, thereby creating an excess of positive ions outside the membrane. Importantly, Na^+ cannot pass easily through ionophores in the cell's membrane, thereby preventing complete reversal of the work carried out by sodium–potassium pumps. However, it should be clear that anything that speeds or slows the passage of ions through the membrane can increase or decrease the resting potential.

There are also channels for Ca^{2+} ions as well as *gated* ion channels, which open and close in response to specific stimuli, but these are not involved in the resting potential and have special functions, described next.

Stimulation of the Axon

GENERATING AN ACTION POTENTIAL. The resting potential of a neuron describes the distribution of ions in the absence of stimulation, but this membrane potential can vary substantially in response to a variety of stimuli. When the membrane potential becomes less negative (i.e., moves toward zero and positive numbers), it is called *depolarization*. When the membrane potential becomes more negative (i.e., moves further away from zero), it is called *hyperpolarization*. Normally, changes in ion distribution are responsible for deviation from the resting potential, but to illustrate the process, we can change the resting potential artificially. We can hyperpolarize a cell by inserting a stimulating microelectrode into a neuron and applying electricity to make the inside even more negative than the outside. The more current we apply, the greater the hyperpolarization. When the current is turned off, the cell returns to its normal resting potential of about –70 mV. We can depolarize the cell by reversing the polarity of the microelectrode and making the inside of the cell less negative with respect to the outside, but depolarizing a neuron can lead to some startling changes. Small amounts of depolarization simply cause the resting potential to decrease. When the electricity is turned off, the normal resting potential returns. But if the neuron is depolarized to about –55 mV, called the *threshold*, the entire resting potential and the processes that maintain it break down. Follow along in Figure 4-3 as this process is explained.

This breakdown occurs because of special gated ion channels that are sensitive to the number of positive charges inside the cell. When the potential difference is reduced beyond the threshold, these *voltage-gated ion channels* open, allowing the free flow of ions across the membrane. First, sodium channels open, and Na^+ ions, which have great difficulty crossing the cell membrane during the resting potential, rush into the cell driven by their concentration gradient and their electrostatic charge. Also embedded in the cell membrane are voltage-gated potassium channels. In comparison to Na^+ channels, the

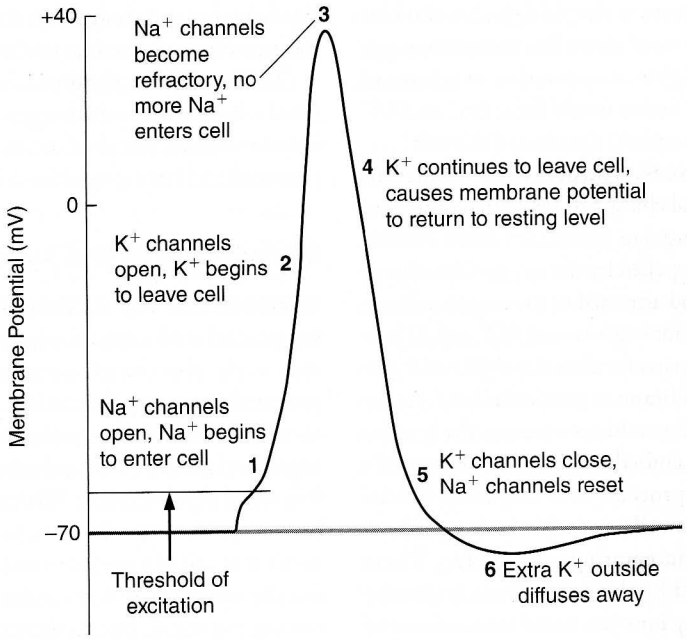


FIGURE 4-3 The flow of ions during an action potential. (Adapted from Carlson, 2011, fig. 2.18, p. 42, reprinted with permission.)

opening of K^+ channels requires a greater degree of depolarization. Triggered by the *influx* (inflow) of Na^+ ions, K^+ channels open and K^+ ions rush out of the neuron, driven by their concentration gradient and the transient positive charge created by the influx of Na^+ ions. As a result, the resting potential of the membrane is neutralized, and, in fact, the polarity is actually reversed so that the inside of the neuron reaches approximately +40 mV. At this point, Na^+ channels close, marking the end of the *rising phase* of the action potential. K^+ channels remain open, and the *efflux* (outflow) of K^+ continues; this is called the *repolarization phase* of the action potential. K^+ channels close gradually, allowing slightly too many K^+ ions to leave the cell, resulting in hyperpolarization of the cell membrane. Over time, sodium–potassium pumps restore the cell's resting potential.

This breakdown and restoration of the resting potential is known as an *action potential*, and it occurs very quickly. Some cells are capable of producing and recovering from up to a thousand action potentials each second. The term *firing* is often used to indicate an action potential. It is by means of action potentials that the cells in the nervous system integrate and convey information.

CONDUCTION OF ACTION POTENTIALS ALONG THE MEMBRANE. An action potential is generated at the section of the neuron's axon that lies adjacent to the axon hillock. But it does not stay there. The Na^+ ions that move into the cell through ion channels also move sideways along the inside surface of the membrane. This passive movement, due to diffusion and electric charge, reduces the resting potential of the surrounding membrane—that is, it depolarizes it. This depolarization causes voltage-gated ion channels to open, which, in turn, depolarizes the adjacent section of membrane. Myelinated areas of the axon have no direct contact with extracellular fluid, and, for this reason, Na^+ cannot flow into the cell at these sections. However, recall that myelinated axons contain small, uninsulated Nodes of Ranvier. As the axon potential sweeps down the axon, away from the stimulus that produced it, it does so passively underneath sections of myelin sheath and is retriggered or regenerated by the opening of Na^+ channels at each Node of Ranvier. We say that action potentials are *nondecremental* because they reach the axon terminal with the same strength as which they were initiated near the axon hillock.

Action potentials are conducted much more quickly along myelinated, compared to unmyelinated, axons as they jump from node to node; this is called *saltatory conduction*. Depending on the type of axon, an action potential can move as fast as 120 meters per second (431 km/hour or 268 miles/hour).

THE ALL-OR-NONE LAW. Action potentials are always the same. As long as a stimulus is strong enough to depolarize a cell to its threshold, an action potential will occur. Increases in the magnitude of the depolarizing stimulus beyond this point will not change the size of the action potential. This principle is known as the *all-or-none law*.

If all action potentials are the same, how does a neuron convey information about the strength of the stimulus depolarizing it? This information is reflected in the rate at which action potentials are generated. If a depolarizing stimulus is applied continuously to a cell, it will cause the cell to produce repeated action potentials. Weaker stimuli will permit the membrane a bit of recovery time, perhaps producing fewer than 100 action potentials per second, whereas stronger stimuli permit less recovery time, perhaps producing 1,000 action potentials per second. Therefore, the stronger the depolarizing stimulus, the faster the membrane will fire. This process, known as the *rate law*, is illustrated in Figure 4-4.

Stimulation of the Dendrites and Cell Body

POSTSYNAPTIC POTENTIALS. What has just been described is what happens if one depolarizes the membrane of an axon. The action potential is invariable in axons because axons have only voltage-gated ion channels and nothing else that can modulate the effect of depolarization. In contrast, the dendrites and cell body contain a great many proteins and enzymes that influence the behavior of ion channels and cell excitability. If you were to insert a microelectrode into the membrane of a dendrite or cell body and disturb the cell's resting potential, the same depolarizing stimulus that caused an action potential in an axon might give rise to very different events, depending on which modulating influences are active. Because the consequence of this disturbance is variable, we refer to depolarization in the cell body and dendrites as *graded* or *postsynaptic potentials* (PSPs), rather than action potentials (PSPs are normally created in membranes located at synapses, which will be discussed later). Postsynaptic potentials arise from the same type of ion flows as action potentials, and they spread across the membrane of a dendrite or cell body in a similar manner. The intensity of PSPs is proportional to the magnitude of the disturbance; however, this intensity decreases as the distance from the site of stimulation lengthens. The region of the axon adjacent to the axon hillock is the place where variable PSPs have the potential to be converted to unvarying action potentials.

EXCITATION. If stimulation of dendrites or the cell body results in the opening of voltage-gated Na^+ channels, Na^+ ions will rush into the cell and the resting potential will move closer to the action potential threshold. In other words, the neuron will be depolarized. This depolarization has a special name: *excitatory postsynaptic potential* (EPSP). With enough EPSPs, the cell may be depolarized past its threshold and create action potentials in its axon. As described earlier, the more the cell is depolarized past its threshold, the faster it will fire.

INHIBITION. If stimulation of dendrites or the cell body results in the opening of voltage-gated K^+ channels, K^+ ions will rush out of the cell and the resting potential will increase; that is, the neuron will be hyperpolarized. As a result, it is harder for the cell to produce action potentials.

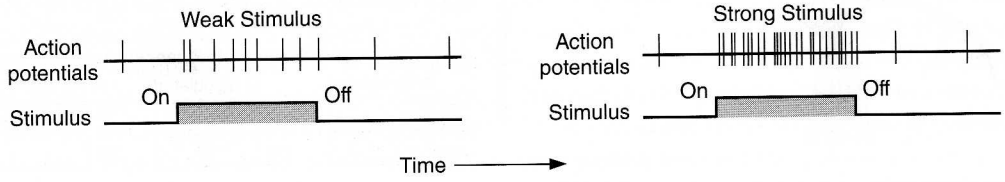


FIGURE 4-4 The rate law. The magnitude of an action potential is always the same. The strength of a stimulus producing an action potential is encoded by the rate at which a neuron fires. (Adapted from Carlson, 2011, fig. 2.20, p. 43, reprinted with permission.)

This type of stimulation is called an *inhibitory postsynaptic potential* (IPSP). IPSPs may also result from the opening of voltage-gated Cl^- channels. Recall that, at resting potential, the forces of diffusion and electrostatic charge perfectly offset each other so that Cl^- ions maintain their concentration across the membrane. However, if the cell has been depolarized somewhat by EPSPs, the opening of Cl^- channels will result in an influx of Cl^- ions, thereby offsetting the depolarization caused by the EPSPs.

SUMMATION OF EXCITATION AND INHIBITION. Each PSP, in and of itself, is of very little consequence to a cell. However, neurons integrate the often thousands of concurrent excitatory and inhibitory signals they receive at their many synapses, and this determines the rate at which action potentials will be generated or whether any will be generated at all. There are two major types of integration: (a) *temporal summation* and (b) *spatial summation*.

Temporal summation occurs when a neuron experiences several PSPs closely in time (see Figure 4-5, top panel). In the case of EPSPs, although each one may be too small to initiate an action potential, they may summate and reach threshold. Spatial summation occurs when two or more PSPs occur in close proximity on a neuron. The neuron may have Na^+ ions entering in some regions (excitation) and Cl^- ions entering or K^+ ions leaving in other regions (inhibition). These local changes in ion distribution may cancel each other out if they are different or add together if they are the same (see Figure 4-5, bottom panel). The net sum of these effects must be able to depolarize

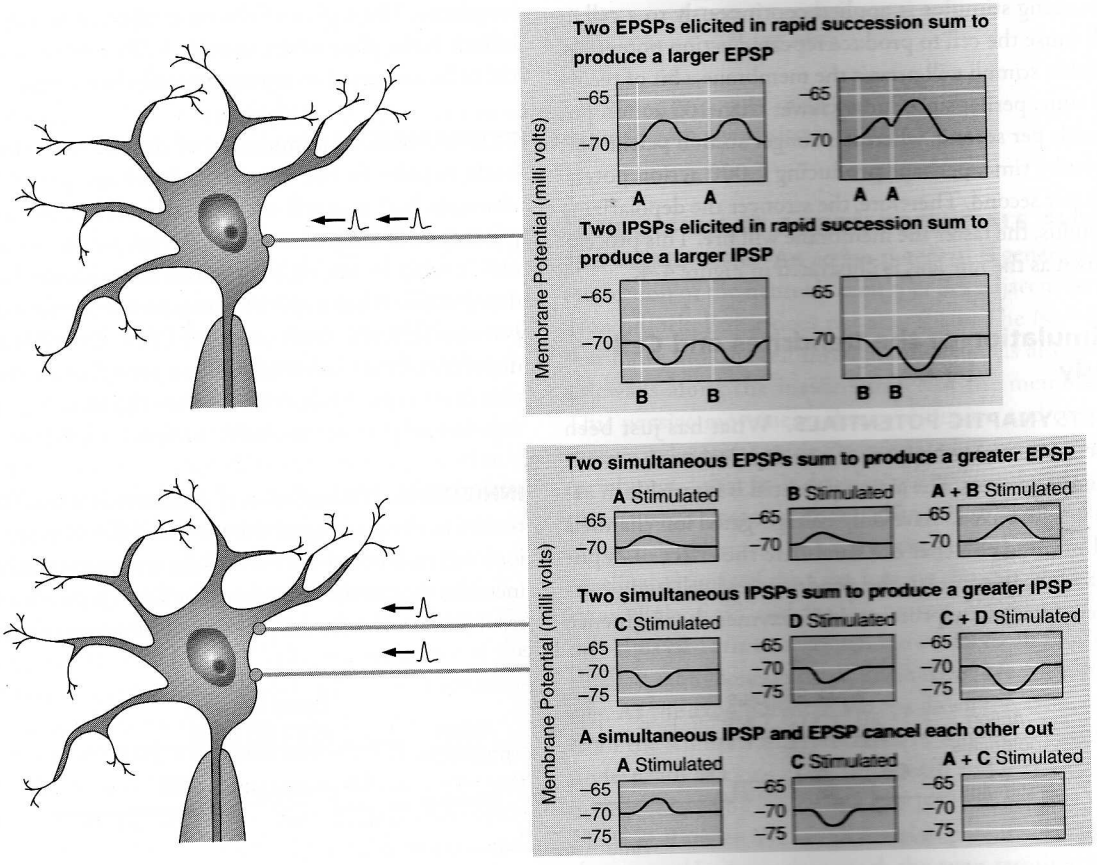


FIGURE 4-5 Temporal and spatial summation of PSPs on a neuronal dendrite or cell body. Temporal summation occurs when a neuron experiences several PSPs closely in time (*top panel*). Spatial summation occurs when two or more PSPs occur in close proximity on a neuron (*bottom panel*).

the cell beyond the threshold if an action potential is to occur.

You may be wondering what determines whether voltage-gated Na^+, K^+, or Cl^- channels will open when the dendrites or cell body of a neuron receive stimulation. Opening of these ion channels is controlled by activation of various receptor subtypes by neurotransmitter chemicals. This complex process will be explained later.

Action Potentials from Sensory Neurons

We have seen how postsynaptic potentials and action potentials are created when a section of a neuron's membrane is depolarized and how, if depolarized past its threshold, an action potential is triggered that moves along an axon. But our discussion thus far has focused on artificially producing disturbances in the cell's membrane by inserting a stimulating microelectrode into the cell. Where do natural action potentials come from?

Action potentials arise in neurons from several sources. One of these is the outside world. Sensory neurons are specialized nerve cells that are depolarized or hyperpolarized by events in the environment. In the skin are neurons whose cell bodies are depolarized by pressure, sending action potentials along their axons into the brain and causing us to experience the sensation of touch. The stronger the stimulation, the greater the depolarization and the faster sensory neurons generate action potentials. The skin also has nerve cells that are specialized to detect heat, cold, and pain. Cells in the ear are depolarized by vibration, and cells in the muscles are depolarized by movement. In fact, all that we know about the outside world comes to our brains in the form of action potentials generated by these specialized receptor neurons.

THE SYNAPSE

We still have not come to the most interesting part: how neurons communicate with one another. A nerve cell is like any other cell in the body; it is completely surrounded by a membrane. In order for the information received from the outside world to get from the sensory receptor neuron to other neurons in the brain, there must be a mechanism by which one cell is able to communicate with another. Electron microscopes reveal that although the membranes of adjacent neurons come extremely close to each other, their membranes never touch, and there is no way that an action potential on one cell can directly depolarize the membrane of another cell (although this type of conduction does occur in other tissues, such as the heart). The way in which neurons communicate across this gap is of vital interest to behavioral pharmacologists because this process is altered, in one way or another, by many drugs that affect behavior.

Information is transferred between neurons at *synapses*. A synapse, which can be seen in Figure 4-1, occurs where the terminal buttons of one cell (the *presynaptic cell*) intertwine with structures of another cell (the *postsynaptic cell*). Between the presynaptic terminal buttons and the postsynaptic cell is a small gap called the *synaptic cleft*. Synapses are most frequently located between terminal buttons and dendrites (*axodendritic synapses*) or between terminal buttons and cell bodies (*axosomatic synapses*). They may also be located on or near another neuron's axon or terminal buttons (*axoaxonic synapses*), thereby allowing one neuron to modulate another neuron's influence on the postsynaptic cell.

Action at a Synapse

NEUROTRANSMITTERS. Another very important feature of the synapse is the presence of *synaptic vesicles* within terminal buttons. These are spherical structures, of which there may be a few hundred or nearly a million, each containing chemicals called *neurotransmitters* that undergo *exocytosis* (i.e., release from the vesicles into the synaptic cleft) in response to an action potential. Synaptic vesicles are more densely packed in the *release zone* of the terminal button where there also exist many voltage-gated calcium (Ca^{2+}) channels. Upon arrival of an action potential, these channels open, permitting an influx of Ca^{2+} ions into the terminal button. Ca^{2+} influx triggers the movement and fusion of synaptic vesicles with the presynaptic membrane and the exocytosis of neurotransmitter. Neurotransmitter molecules diffuse across the cleft where they come in contact with the membrane of the postsynaptic cell.

There are places in the brain where neurotransmitters are not released directly at synapses, but rather are secreted from regions along the axon in the general

vicinity of a number of cells and diffuse to their synapses where they influence the activity of many cells at the same time. Such release is usually long lasting compared to the brief impulses of activity at synapses. Thus, the excitability of entire brain systems can be modulated.

NEUROMODULATORS. A *neuromodulator* is a chemical that is synthesized and released by neurons and that modulates the effects of neurotransmitters. It may have short- or long-term effects. Neuromodulators may act within the postsynaptic cell, or they may also have an effect on the presynaptic cell to modify the release of a neurotransmitter. Neuromodulators are typically released in greater amounts and travel further distances, compared to neurotransmitters. Substances that act as neurotransmitters in one synapse may also act as neuromodulators of transmission at a different synapse.

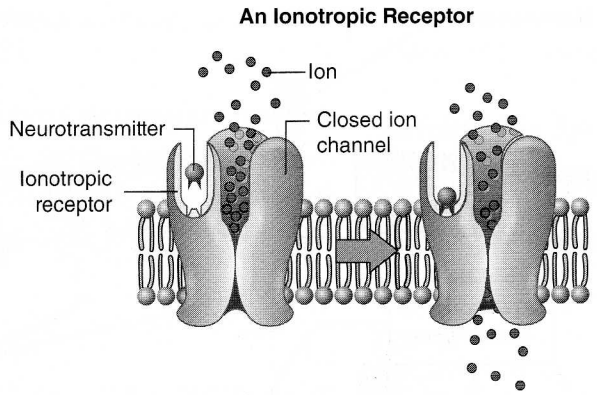
RECEPTORS. Recall that much of the machinery needed for cell communication is molecules of protein. A *receptor* or *receptor complex* is a specialized protein that spans the membrane of the postsynaptic cell and contains a binding site to which a specific neurotransmitter molecule can briefly attach, much like a key fitting into a lock. When a neurotransmitter with the correct configuration (the key) attaches to a receptor (the lock), the receptor changes its shape (we sometimes say the receptor has been activated). This reconfiguration alters the functioning of the cell, causing certain events to occur such as a shift in its resting potential or a change in its biochemistry.

Given that the lock-and-key analogy has become the standard way of illustrating neurotransmitter–receptor binding, one would think that each neurotransmitter molecule must have only one receptor to which it can bind. This is not the case. As you will see in the Neurotransmitters section later in this chapter, there are often many different receptor *subtypes* to which a particular neurotransmitter molecule can bind. These subtypes often exist in different regions of the brain, and their activation can produce varying effects in the cell. In this way, a single neurotransmitter can produce a variety of results. Such changes can be brought on directly or indirectly.

IONOTROPIC RECEPTORS. In some synapses, postsynaptic receptor proteins contain binding sites directly connected to a gated ion channel; these are called *ionotropic receptors* (see Figure 4-6, top panel). Neurotransmitter binding activates the receptor, leading to a reconfiguration of the protein so that the ion channel opens or closes and there is an influx or efflux of particular ions. Depending on the ion channel, this could either increase or decrease the resting potential of the membrane. This effect occurs very rapidly, in the order of milliseconds, and lasts only briefly.

METABOTROPIC RECEPTORS. In other cases, the effects of receptor activation are indirect, initiating a cascade of events that occur more slowly and are longer lasting. The binding sites on *metabotropic receptors* are not directly connected to an ion channel. Instead, receptor sites are situated on the extracellular portion of a long protein that weaves its way back and forth seven times across the cell membrane, like a snake (this is called a seven-helix structure; see Figure 4-6, bottom panel). The intracellular portion of the signal protein is linked to another specialized structure called a *G protein* (short for *guanine nucleotide-binding protein*). When a neurotransmitter molecule binds to its receptor, a subunit (portion) of the G protein breaks away. The subunit may travel a short distance inside the cell's membrane to activate a nearby ion channel, thus stimulating an EPSP or IPSP. Or, the subunit may initiate a biochemical (enzymatic) reaction that leads to the synthesis of another molecule called a *second messenger* (neurotransmitters are considered first messengers).

SECOND MESSENGERS. Second messengers can do a number of things inside the postsynaptic cell (follow along in Figure 4-7). The best known second messenger is *cyclic adenosine monophosphate* or *cyclic AMP* (cAMP). Another common second messenger is *cyclic guanosine monophosphate* or *cyclic GMP* (cGMP). Often, a second messenger interacts with gated ion channels from inside the cell, with similar but more long-lasting effects to those of directly gated ion channels. Or, the second messenger can alter the operation of nongated ion channels in a way that changes the resting potential or the cell's sensitivity to other stimuli.



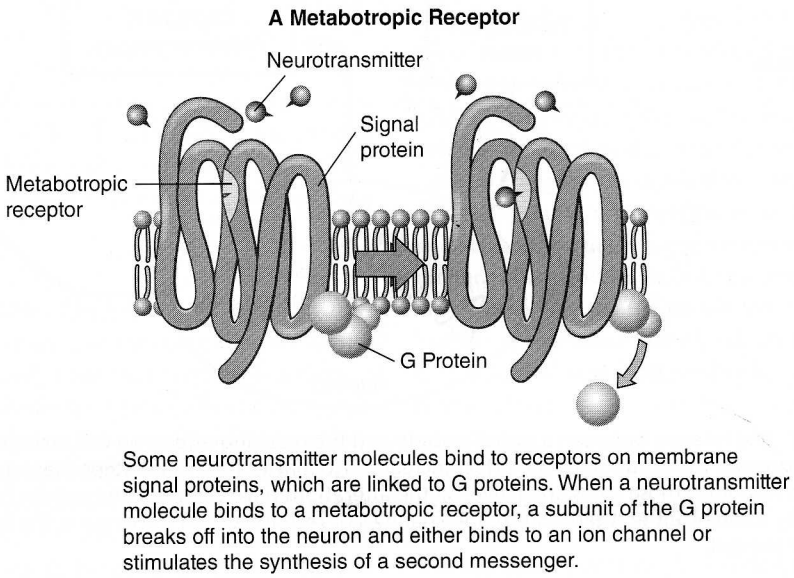


FIGURE 4-6 Ionotropic and metabotropic receptors (Adapted from Pinel, 2011, fig. 4.12, p. 89, reprinted with permission.)

Second messengers may also have even longer-term or permanent effects because they activate a type of protein called a *kinase*. For example, cAMP activates *protein kinase A*, whereas cGMP activates *protein kinase G*. A kinase is much more persistent than a second messenger and can remain active for many minutes or even for hours. Kinases alter the functioning of both ion channels and receptors, but they do so for a much longer time than second messengers. Kinases also influence many other regulatory processes in the cell, including the release of second messengers from other receptors and the efficiency of ion pumps.

Kinases may also activate (phosphorylate) transcription factors such as *CREB* and *c-fos*. Genes in the cell nucleus have switches that can turn them on or off. These switches are turned on and off by chemicals called *transcription factors*. Whether a particular gene is active at any given time is determined by the

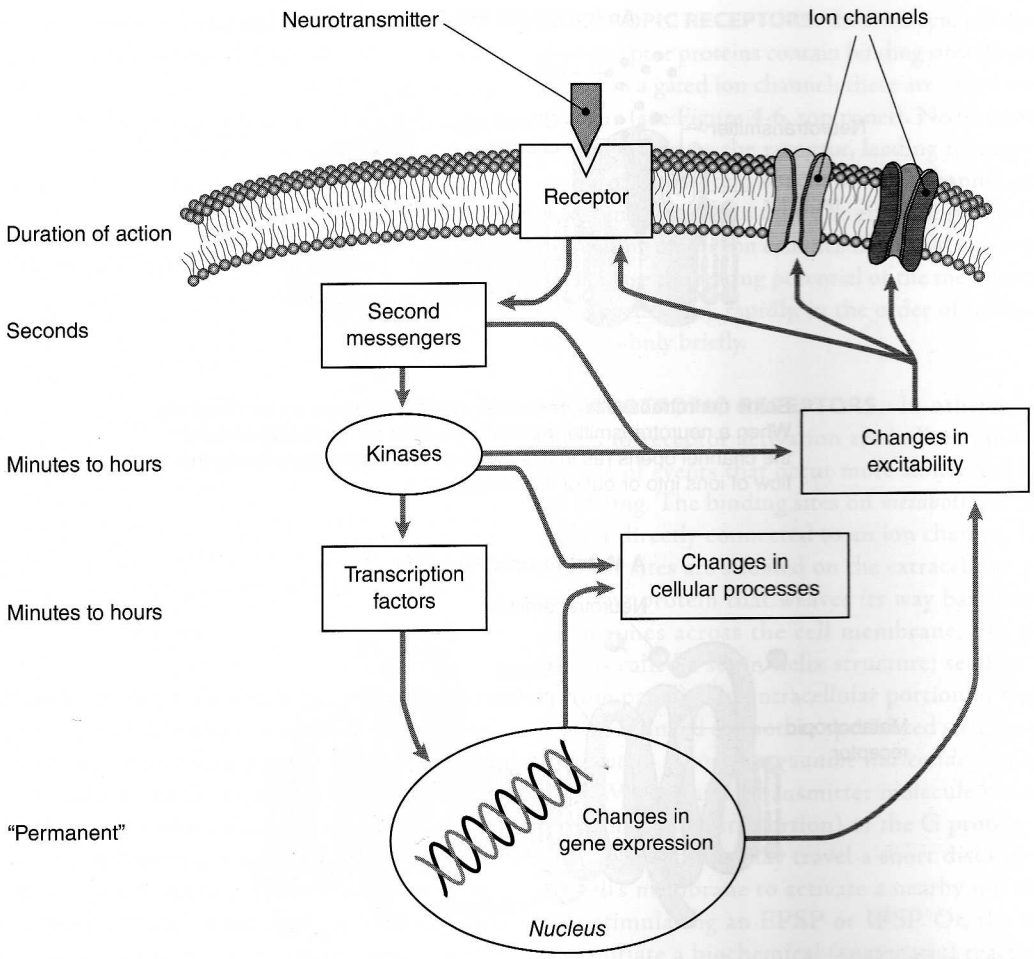


FIGURE 4-7 The relation between a signal cascade and the resulting effects on cell excitability. As the cascade progresses, the duration of the effect increases. No matter how many steps there are in the cascade and how long those steps are active, all the alterations have common end points. Every change in excitability is the result of alterations to ion channels or receptors or of a change in the biochemical processes of the cell.

presence or absence of particular transcription factors. Thus, when kinases activate transcription factors, they are controlling the expression of particular genes in the cell. Genes contain the code for the order in which amino acids need to be strung together to create a particular protein, and the process of creating these proteins from the genetic code is called *transcription*. The proteins created by the DNA could be receptor sites, ion channels, ion pumps, or any of the other molecules used by the cell in receiving and transmitting information, or they could be transcription factors for other genes. Thus, a transcription factor may turn on the gene that makes receptor sites for a given transmitter. With more receptor sites, the cell will become more sensitive to that neurotransmitter. In the same way, some ion channels may become more numerous, and others may become less numerous. Second messengers (via kinases and transcription factors) can even cause a synapse to be made or removed, thus permanently altering the connections of a cell. Changes in neuron excitation or sensitivity that arise from changes in gene expression can be very long lasting and are thought to

be responsible for the formation and storage of memories in the brain.

Presynaptic Effects of Neurotransmitters

AUTORECEPTORS. Receptor sites for neurotransmitters are located not only on the postsynaptic neuron but also on the presynaptic neuron. Some of these are called *autoreceptors*. These metabotropic receptors provide feedback on the amount of neurotransmitter released in the synaptic cleft in order to regulate its levels through the activity of G proteins and second messengers. If levels of the neurotransmitter get too high, the autoreceptors will cause a reduction in the synthesis and release of the transmitter. It is believed that a mechanism such as this causes a delay in the effectiveness of some psychotherapeutic drugs, such as antidepressant medications (see Chapter 13). Antidepressants produce a buildup of crucial neurotransmitters, but autoreceptors detect this excess and reduce production and release of the neurotransmitter molecules, thus blocking the effectiveness of the drug. It sometimes takes a few weeks to exhaust the autoreceptors before the drug can make changes in the functioning of the synapse.

HETERORECEPTORS. The release of neurotransmitters from the presynaptic cell to alter the excitability of a postsynaptic cell is the most common and best-understood mechanism by which cells communicate, but it is not the only mechanism. In addition to autoreceptors, the presynaptic cell contains *heteroreceptors*. These are metabotropic receptor sites that function very similarly to autoreceptors except that they respond not to the release of neurotransmitter by the cell upon which they reside, but to chemicals released by the postsynaptic cell or other nearby cells when they become depolarized. This transmission of chemical information from a postsynaptic to presynaptic cell is termed *retrograde signaling* and is thought to be a mechanism through which the postsynaptic neuron can modulate its level of stimulation by altering neurotransmitter synthesis and release by the presynaptic neuron. This is called *depolarization-induced suppression of excitation* (DSE) or *depolarization-induced suppression of inhibition* (DSI), depending on whether activity of the synapse was excitatory or inhibitory. In fact, receptors for THC are located presynaptically and respond to a chemical released by the postsynaptic neuron (see Chapter 14).

Terminating Synaptic Action

After the arrival of an action potential at the terminal button initiates the release of a transmitter into the synaptic cleft, it is important to have some mechanism by which to rid the transmitter from the cleft. Otherwise, the transmitter would stay in the cleft and continue to influence the postsynaptic cell. Every synapse has a system to accomplish this purpose and does so in one of two ways: (a) The presynaptic cell may quickly reabsorb the intact neurotransmitter molecule, taking it back into the cytoplasm of the terminal button where it gets repackaged into vesicles (which also get recycled) for future use. This is the most common process. It is called *reuptake* and is accomplished by a specialized mechanism that actively employs *transporter protein* molecules embedded in the membrane of the presynaptic cell. New research suggests that glial cells are also actively involved in the reuptake of neurotransmitter (specifically, glutamate, described later in this chapter); (b) The synapse may contain an enzyme, produced in and released from the same neuron as the neurotransmitter. This process, called *enzymatic degradation* or *deactivation*, breaks the neurotransmitter into its precursors (constituent parts), which may also be taken back into the presynaptic cell to be remanufactured for future release.

THE NERVOUS SYSTEM

The nervous system can be divided into various parts, but the most basic distinction is between the *central nervous system* (CNS) and the *peripheral nervous system* (PNS). The CNS is made up of the brain and spinal cord, and the PNS is everything outside the brain and spinal cord. In both systems, neurons are organized in a similar manner; cell bodies tend to be located together in clusters, and the axons from these cells also tend to bundle together to form a pathway connecting to other clusters of cell bodies. We find, therefore, that the nervous system is made up of groups of cell bodies with bundles of axons running between them. In the PNS, these groups of cell bodies are called *ganglia* (singular is

ganglion), and the bundles of axons are called *nerves*. In the CNS, the cell body groups are called *nuclei* (singular is *nucleus*) or *centers*, and the bundles of axons are called *tracts*. Because axons are generally covered with myelin, which is white, the nerves and tracts are called *white matter*. The unmyelinated cell bodies are called *gray matter*.

The PNS

The PNS may be further divided into two functional units: (a) the *somatic nervous system* and (b) the *autonomic nervous system*.

SOMATIC NERVOUS SYSTEM. The somatic nervous system is the means by which the brain and spinal cord receive information from, and allow us to interact with, our environment. It is made up of sensory nerves that convey information from the senses to the CNS, such as the nerves running from the sensory receptors in the eyes, ears, and skin. The somatic nervous system also contains the motor nerves, which have their cell bodies in the spinal cord and send axons directly to glands or *striated muscles* (muscles over which we normally have voluntary control). The motor nerves control these muscles at neuromuscular junctions, which are very much like synapses. Acetylcholine (ACh) is the transmitter at most neuromuscular junctions, and the receptor sites are of the nicotinic cholinergic type. You will learn more about acetylcholine and many other chemical transmitters and their receptor subtypes in the upcoming section on Neurotransmitters. The somatic nervous system also includes the *cranial nerves*, which are attached to the undersurface of the brain. Mostly, these nerves convey motor commands and/or sensory information to and from areas of the face and neck.

AUTONOMIC NERVOUS SYSTEM. Whereas the somatic nervous system usually carries information into the CNS from our conscious senses, the autonomic nervous system is concerned with sensory information that we are usually unaware of: information about blood pressure and blood gases, the functioning of organs, and levels of hormones. Whereas the somatic system usually commands muscles over which we have voluntary control, the autonomic nervous system commands the muscles of the heart and intestines, the secretions of glands, and other regulatory systems over which we normally have no conscious control.

The autonomic nervous system is actually divided into two distinct divisions that control the body's organs and glands in a highly coordinated balancing act (these divisions can be seen in Figure 4-8). The division that is dominant and in control most of the time is called the *parasympathetic division*. It generally keeps the internal functioning of the body running smoothly, in a *rest-and-digest* mode of operation. The other autonomic nervous system division, called the *sympathetic division*, is connected to the same internal organs as the parasympathetic division. In times of stress and danger, it takes over from the parasympathetic division to prepare the body for a sudden expenditure of energy, as is required for fighting or running. Blood is directed away from the digestive system to the arms and legs, the pupils dilate, and heart and breathing rates increase. This series of changes is called the *fight-or-flight response*, which is energetically expensive and taxing on the body. Therefore, once danger has passed, control of the body's organs and glands is once again taken over by the parasympathetic division to restore a relaxed, balanced state.

The parasympathetic and sympathetic divisions of the autonomic nervous system are anatomically, functionally, and neurochemically distinct. Cell bodies of parasympathetic neurons originate in the sacral region of the spinal cord and in nuclei of the cranial nerves (especially the vagus nerve, which, unlike the other cranial nerves, controls the visceral organs); cell bodies of the sympathetic division originate in the thoracic and lumbar regions of the spinal cord. The parasympathetic system uses ACh as a transmitter to control glands and muscles. Consequently, drugs that alter transmission at cholinergic synapses interfere with parasympathetic functioning. Perhaps the best example of such drugs is atropine, which is a cholinergic muscarinic blocker, otherwise called an *anticholinergic*. Atropine has been used by optometrists to dilate the pupils in the eye so that the retina at the back of the eye can be examined. When atropine is placed in the eye, it blocks the receptor sites at parasympathetic neuromuscular junctions. Because the parasympathetic division can no longer control the size of the pupil, it dilates. The muscles that control the eye's lens are also under parasympathetic control, so the atropine also makes vision blurry. Some drugs, such as the tricyclic antidepressants

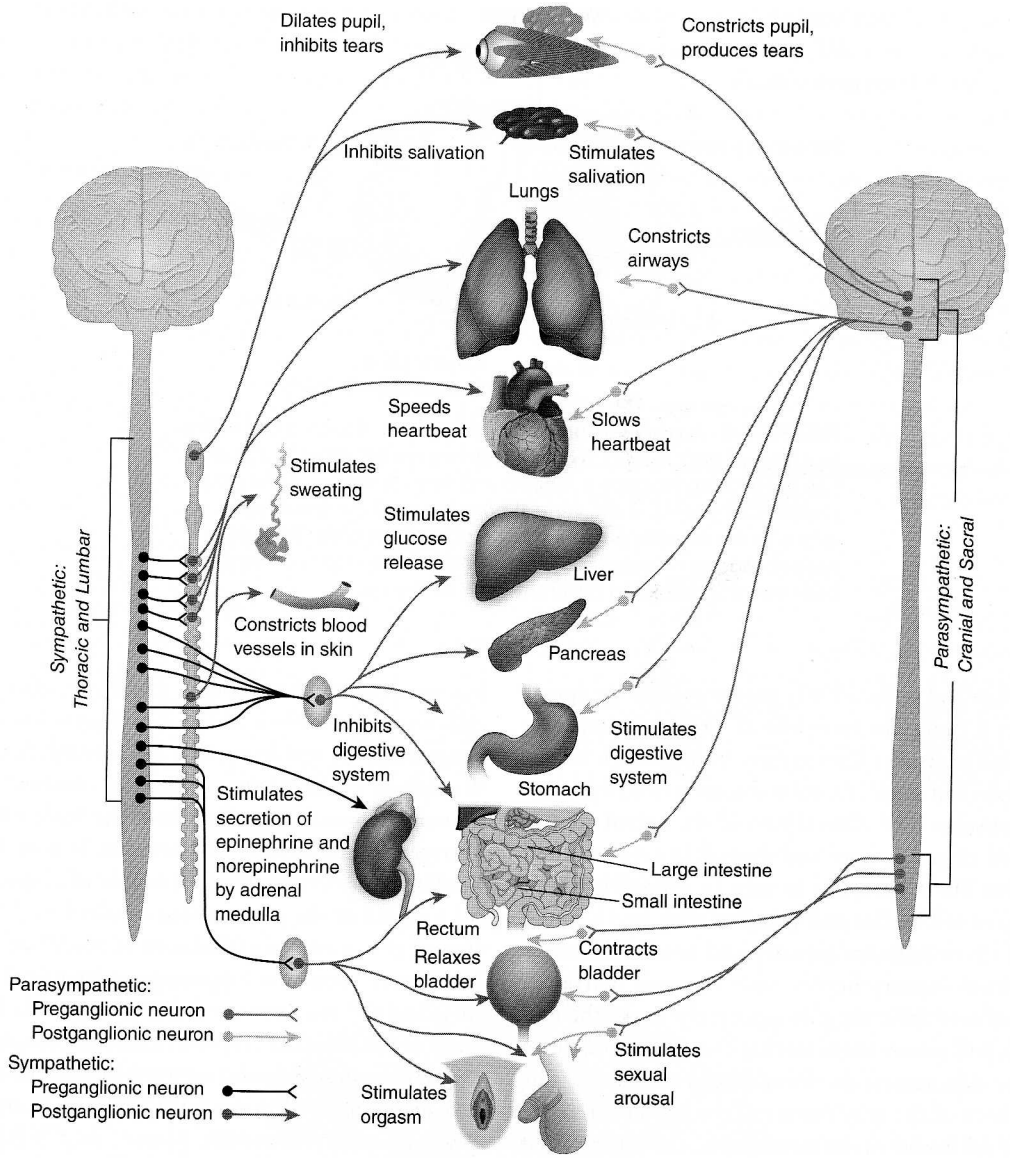


FIGURE 4-8 Roles of the sympathetic (*left*) and parasympathetic (*right*) divisions of the autonomic nervous system. (Adapted from Carlson, 2011, fig. 3.23, p. 84, reprinted with permission.)

and antipsychotics (see Chapters 12 and 13), have anticholinergic side effects that include blurred vision and dry mouth.

The primary transmitter in the sympathetic system is epinephrine (adrenaline). In times of stress, the adrenal glands secrete epinephrine into the blood, directly stimulating receptors in the sympathetic division and causing the fight-or-flight response. Drugs such as amphetamine and cocaine that stimulate adrenergic synapses will also cause sympathetic arousal, such as increased heart rate and blood sugar.

The CNS

SPINAL CORD. The CNS has two basic parts: the *brain* and the *spinal cord*. Some integration of

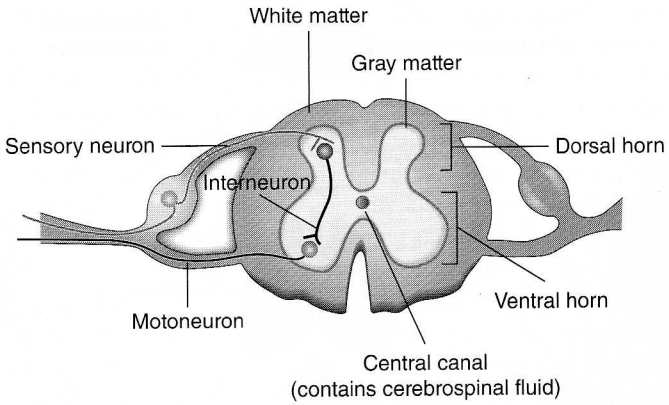


FIGURE 4-9 A cross section of the spinal cord, showing the white matter and gray matter. Axons of sensory nerves come in through the dorsal horn (toward the back) and form synapses in the gray matter. Cell bodies in the ventral horn (toward the front) send axons to the muscles out the ventral side of the cord. The white matter consists of bundles or tracts of myelinated axons running between the brain and different parts of the body.

information and reflex activity goes on within the spinal cord, but it functions primarily as a relay station. The spinal cord transmits information from sensory nerves to the brain and carries motor commands from the brain to the muscles. The central part of the spinal cord is composed of gray matter and shaped, in cross section, somewhat like a butterfly, as seen in Figure 4-9. It is made up of cell bodies and synapses with *interneurons*, which help coordinate sensory and motor behavior. Axons from sensory nerves enter the gray matter of the spinal cord from the side nearest the back (the *dorsal* side), and motor axons leaving the spinal cord do so from the side nearest the front (the *ventral* side). The *ventral horn* of the gray matter of the spinal cord contains the cell bodies of the *motoneurons*, the neurons that directly control the action of muscles. This area also mediates many reflexes. The *dorsal horn* contains cells that convey sensory information. Surrounding the gray matter are a number of tracts of axons running both up and down the spinal cord, connecting the brain to various parts of the body.

BRAIN. It has been estimated that the human brain contains 10^{11} (i.e., 100 billion) neurons. On average, each neuron has synapses on 1,000 other neurons and receives an average of 10,000 synapses (Costa, 1985). For many years, it was thought that the number of brain cells was fixed at birth and that cells were lost as aging progressed. We now know that new nerve cells can form throughout life in species as diverse as canaries, rats, and humans. However, not all areas of the brain experience *neurogenesis*, the birth of new neurons. In adult humans, neurogenesis occurs only in a couple of distinct areas: (a) a region of the *hippocampus* involved in the formation of new memories (Eriksson et al., 1998; you will learn more about the hippocampus later in this chapter); and (b) the *subventricular zone* (which lines the walls of the brain's lateral ventricles, cerebrospinal-filled cavities) from which new neurons migrate to the *olfactory bulbs*, involved in the sense of smell (Curtis et al., 2007; Doetsch et al., 1999). Most of the CNS is able to restructure and reorganize its connections during learning and development, and repair itself to some degree following injury—we call this *neuroplasticity*—but neurogenesis is a special case indeed.

The brain is a complicated structure made up of numerous nuclei and complex fiber tracts connecting those nuclei. For this reason, the brain has been called a "great raveled knot." In recent years, neuroscientists have made great strides in unraveling the knot, but it still contains many mysteries and is the subject of intensive study. The brain is too complex a structure to be explained in

a simple fashion, but we will introduce some of the features that appear to be important in an understanding of many drug effects. Figure 4-10 illustrates the brain and identifies some of its structures.

Hindbrain Structures

MEDULLA OBLONGATA. The area at the base of the brain, where the spinal cord arises, is called the *medulla oblongata* (or just the *medulla*). It is, in part, made up of fiber tracts running to and from the spinal cord and connecting to higher centers in the brain, such as the motor cortex (an area involved in commanding motor activity; you will learn more about this later in this chapter). In addition, the medulla contains part of the *descending reticular formation* (to be discussed shortly), which consists of numerous nuclei that act as control centers for the autonomic nervous system. Therefore, proper functioning of the autonomic nervous system depends on the general level of arousal in the medulla. These control centers regulate consciousness as well as heart rate, blood pressure, breathing, muscle tone, and even reflexes such as coughing, swallowing, sneezing, and vomiting. The respiratory center, which controls breathing, is very sensitive to many drugs. Barbiturates, opioids, and alcohol depress this center and, consequently, depress breathing. Death from a drug overdose is usually a result of suffocation because the respiratory center becomes depressed to the point where breathing stops. Quite often people who survive drug overdoses have brain damage because low oxygen levels in their blood resulted from extended depression of their respiratory center.

The vomiting center, which is named the *area postrema*, is also sensitive to drugs. This center is one of very few areas in the brain that is not shielded by the blood–brain barrier. It is therefore able to monitor the blood for toxins and can initiate vomiting, presumably to rid the digestive system of a poison that has just been ingested. Some drugs, such as opiates and nicotine, stimulate this center and cause nausea and vomiting even though the drug was inhaled or injected.

PONS. The pons (Latin for *bridge*) is a large bulbous structure located in the hindbrain, above the medulla. It too contains nuclei of the reticular formation that play a role in sleep and arousal. The pons also bridges and refines motor commands conveyed between parts of the cortex (including the motor cortex) and the cerebellum (see next). The pathway between the cortex, pons, and

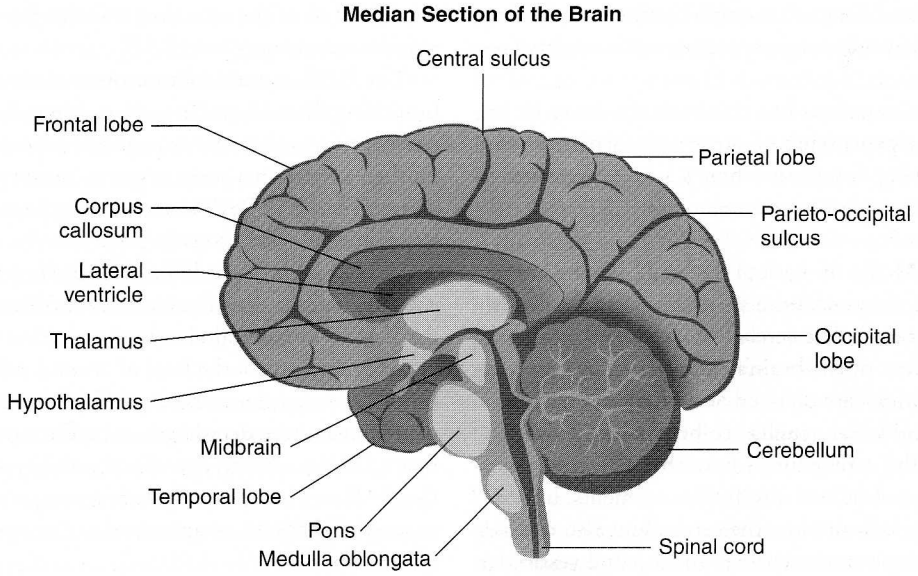


FIGURE 4-10 A cross section of a human brain. Note the locations of some of the structures mentioned in the text.

cerebellum is a superhighway of motor information, containing about 20 million axons.

The *locus coeruleus* is a group of cell bodies residing in the pons. It receives input from many sources, both inside and outside the CNS, and projects its axons diffusely to areas you will soon become more familiar with, such as other hindbrain regions, the thalamus, limbic system, cortex, and other higher-brain centers, as well as to the cerebellum and spinal cord. Its synapses use norepinephrine as a transmitter (more about this in the Neurotransmitters section). It is believed that the locus coeruleus contains about 50% to 70% of the norepinephrine-containing neurons in the brain. This system, along with several other similar systems (such as the serotonin-containing raphe nuclei, described later in this chapter), projects to higher-brain centers through a pathway called the *medial forebrain bundle*. Depression is associated with abnormal functioning of these systems.

Activity of the locus coeruleus is controlled by a large inhibitory input of synapses that release the neurotransmitter GABA. Activity in the locus coeruleus is associated with arousal, fear, panic, and anger. *Positron emission tomography* (PET), a brain imaging technique, shows that the locus coeruleus and brain areas to which it projects become highly active during a panic attack. Drugs like the benzodiazepines (e.g., Valium), which increase the inhibitory effects of GABA, relieve anxiety (see Chapter 7), and drugs like amphetamine and cocaine, which stimulate adrenergic synapses, cause anxiety (see Chapter 10).

The locus coeruleus has also been shown to be involved in the processing of sensory information and has an alerting function when a novel stimulus is experienced.

CEREBELLUM. At the back of the brain, attached to the dorsal side of the pons, sits a structure called the *cerebellum* ("little brain"). The cerebellum functions primarily as a component of the brain's extensive motor system. Voluntary actions are planned and initiated by parts of the cortex and basal ganglia (to be discussed shortly) and sent to the cerebellum where they are integrated, coordinated, and refined into fluid movements. In addition to motor information, the cerebellum also receives visual, auditory, somatosensory (touch), and vestibular (balance) information from the cortex, as well as information regarding movement of the muscles sent through the spinal cord. It integrates all of this information and sends signals back to the motor cortex, via a structure called the thalamus, to modify motor commands. These feedback loops make smooth and accurate muscle movements possible. The cerebellum also helps maintain posture, fine-tunes the timing of movements, smoothes eye movement as focus shifts from one fixation point to another, and is important for procedural memory; that is, the learning and memory of movements, such as how to ride a bike. People with damage to the cerebellum are slow and clumsy and often appear to be intoxicated with alcohol. It is quite likely that many of the motor effects of alcohol are due to a specific effect on the cerebellum.

Midbrain Structures

RETICULAR FORMATION. The reticular formation is a diffuse system consisting of more than 110 individual nuclei located in the core of the brainstem. As mentioned earlier, some of these nuclei project axons downward, into the spinal cord; this is referred to as the *descending reticular formation*. These projections are involved in autonomic nervous system activity (e.g., breathing and heart rate), reflexes (e.g., coughing and swallowing), as well as posture, balance, and motor movement. In addition, some nuclei of the reticular formation project axons upward, through the thalamus and into the cortex; this is referred to as the *ascending reticular formation* or the *reticular activating system* (RAS).

The RAS contains numerous centers with widely branching fiber tracts. It receives input from axons of sensory nerves that run through the reticular formation on their way from a sense organ to sensory areas of the cortex. Thus, the RAS is activated by incoming stimulation and projects axons forward into the entire cortex and higher parts of the brain so that when the RAS becomes active, so does the entire brain. One function of the RAS is to maintain levels of activation in the cortex and thereby control the level of arousal, selective attention, and wakefulness. Because GABA is an inhibitory neurotransmitter, drugs such as barbiturates, which enhance GABA activity, decrease the ability of neurons in the RAS to fire repeatedly and, consequently, decrease arousal. If the RAS of an animal is damaged, it will fall into a coma.

One subset of nuclei located within the reticular formation is referred to as the *raphe nuclei* or *raphe system*,

some of which project downward, to the lower hindbrain and spinal cord, and some upward, to the thalamus, limbic system, and cortex. Unlike the RAS, artificial stimulation of some raphe nuclei causes sleep and damage to them produces an animal that seldom sleeps. This finding shows that sleep is not just a lack of stimulation in the RAS but an active process as well. Most raphe nuclei use serotonin as a neurotransmitter, and drugs that alter serotonin activity also seem to interfere with sleep.

PERIAQUEDUCTAL GRAY (PAG). The PAG is involved in pain sensation and in defensive behavior. The PAG serves as one of several relays for axons that carry pain signals from the dorsal horn of the spinal cord to the cortex. Stimulation of the PAG causes an immediate loss of pain sensation (analgesia). This is because the PAG is rich in receptor sites for opioid drugs (e.g., morphine) and their endogenous counterparts, endorphins and enkephalins (you will learn more about these in the Neurotransmitters section of this chapter and in Chapter 11 on Opioids). These neurons send axons to the raphe nuclei of the hindbrain, which, in turn, project downward to release serotonin in the spinal cord, indirectly stimulating further release of endorphins in the spinal cord, inhibiting pain. Thus, opioid drugs can block pain by stimulating cells in the PAG and the spinal cord.

Also located in the PAG is a system that has been described as a "punishment" system. These are sites where electrical stimulation appears to have a punishing effect on experimental animals. Animals will learn to perform a task in order to avoid stimulation in this area. It has not been determined whether the pain perception and the punishment functions of these systems are related, but it is certainly tempting to speculate that they are. The PAG also receives input from a limbic structure called the *amygdala*, a center that mediates fear and fear conditioning.

SUBSTANTIA NIGRA. The substantia nigra is a motor area of the brain, which is highly interconnected with another motor region, the basal ganglia (to be described shortly). Cell bodies that reside in the substantia nigra produce the neurotransmitter dopamine (DA); degeneration of these cells is associated with Parkinson's disease. You will learn more about this structure and dopamine in the upcoming Neurotransmitter section.

VENTRAL TEGMENTAL AREA (VTA). The VTA is a vital component of the brain's reward circuit, for both natural and drug reinforcers. It is the site of origin for a projection pathway called the *medial forebrain bundle*. The VTA contains cell bodies of dopamine-producing neurons that project to and release dopamine in multiple regions of the brain, including the thalamus; hypothalamus; substantia nigra; nucleus accumbens; areas of the limbic system including the hippocampus, septal nuclei, and amygdala; and the prefrontal cortex (information on unfamiliar brain areas is upcoming in this chapter). Stimulation of the medial forebrain bundle projection that runs between the VTA and the nucleus accumbens is associated with pleasure and has been implicated in drug euphoria and addiction, as well as in schizophrenia (see Chapter 12). In addition to dopamine, the VTA also contains neurons that produce GABA (Olson & Nestler, 2007) and glutamate (Yamaguchi, Sheen, & Morales, 2007), which regulate dopamine neuron activity and send projections to other brain regions.

Forebrain Structures

BASAL GANGLIA. The basal ganglia (*basal* means "at the base of"; *ganglia* refers to a group of cell bodies) are located just under the cortex and are important in controlling voluntary movement, action selection and switching between motor behaviors, motor habits, and eye movement. In addition to motor actions, the basal ganglia control some cognitive processes such as memory for locations in space and classical conditioning of behaviors. Given the wide variety of functions they control, it is not surprising that the basal ganglia contain several interconnected nuclei. The *striatum* (also called the *neostriatum*) is the largest component of the basal ganglia and is the major input center for information from the cortex and thalamus. The striatum can be subdivided as follows: the *dorsal striatum* includes the *caudate nucleus*, the *putamen*, and the *fundus*, which links them; the *ventral striatum* includes the *olfactory tubercule* and the *nucleus accumbens*, which you recall is part of the medial forebrain bundle—the brain's pleasure pathway. Projections from the striatum are sent to the *globus pallidus* (or *pallidum*), which is the output side of the basal ganglia. The globus pallidus projects to an additional component of the basal ganglia, called the *subthalamic nucleus*, and also sends projections back, via the thalamus, to a motor area of the cortex. Together, the basal ganglia, the thalamus,

and the cortex make up the "motor loop" and control all voluntary movement. You may read other texts or papers that consider the substantia nigra to be part of the basal ganglia. It is, as you have learned, located in the midbrain but is highly interconnected with the basal ganglia and is therefore sometimes considered a substructure.

Parkinson's disease is the result of a malfunction of the basal ganglia, specifically a depletion of dopamine release in the dorsal striatum due to the death of dopamine cells originating in the substantia nigra. This pathway is known as the *nigrostriatal system*; you will learn more about it in the Neurotransmitters section on dopamine. People suffering from Parkinson's disease have tremors, rigidity in the limbs, and difficulty initiating movement. In many people, the symptoms of Parkinson's disease can be alleviated if the patient is given DOPA (or *L-dopa*), the metabolic precursor of dopamine. Unlike dopamine, which cannot pass through the blood–brain barrier, DOPA is taken into the brain and transformed into dopamine, which then increases activity at these synapses in the basal ganglia. We also know that drugs like the antipsychotics, which block DA receptors, have side effects that resemble Parkinson's disease (see Chapter 12).

By now, you have read about quite a number of brain structures that participate in the planning, execution, and refinement of motor movements. In the section on the cortex, you will encounter what might be considered the most important of these structures—the motor cortex. The system that connects the motor cortex to the muscles is called the *pyramidal motor system*; consequently, the system involving the basal ganglia and substantia nigra is called the *extrapyramidal motor system*.

LIMBIC SYSTEM. The limbic system is quite possibly the most difficult brain system to describe, mainly because of varying opinions as to which of the hundreds of complexly interconnected nuclei truly belong in this category. The many structures that form the limbic system integrate such vast processes as learning, memory, emotion, motivation, and executive functions including decision making and planning. They are a target for a variety of drugs.

Early neuroanatomists defined the limbic system as a looped circuit that included the *hippocampus*, *mammillary bodies* (located in the *hypothalamus*), *thalamus*, and *cingulate gyrus*. In the past 50 or so years, many more structures have been included in this seemingly ever-expanding megasystem. Many of these are areas of the cortex, including, but not limited to, the *insular cortex*, *orbitofrontal cortex*, *dorsolateral prefrontal cortex*, *subcallosal gyrus*, and *parahippocampal gyrus*. Others are areas below the cortex, including, but not limited to, the *olfactory bulb*, *amygdala*, *septal nuclei*, and *fornix*. The nucleus accumbens, which you recall forms part of the ventral striatum of the basal ganglia, and the ventral tegmental area, which is a midbrain structure, may also be considered part of the limbic system due to their intricate connections and extensive communication with other limbic structures. In addition, the hypothalamus is considered by many to be part of the limbic system. All of these structures communicate extensively with each other and with other structures outside of limbic system circuitry. As you can see, this megasystem can be quite confusing. But if we try to imagine separating memory from emotion or motivation from learning, the intertwined circuitry of the limbic system makes sense.

We will not discuss all areas of the limbic system (some of its structures can be seen in Figure 4-11). The nucleus accumbens and ventral tegmental area have been discussed already, and some important areas of the cortex will be discussed in the next section. In this section, we will review the functions of only two limbic system structures: the hippocampus and the amygdala. The thalamus and hypothalamus will be discussed next as additional forebrain structures; keep in mind, however, that they communicate extensively with the limbic system.

The *hippocampus* is a large limbic structure, located beneath the cortex in the temporal lobe (see Cortex section that follows shortly). It plays important roles in learning and memory. Removal of the hippocampus in humans (as was done years ago to treat epilepsy) causes amnesia, particularly for the more recent events of one's past, and an inability to form new declarative memories. The hippocampus is also important for spatial memory. In rats, destruction of the hippocampus prevents learning of even a very simple maze, such as an open field with no walls. In individuals who have experienced stress for prolonged periods (or have posttraumatic stress disorder), the size of the hippocampus is reduced, likely due to the detrimental effects caused by stress hormones, which bind to receptors there. The hippocampus is highly interconnected with another limbic region, the amygdala.

Most drugs have effects on the hippocampus, although they can be difficult to spot in traditional behavioral tests. Drug effects on the hippocampus may be related to

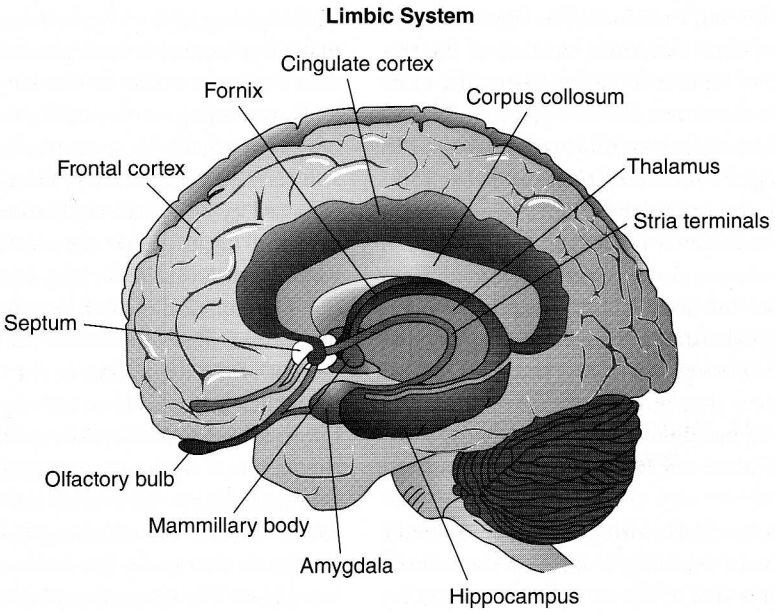


FIGURE 4-11 Components of the limbic system.

state-dependent learning. Place preference, created by associating a place with a drug (discussed in Chapter 2), is also mediated, at least in part, by the hippocampus.

Like the hippocampus, the *amygdala* sits below the cortex in the temporal lobe. It is implicated in the processing of emotions, especially negative emotions such as fear and rage; in the formation of emotional memory; and in behavioral reactivity, especially aggression. Like other limbic structures, the amygdala is highly interconnected with many brain regions. It receives sensory information from the cortex as well as information about pain and stress levels. Many studies have found hyperactivity of the amygdala in individuals with posttraumatic stress disorder (Hughes & Shin, 2011). Destruction of the amygdala causes a normally aggressive animal to become calm and placid. In humans, amygdala damage reduces stress responsivity and prevents emotional reaction to memories. Amygdalectomy (removal of the amygdala) was once a court-ordered procedure in the United States for particularly violent prison inmates; they became much more docile following surgery. Stimulation of an animal's amygdala elicits aggression and attack against other animals or even objects in the vicinity. In patients remaining conscious during brain surgery, stimulation of the amygdala elicits a sense of fear and anxiety.

THALAMUS. The thalamus is located in the center of the brain, above the hypothalamus. It acts as a sort of relay center, transmitting information from sensory organs, such as the inner ear and retina of the eye, to the areas of the cerebral cortex where the information can be further processed. The thalamus also relays nonsensory information, including motor messages from the cerebellum to the cortex. Further, in communication with the reticular formation, the thalamus regulates general arousal and excitability of the cortex.

HYPOTHALAMUS. The hypothalamus is the primary recipient of information flowing from the limbic system. It is a tiny structure, only about the size of a pearl, but it contains more than a dozen individual nuclei that serve a wide variety of functions. In a way, these functions are all related in that they are all concerned with maintaining homeostasis, or functional balance, in the body. For example, the hypothalamus regulates body temperature, blood pressure, fluid balance, and concentrations of glucose and sodium. It controls metabolism and motivates us to eat or drink when our body needs energy or fluid and to stop when balance has been restored. It mediates circadian rhythm, sexual motivations, and hormonal balance. It governs

instinctual behavior and emotions. The hypothalamus can perform all of these functions because of the tremendous amount of input it receives and because of its ability to output instructions just as widely.

The hypothalamus receives information from CNS regions, including the limbic system and other forebrain structures, the reticular formation, hindbrain structures such as the area postrema, and the spinal cord. The hypothalamus also receives information from the PNS about the functioning of organs (via the vagus cranial nerve) and light/dark cycles (via the retina), and contains specialized receptors, such as thermoreceptors and osmoreceptors, that monitor body temperature and the balance of bodily ions, respectively. In addition, the hypothalamus contains receptors for various hormones.

When balance needs restoring, the hypothalamus sends instructions to the body, mainly via two routes. First, information is sent to the medulla, which you recall contains part of the descending reticular formation wherein control centers for the autonomic nervous system are located. Through this route, the hypothalamus can control heart and breathing rates, digestion, perspiration, vasoconstriction, and other autonomic functions. Second, the hypothalamus acts as a link between the nervous system and the endocrine (hormone) system. It does so by controlling the *pituitary gland*. In some cases, hormones synthesized in the hypothalamus, such as vasopressin or oxytocin, are released directly into the posterior (rear) portion of the pituitary gland by the axon terminals of hypothalamic cells. This pathway is called the *tuberoinfundibular tract* or the *hypothalamo-hypophysial tract* (*hypothalamo* referring to the hypothalamus; *hypophysial* referring to the pituitary, which is sometimes called the *hypophysis*). Alternatively, some cells originating in the hypothalamus control the pituitary gland in a more indirect way, secreting hormones (called *releasing factors* or *releasing hormones*) into the blood of a circulatory system that runs between the hypothalamus and the anterior (front) portion of the pituitary. This system is called the *hypophyseal portal system*. Release of factors, such as corticotropin-releasing hormone or gonadotropin-releasing hormone, stimulates the anterior pituitary to secrete its own hormones, such as ACTH or luteinizing hormone, into the bloodstream. These hormones then travel throughout the body, affecting various target organs or glands.

Lesioning various hypothalamic nuclei disrupts its many functions. For example, lesions can abolish or induce excessive eating or drinking in experimental animals, depending on the nuclei affected. Stimulating parts of the hypothalamus appears to be rewarding as animals will learn to press levers or engage in activities that are followed by electrical stimulation of certain areas. It is thought that these are the reinforcement centers activated by natural reinforcing stimuli like food and water. The function of such systems is to ensure that the organism will repeat actions that have led to the satisfaction of the drive; that is, they are motivational centers. They have also been called *pleasure centers* because humans sometimes report experiencing pleasure when these areas of the brain are stimulated electrically.

Although it is not entirely clear how drugs affect neurotransmitters in various regions of the limbic system, it appears that many benzodiazepine receptors are located here. The benzodiazepines enhance the inhibitory effects of GABA, and this increased inhibition in the limbic system may be one mechanism by which the benzodiazepines, such as chlordiazepoxide (Librium) and diazepam (Valium), reduce aggression in nonhumans and produce a calming effect (see Chapter 7).

CORTEX. The *cortex* (or *neocortex*) makes up the uppermost surface of the brain. It is, on average, about 3 mm thick and is highly convoluted, giving the brain the appearance of a walnut. Because of its convolutions, about two-thirds of the cortex cannot be seen. If it were flattened out, it would cover an area of 2.5 square feet. The cortex contains mostly glial cells and neuronal cell bodies and dendrites.

The cortex is undoubtedly the most complex and advanced part of the brain. Its neurochemistry is not well understood, but glutamate and GABA are known to be its predominant excitatory and inhibitory transmitters. Dissociative anesthetics like PCP and ketamine (see Chapter 15) act at NDMA receptors for glutamate, and these drugs probably exert their effects directly on the cortex.

One of the functions of the cortex is to handle the integration of sensory information. Information from sense organs is projected to different parts of the cortex. Visual information is projected to the *primary visual cortex* at the back of the brain, in what are called the *occipital lobes*; sound is projected to the *primary auditory cortex*,

located in the *temporal lobes*. The *primary somatosensory cortex*, located in the *parietal lobes*, handles sensory input from the body, as well as the sense of taste. You may have noticed that all of these cortices have *primary* in their name. This is because there are additional areas of the cortex, called *secondary* and *association* cortices, where sensory information is further processed, integrated with other sensory perceptions, and stored as memories. For example, memory of a loved one does not consist solely of information about his or her appearance, but about the sound of his or her voice, the feelings you have when you are with him or her, and much, much more.

The *primary motor cortex* is the principal area responsible for commanding voluntary motor actions; it is located close to the somatosensory cortex, in the *frontal lobes*. Cell bodies residing in the primary motor cortex send their axons down through the midbrain and pons, into the lower portion of the medulla where they cross over to the contralateral (opposite) side of the body and enter the spinal cord. There, they form connections with motoneuron cell bodies, which connect with striated muscles. Because of this crossover in the lower medulla, neurons originating in the left side of the motor cortex initiate movement on the right side of body and vice versa. Other axons from the motor cortex go to the basal ganglia and the cerebellum, which modify the direct output of the motor cortex and coordinate bodily movement. Motor commands are anticipated and planned outside of the primary motor cortex, in association motor areas. Many of these areas of the cortex are shown in Figure 4-12.

While sensory and motor functions are handled mainly by central and posterior parts of the cortex, higher mental processes of thought and cognition are governed mostly in *rostral* areas of the brain (*rostral* means toward the front; it is easy to remember if you think "rostral is toward the nostril"). All of the cortex that sits rostral to the primary motor cortex and its adjacent association motor areas in the frontal lobe is referred to as the *prefrontal cortex*. The prefrontal cortex sends and receives information from areas of the limbic system, such as the amygdala and septal nuclei. It too can be subdivided into various regions, such as the *orbitofrontal cortex* (just behind the eye sockets) and the *dorsolateral prefrontal cortex*

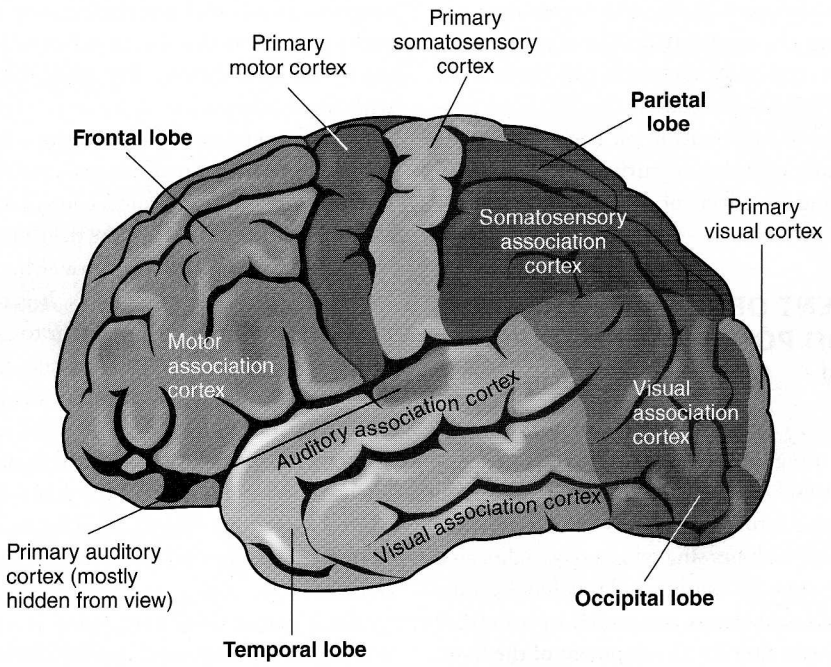


FIGURE 4-12 The cortex showing some of its major areas. (Adapted from Carlson, 2011, fig. 3.11, p. 70, reprinted with permission.)

(sitting toward the back [*dorsal*] of the orbitofrontal cortex, toward the top of the skull).

Areas of the prefrontal cortex govern an astonishing array of high-level cognitive functions: abstract reasoning; insight; planning; motivation; judgment; decision making; attention; task switching; impulse inhibition; memorization; expression of situationally appropriate emotions; monitoring and acting in accord with consequential relationships between stimuli, actions, and reinforcers (including predicting the availability of drugs); and the ability to prioritize behaviors and adapt to change. Perhaps not surprisingly, the prefrontal cortex is strongly affected by alcohol. In addition, individuals with schizophrenia have diminished dopamine activity in the prefrontal cortex, which might explain some symptoms, such as social withdrawal and blunted emotional responsiveness (see Chapter 12).

Two additional cortical structures deserve mentioning, as these are part of the limbic system and very important to its functioning. The *cingulate cortex* and *entorhinal cortex* mediate attention; response competition and selection; suppression of prepotent response tendencies; conditioned drug seeking; and craving, learning, and memory. Degeneration or dysfunction in these areas is implicated in Alzheimer's disease and depression.

Understanding the anatomy and neurochemistry of these complex cortical structures is still elusive, but modern imaging studies (discussed shortly) have provided a great deal of information on their role in the expression of many complex cognitive and behavioral functions, including the effects of drugs and the process of addiction.

DEVELOPMENT OF THE NERVOUS SYSTEM AND POTENTIAL FOR DISRUPTION

In the early 1960s, a drug called *thalidomide* was prescribed to many pregnant women to treat the nausea of morning sickness. Unfortunately, the drug interfered with the developing fetus, and many of these mothers gave birth to babies with missing or severely malformed limbs. Since the time of thalidomide, it has become widely recognized that drugs consumed by a mother during pregnancy can alter the development of the fetus. Drugs that cause such malformations are called *teratogens* (literally, "monster makers").

The developing nervous system is particularly vulnerable to disruption by drugs, and there are two reasons to believe that behaviorally active drugs are especially potent teratogens. First, in order to be behaviorally active, drugs must readily penetrate the brain, and this property also gives these drugs easy access across the placenta to the body of the developing fetus. Second, drugs that act to alter the functioning of neurotransmitters are particularly dangerous because of the way the nervous system develops.

The growth of the nervous system is a complex and delicate process involving the formation, migration, and interconnection of billions of nerve cells. All these cells form during the first 12 weeks after conception. During this time, therefore, brain cells are forming at a rate of 150,000 cells per minute. These cells do not develop in the part of the brain they are destined to occupy during adulthood. Many neurons have to migrate from one place in the brain to another. This journey must take place only at particular times in the development of the brain and in the appropriate order, or the brain will develop incorrectly. When these cells reach their target area, their growth is still not completed. They must attach themselves to their neighbors and send out their axons along prescribed paths to make contact with other cells in the developing brain. In addition, they must then form synapses with these other cells.

The formation, differentiation, and migration of cells; the projection of axons; and the formation of synapses are under chemical control. Chemicals are released by different parts of the developing brain, and the migrating cells and axons move either toward or away from these sources of chemicals. It is now believed that these control chemicals are similar to substances used as neurotransmitters in the adult brain. Consequently, if a mother consumes a psychoactive drug at crucial times during the development of the fetal brain, it could interfere with the delicate chemical signaling taking place in the developing brain of the fetus. If these chemical control signals are altered, masked, or inhibited, the development of the fetal brain may be disrupted (Abel & Sokol, 1989).

Such disruptions may cause severe brain malformation of the sort seen in *fetal alcohol syndrome* (described in Chapter 6), or they may cause much less apparent disruptions in the functioning of the brain

that can be detected only after careful systematic study of the organism's behavior. This kind of damage is called *functional teratology* or *behavioral teratology*. Functional teratology is an exciting and comparatively new field of research. Early functional teratology research has been done on laboratory animals, but more recently this research has been extended to studies on humans (Bushnell, Kavlock, Crofton, Weiss, & Rice, 2010). What is clear is that exposure to low levels of behaviorally active drugs during certain stages of fetal development can cause alterations in the functioning of the nervous system, which can be apparent at many stages throughout the organism's life span (Boer et al., 1988; Spear, 1997).

NEUROTRANSMITTERS

In recent years, more than 50 different substances have been identified that meet all criteria required for a chemical to be considered a neurotransmitter, and another 50 have been found that meet most criteria. These criteria are (a) the substance is synthesized within the neuron by coexisting enzymes, (b) the substance is released in response to cell depolarization, (c) the substance binds to receptors to alter the postsynaptic cell, and (d) the substance is removed or deactivated by some mechanism within the synaptic cleft. Figure 4-13 illustrates the steps involved in the synthesis, release, action, and deactivation of most neurotransmitters. You will notice some of the above-mentioned criteria within these steps.

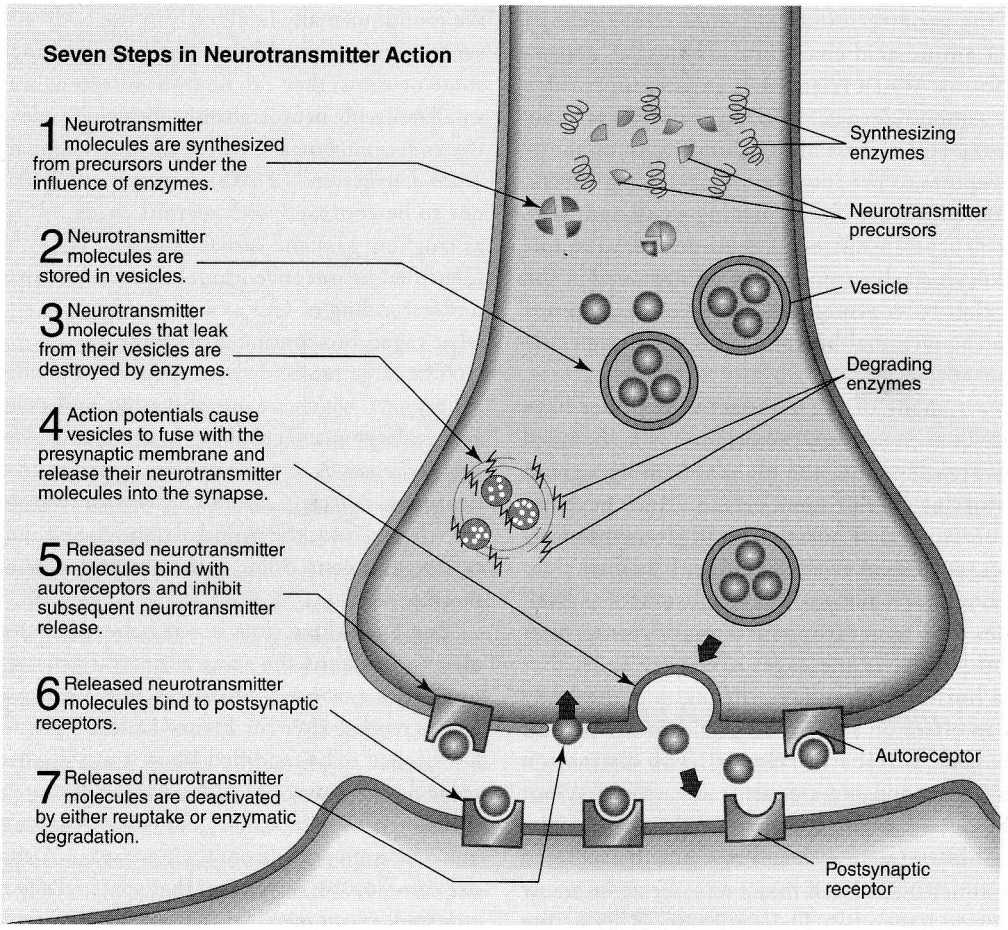


FIGURE 4-13 Steps involved in the synthesis, release, action, and deactivation of most neurotransmitters. (Adapted from Pinel, 2011, fig. 4.18, p. 96, reprinted with permission.)

Most neurotransmitter substances are *small molecule* neurotransmitters, which are stored in synaptic vesicles and released from the terminal button in response to an action potential. These neurotransmitters are synthesized from precursors under the guidance of enzymes created in the neuron's cell body and then transported to the axon terminal. Small molecule neurotransmitters act principally in their release zone to stimulate ionotropic or metabotropic receptors in a rapid, brief manner.

Neuroactive *peptides*, which are comprised of short chains of amino acids, are *large molecule* neurotransmitters. Neuropeptides are synthesized and packaged into vesicles within the neuron's cell body as amino acid chains that are much larger than their active end products. During transport from the cell body to the axon terminal, enzymes *cleave* (chop) the larger amino acid chain into its smaller neuropeptide forms. When released, many neuropeptides act as neuromodulators, diffusing away from their release zone and almost always binding to metabotropic receptors to produce slow, long-lasting effects. An additional feature distinguishing small and large molecule neurotransmitters is their deactivation following exocytosis. Neuropeptides are degraded in the synaptic cleft by enzymes and do not undergo reuptake into the terminal button, as do small molecule neurotransmitters.

For years, many of the neuroactive peptides have been known as *hormones*. A hormone is a chemical messenger released into the bloodstream by a gland or by endocrine cells of some organs. Many peptides were first identified as hormones and given appropriate names, such as growth hormone. It is now clear that the body uses many of these substances as both hormones and neurotransmitters. Whereas neurotransmitters carry messages over very short distances, a hormone circulates throughout the body and has an effect on some biological process distant from the place where it is released. The distinction between a hormone and a neurotransmitter may not always be clear. Early in the chapter, there was a discussion of how a neurotransmitter may be secreted near a brain structure and may exert effects on many synapses simultaneously. These substances are acting more as a hormone than a transmitter and are sometimes called *neurohormones* when they act in this capacity.

Table 4-1 lists examples of the most common neurotransmitter and neuromodulator substances. The earliest discovered and best understood neurotransmitter is *acetylcholine* (ACh), which is a small molecule neurotransmitter. Another family of small molecule neurotransmitters, called *biogenic amines* or *monoamines*, is composed of the *catecholamines*, which include *dopamine* (DA), *norepinephrine* (NE), and *epinephrine* (E), and the *indoleamines*, *serotonin*, which is often called *5-hydroxytryptamine* (5-HT), and *histamine*. Some transmitters are amino acids. Four of the most common are the excitatory amino acids *glutamate* and *aspartate* and the inhibitory amino acids *gamma-aminobutyric acid* (GABA) and *glycine*. Many of these amino acids are found normally in all cells in the body where they serve metabolic and other biochemical functions. In some neurons, they can be transmitters as well. Other small molecule neurotransmitters include *adenosine* and the *endocannabinoids*, which include *anandamide* and *arachidonylglycerol* (2-AG). Recently, *nitric oxide* (NO; not to be confused with nitrous oxide, NO_2, known as laughing gas) and *carbon monoxide* (CO) have been identified as unconventional neurotransmitters. Our understanding of CO as a neurotransmitter is somewhat vague, but continues to grow.

The large molecule neuropeptides include the *opioid peptides*, which are morphine-like molecules such as *beta-endorphin, enkephalins, dynorphins, endomorphins, and nociceptin*. A number of other peptides known to be neurotransmitters, neuromodulators, or neurohormones are released from the hypothalamus, the pituitary gland, or various organs. Some of these peptides are also listed in Table 4-1.

For a very long time it was believed that a neuron always produced the same neurotransmitter at every one of its synapses. This principle, known as *Dale's law*, is named after Sir Henry Dale, its proposer. The law needed to be modified when it was discovered that some neurons may produce and release more than one substance, usually a small molecule neurotransmitter and a neuropeptide, from their synapses. Although it is not common, we now know that some cells in some circumstances can release different substances at different synapses.

TABLE 4-1 Examples of Neurotransmitters and Neuromodulators in the Central Nervous System

Small Molecule Neurotransmitters

Acetylcholine (ACh)

Biogenic amines (monoamines)

Catecholamines

Dopamine (DA)
Norepinephrine (NE)
Epinephrine (E)

Indoleamines

Serotonin (5-HT)
Histamine

Amino acids

Excitatory amino acids

Glutamate
Aspartate

Inhibitory amino acids

Gamma-aminobutyric acid (GABA)
Glycine

Others

Adenosine

Endocannabinoids

Anandamide
2-AG

Gaseous neurotransmitters

Nitric oxide (NO)
Carbon monoxide (CO)

Large Molecule Neurotransmitters

Opioid peptides

Enkephalins
Endorphins
Dynorphins
Endomorphins
Nociceptin

Hypothalamic peptides

Oxytocin
Vasopressin
Somatostatin
Gonadotropin-releasing hormone (TRH)
Corticotropin-releasing hormone (CRH)

Pituitary peptides

Growth hormone
Thyroid-stimulating hormone (TSH)
Prolactin
Luteinizing hormone (LH)
Adrenocorticotrophic hormone (ACTH)

Brain-gut peptides

Cholecystokinin (CCK)
Neuropeptide Y
Galanin
Substance P

Miscellaneous peptides

Insulin

Neurons are classified according to the primary neurotransmitter they release. Those that release acetylcholine are called *cholinergic* neurons. Epinephrine is also known as adrenaline (the name used primarily in Europe), so synapses that use epinephrine and norepinephrine are called *adrenergic* and *noradrenergic*, respectively (which is a good thing—try saying "epinephrinergic" or "norepinephrinergic"!). Those that use dopamine are *dopaminergic*, those that use serotonin are *serotonergic*, and so on.

Even though each neuron almost always releases the same transmitter(s), its effect on various cells can be quite different. The effect of a transmitter depends on the nature of the receptor site to which it binds. Because any transmitter may have a number of different receptor sites, activity at its synapses may produce many different effects. These receptor sites may cause IPSPs or EPSPs; they may be directly connected to an ion channel, or they might use a second messenger. Thus, a substance released from a neuron into the cleft can be either an excitatory or inhibitory neurotransmitter or a neuromodulator. Using the lock-and-key analogy, whatever lurks behind a locked door does not depend on the size or shape of the key.

Drugs and Neurotransmission

Communication between neurons is a chemical process, and it is primarily at synapses that drugs have the opportunity to interfere with neurotransmitter synthesis, release, action, and deactivation. Figure 4-14 illustrates some of the ways in which drugs can alter neurotransmission. The mechanisms of drug action illustrated on the left of Figure 4-14 are *agonistic*—they are drug

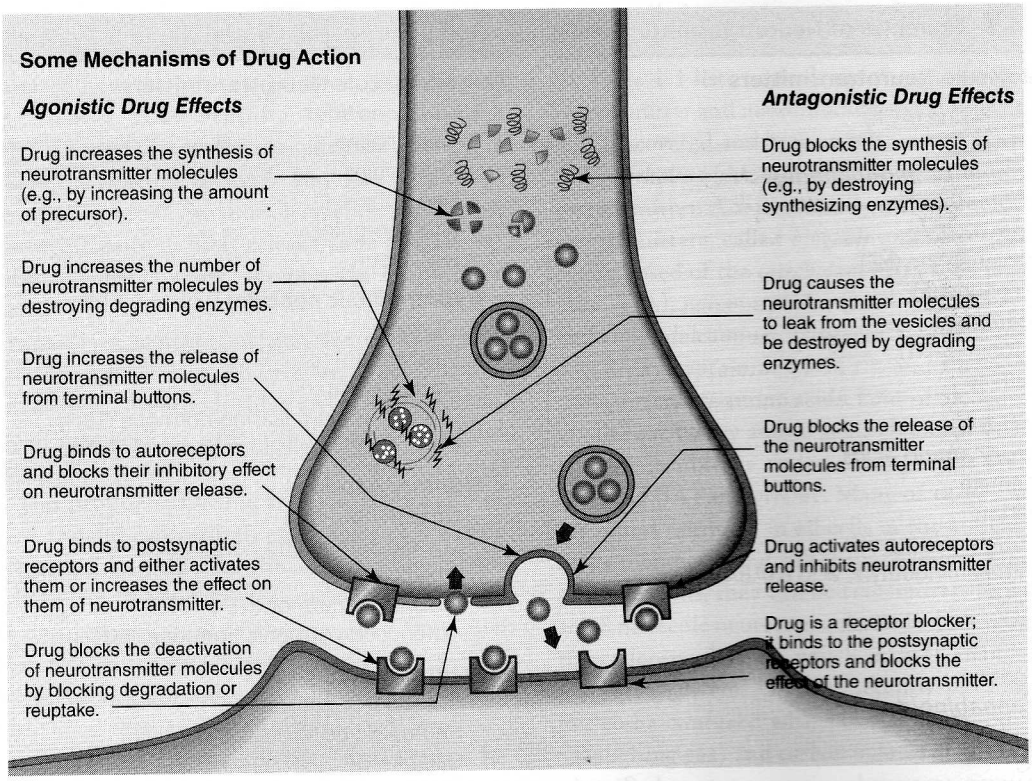


FIGURE 4-14 Mechanisms of agonistic and antagonistic drug effects. (Adapted from Pinel, 2011, fig. 4.19, p. 97, reprinted with permission.)

actions that facilitate either excitatory or inhibitory cell communication of a particular neurotransmitter. The mechanisms of drug action illustrated on the right of Figure 4-14 are *antagonistic*—they are drug actions that impede either excitatory or inhibitory cell communication by a particular neurotransmitter.

When an externally administered drug binds to and activates a receptor, mimicking the effects of a neurotransmitter, it is referred to as a *direct agonist*. A drug that has a high binding affinity (attraction) for a particular receptor but that activates that receptor only weakly, to a lesser degree than would its natural ligand (neurotransmitter), is referred to as a *partial agonist*. The term *partial agonist* is sometimes used interchangeably with the term *mixed agonist–antagonist*; however, they do mean different things. Mixed agonist–antagonist drugs were so-named before researchers discovered the existence of multiple subtypes of receptors in the brain for various neurotransmitter molecules. A mixed agonist–antagonist is a drug that acts as an agonist at one receptor subtype while also acting as an antagonist at another receptor subtype. Drugs sometimes bind to receptor sites but do not activate them at all, instead preventing the neurotransmitter from binding and exerting its effect. These drugs are *receptor blockers* or *direct antagonists*.

Keep in mind that drug molecules can bind to both postsynaptic receptors and autoreceptors. When drugs act as receptor blockers, binding will decrease neurotransmission to the postsynaptic cell as well as activity in the autoreceptor. This decrease in autoreceptor activity stimulates the cell to produce more neurotransmitter to compensate for the decreased activity at the postsynaptic site, thus canceling the effect of the receptor blocker on the postsynaptic cell. Such a drug would have no net effect on neurotransmission. If the blocker has a greater effect on the autoreceptor than on the postsynaptic receptor, then the longer-term result might be an increase

in transmission across the synapse because the presynaptic cell will overcompensate by releasing too much transmitter.

Other agonistic and antagonistic actions illustrated in Figure 4-14 are considered *indirect* because the drug molecule does not exert its effects by mimicking the neurotransmitter. Some neurotransmitter receptor complexes have more than one binding site. For example, the $GABA_A$ receptor protein contains a binding site for the neurotransmitter GABA and additional sites to which drug molecules, such as ethanol (alcohol) and benzodiazepines (anxiety-reducing drugs), can bind to enhance GABA's effects. Because GABA's binding site can be occupied only by GABA, binding by alcohol or benzodiazepines to other receptor sites is referred to as *noncompetitive binding*. An illustration of the GABA receptor complex and its binding sites can be seen in Figure 7-1 of Chapter 7.

Table 4-2 lists some of the major neurotransmitters and neuromodulators that you will encounter throughout the remainder of this text, as well as examples of some drugs that affect their neurotransmission. Also included in the table are the main receptor subtypes for each of the transmitters. This book indicates receptor subtypes using a subscript (e.g., D_1 or D_2), but in other books and papers, you may sometimes see receptor subtypes designated without subscripts (e.g., D1 or D2). Do not be confused—these refer to the same thing.

Acetylcholine

Acetylcholine (ACh) was the first neurotransmitter to be discovered. It is synthesized in cholinergic cells by combining *acetate* and *choline* with the help of the enzyme *choline acetyltransferase*. ACh molecules that leak from presynaptic storage vesicles and those released into the synaptic cleft in response to an action potential are quickly degraded by the enzyme *acetylcholinesterase* (AChE). The choline molecule is taken back into the presynaptic cell by choline receptor transporter proteins located in the membrane of the axon terminal. Several drugs interfere with the activity of AChE—consequently, they interfere with transmission across cholinergic synapses. This is the mechanism of action of many commonly used insecticides and even some older nerve gases, such as sarin.

There are two major systems of cholinergic neurons that project through the brain (refer to the top-left panel of Color Plate A). Within the *basal forebrain* sit two structures called the *basal nucleus of Meynert* and the *medial septal nuclei* (recall that the septal nuclei form part of the limbic system). These two structures project their axons throughout the neocortex as well as to the thalamus, hippocampus, and amygdala where they release ACh from axon terminals. This cholinergic system plays an important role in cortical activation and in learning and memory. Alzheimer's disease, which is a form of dementia characterized by severe deficits in learning and memory, is marked by a profound loss of ACh neurotransmission. The second major ACh system originates in a part of the pons called the *mesopontine tegmentum area* (also referred to as the *pontomesencephalotegmental complex*). This system also projects to the thalamus as well as to the hypothalamus, reticular formation, cerebellum, and the basal ganglia, and plays a role in REM sleep (deep, dreaming sleep). In addition, it is worth noting that receptors for ACh are also found in the ventral tegmental area, which you recall is a vital component of the brain's reward system. ACh neurotransmission is important for the rewarding and addictive effects of drugs such as morphine and heroin.

Some drugs alter the functioning of cholinergic synapses by acting as direct agonists at ACh receptors. Although all ACh receptor sites are stimulated by ACh, they can be classified according to other substances that also affect them. *Nicotinic* cholinergic receptors are ionotropic. When stimulated, the ion channel opens to allow influx of Na^+ ions and efflux of K^+ ions, producing EPSPs. They are stimulated by nicotine (a direct agonist) and inhibited by a drug called *curare* (a receptor blocker). Curare is a poison that some South American tribes place on the point of their spears and arrows. If struck with one of these weapons, an animal's muscles (including the diaphragm, which allows for breathing) will become paralyzed, and the animal will suffocate and die. This happens because nicotinic receptors are also present at neuromuscular junctions, where terminal buttons of motor neurons synapse with muscle fibers in the PNS. When injected into the muscles of the face, the cosmetic drug Botox (botulinum toxin) blocks the release of ACh at neuromuscular junctions, preventing muscles from contracting and lessening the appearance of wrinkles. *Muscarinic* cholinergic receptors are metabotropic. ACh binding activates second messenger systems to open K^+ and Cl^- ion channels

TABLE 4-2 Receptor Subtypes and Examples of Drug Actions for Major Neurotransmitters and Neuromodulators in the Central Nervous System

Small Molecule Neurotransmitters		
Acetylcholine (ACh)	(I): nicotinic (M): muscarinic (A): muscarinic	Nicotine—stimulates nicotinic receptors (agonist) Muscarine—stimulates muscarinic receptors (agonist) Curare—blocks nicotinic receptors (antagonist) Atropine—blocks muscarinic receptors (antagonist)
Biogenic amines (monoamines)		
Dopamine (DA)	(M): "D_1-like" (D_1, D_5) and "D_2-like" (D_2, D_3, D_4) (A): D_2	Cocaine—blocks DA reuptake transporter proteins (agonist) Amphetamine—causes reversal of reuptake transporter proteins (agonist) Chlorpromazine—blocks D_2 receptors (antagonist) AMPT—inactivates tyrosine hydroxylase (antagonist)
Norepinephrine (NE)	(M): alpha$_1$, alpha$_2$, beta$_1$, beta$_2$ (A): alpha$_2$	Amphetamine—stimulates NE release (agonist) Idazoxan—blocks alpha$_2$ autoreceptors (agonist) Reserpine—inhibits transport of NE into synaptic vesicles (antagonist)
Serotonin (5-HT)	(I): 5-HT_3 (M): 5-HT_1, 5-HT_2, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7 (A): 5-HT_1	Fluoxetine—blocks serotonin reuptake transport proteins (agonist) LSD—stimulates 5-HT_2 receptors (agonist) Agomelatine—blocks 5-HT_2 receptors (antagonist)
Amino acids		
Glutamate	(I): NMDA, AMPA, Kainite (M): $mGlu_1$–$mGlu_8$ (A): mGlu	AMPA—stimulates AMPA receptors (agonist) PCP—blocks a binding site inside the NMDA receptor ion channel (antagonist) AP5—blocks glutamate binding site on NMDA receptor (antagonist)
GABA	(I): $GABA_A$ (M): $GABA_B$ (A): $GABA_B$	Alcohol—stimulates $GABA_A$ receptors (agonist) GHB —stimulates $GABA_B$ receptors (agonist) Picrotoxin—blocks $GABA_A$ receptor complex ion channel (antagonist) Allylglycine—inactivates GAD enzyme preventing GABA synthesis (antagonist)
Others		
Adenosine	(M): A_1, A_{2A}, A_{2B}, A_3	Caffeine—blocks A_{2A} receptors (antagonist) Theophylline—blocks adenosine receptors (antagonist)
Anandamide	(M): CB_1, CB_2	THC—stimulates CB_1 receptors (agonist) Rimonabant—blocks CB_1 receptors (antagonist)

Large Molecule Neurotransmitters

Opioid peptides		
beta-Endorphin	(M): mu_1, mu_2, mu_3, $delta_1$, $delta_2$, $kappa_1$, $kappa_2$, $kappa_3$, ORL_1	Morphine—stimulates mu receptors (agonist)
Enkephalins		Methadone—stimulates mu receptors (agonist)
Dynorphins		Naltrexone—blocks mu receptors (antagonist)
Endomorphins		Naloxone—blocks mu receptors (antagonist)
Nociceptin		

(I) = ionotropic; (M) = metabotropic; (A) = autoreceptor.

and hyperpoloarize the cell. Muscarinic receptors are also stimulated by muscarine, found in poisonous mushrooms, and blocked by drugs like scopolamine and atropine from the deadly nightshade plant. In the PNS, muscarinic receptors are involved in the functioning of the autonomic nervous system.

Biogenic Amines (Monoamines)

The catecholamines—DA, NE, and E—and the indoleamine 5-HT are all monoamines, meaning they are synthesized from a single amino acid.

In the case of the catecholamines, the amino acid precursor is tyrosine, which is produced by the body but also consumed in foods. The biosynthetic pathway of the catecholamines is illustrated in Figure 4-15. In the cytoplasm of catecholaminergic axon terminals, tyrosine is converted into *dihydroxyphenylalanine* (DOPA) with the help of the enzyme *tyrosine hydroxylase*. Tyrosine hydroxylase is referred to as a *rate-limiting enzyme*, meaning that the amount of catecholamine synthesized depends on the availability of that enzyme. When axon terminal neurotransmitter levels rise to high levels, tyrosine hydroxylase is inhibited; when the neuron is firing at a high rate and neurotransmitter is being released quickly, tyrosine hydroxylase is facilitated. DOPA is converted to DA via the enzyme *DOPA decarboxylase*. At this point, DA is transferred into synaptic vesicles, and, in dopaminergic neurons, the biosynthetic pathway stops there. In neurons that use NE as their neurotransmitter, however, there is an additional step. The synaptic vesicles of noradrenergic neurons contain an enzyme that dopaminergic neurons do not; this enzyme is called *dopamine beta-hydroxylase* and converts DA into NE. In adrenergic neurons, NE leaks from its vesicles into the cytoplasm of the axon terminal where an additional enzyme, *phenylethanolamine-N-methyl-transferase* (PNMT), converts NE into E. Epinephrine molecules are then transported into their own storage vesicles within the axon terminal.

For the indoleamine 5-HT, the amino acid precursor is *tryptophan*, which is actively transported into the brain from the foods we eat; it is not produced by the body. In serotonergic neurons, tryptophan is converted into *5-hydroxytryptophan* by the enzyme *tryptophan hydroxylase* (the rate-limiting enzyme) and finally into 5-HT by the enzyme *aromatic amino acid decarboxylase*.

When released from their vesicles into the synaptic cleft by an action potential, the monoamines are taken back into the presynaptic cell by specialized dopamine, norepinephrine, and serotonin reuptake transporter proteins embedded in the cell membrane. Most get repackaged in synaptic vesicles for future exocytosis. Neurotransmitter molecules that remain unpackaged get broken down by two enzymes: *monoamine oxidase* (MAO) and *catechol-O-methyltransferase* (COMT). Drugs used to treat major depression (described in Chapter 13) often target the reuptake and enzymatic degradation of the catecholamines so that more neurotransmitter is available. For example, phenelzine (Nardil) is a monoamine oxidase inhibitor (MAOI) and fluoxetine (Prozac) is a selective serotonin reuptake inhibitor (SSRI). Drugs such as cocaine and methylphenidate (Ritalin) also block reuptake transporter proteins so that the monoamines stay longer in the synaptic cleft.

DOPAMINE. Dopaminergic neurons form four major systems in the brain. In one of these systems, called the *tuberoinfundibular pathway*, dopamine acts as a

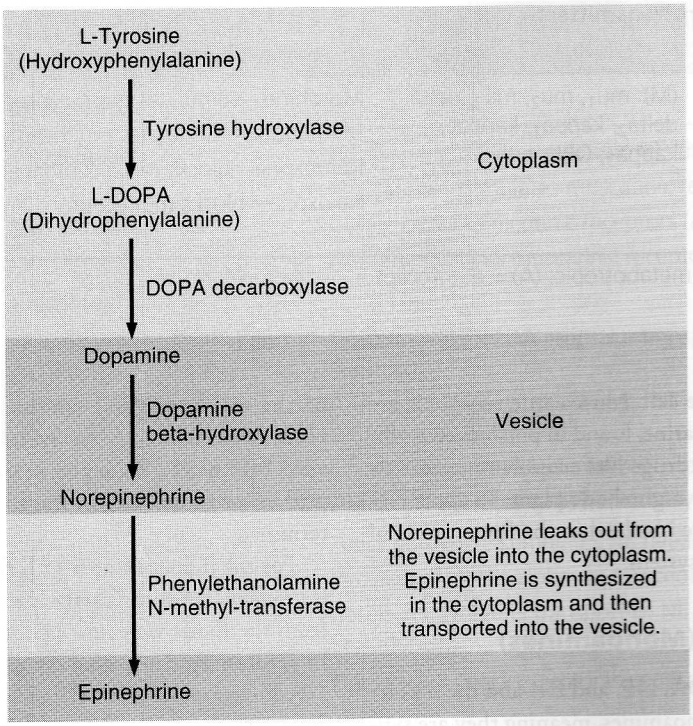


FIGURE 4-15 Biosynthetic pathway of the catecholamines.

neurohormone. Cells in part of the hypothalamus release dopamine directly into the *hypophyseal portal system* (the circulatory system that connects the hypothalamus and pituitary gland) to inhibit the release of prolactin. In the three other major systems, dopamine acts as a neurotransmitter. The location of dopamine cell bodies is indicated by the first part of the pathway's name, and the location of axon terminals is indicated by the second part. In the *nigrostriatal pathway*, dopamine cell bodies in the substantia nigra of the midbrain project their axons to two regions of the striatum called the caudate nucleus and putamen (refer to the top-right panel of Color Plate A). This pathway plays an important role in the control of motor movement, and dopamine cell degeneration in this pathway is linked with Parkinson's disease. In the final two major pathways, dopamine cell bodies reside in the ventral tegmental area. *Meso* is Greek for *middle* (referring to the midbrain), and these pathways are called the *mesocortical pathway* (from the ventral tegmental area to the *cortex*) and *mesolimbic pathway* (from the ventral tegmental area to the nucleus accumbens and parts of the limbic system, such as the hippocampus and amygdala). These latter two pathways receive a lot of attention from researchers because they are important in the motivational aspects of drug use and are also implicated in schizophrenia (see Chapter 12).

The D_1 and D_2 families of receptors are distributed throughout the caudate nucleus and putamen and the mesolimbic system, where they serve opposite functions. D_2 receptor activation leads to the inhibition of the cAMP second messenger system pathway, whereas D_1 receptor activation facilitates this system. D_2 receptors also act as autoreceptors. Drugs used to treat psychotic disorders selectively block D_2 receptors, but some of the newer antipsychotic drugs also have effects on other dopamine receptors (see Chapter 12).

NOREPINEPHRINE. The major noradrenergic system in the brain consists of cell bodies that reside in an area of the pons called the locus coeruleus and project axons widely throughout the cortex, thalamus, hypothalamus, hippocampus, amygdala, cerebellum, and spinal cord

(refer to the bottom-right panel of Color Plate A). Norepinephrine plays a role in attention, sleep and wakefulness, feeding behaviors, and emotion. Dysfunction of the NE system is linked with depression and attention-deficit disorders. All four noradrenergic receptor subtypes are metabotropic; alpha$_1$, beta$_1$, and beta$_2$ are excitatory whereas alpha$_2$ is inhibitory and acts as an autoreceptor. NE receptors are also found in the PNS where they mediate hormonal control of various organs by catecholamines and activation of the autonomic nervous system.

SEROTONIN. The major collections of cell bodies for serotonin sit within brainstem *raphe nuclei* of the pons, medulla oblongata, and reticular formation (refer to the bottom-left panel of Color Plate A). These are called the *dorsal raphe nucleus* and *median raphe nucleus*. The raphe nuclei project their axons to the cortex, thalamus, basal ganglia, hippocampus, and amygdala, as well as areas of the lower brainstem and spinal cord where they control the release of enkephalins to decrease pain sensitivity. Serotoninergic receptor subtypes (5-HT$_1$ through 5-HT$_7$) are all metabotropic, with the exception of the 5-HT$_3$ receptor, which controls Na^+ and K^+ ion channels to produce EPSPs. The remaining subtypes regulate second messengers, such as cAMP; some are inhibitory, and some excitatory. 5-HT regulates a wide variety of functions, including sleep–wake cycle, dreaming, mood, aggression, and appetite.

Amino Acid Neurotransmitters

Of the 22 amino acids that are used in cellular functions and that form the building blocks for proteins in the body, approximately eight are thought to also act as neurotransmitters. Two of the most widespread and abundant of these are the excitatory neurotransmitter-*glutamate* and the inhibitory neurotransmitter *GABA*. The actions of an additional inhibitory amino acid neurotransmitter, *glycine*, are less understood and will be discussed in minor detail.

GLUTAMATE. Glutamate is the major excitatory neurotransmitter in the brain. It is synthesized inside terminal buttons from the amino acid *glutamine*, via the enzyme *glutaminase*, and packaged in synaptic vesicles. Following exocytosis, it is removed from the synaptic cleft by glutamate reuptake transporter proteins embedded in presynaptic terminal buttons and also on surrounding glial cells. When taken up by glial cells, glutamate is converted into its precursor, glutamine, by the enzyme *glutamine synthetase*. Glial cells release glutamine back to the glutamatergic neuron where, once inside terminal button, it is converted to glutamate and stored in synaptic vesicles as previously described.

Unlike the ACh or monoamine systems, glutamatergic axon terminals exist almost throughout the entire brain with widespread projections within the cortex and between the cortex, thalamus, striatum, substantia nigra, and many other structures. Glutamate binds to a number of metabotropic and ionotropic receptor subtypes. There are at least eight metabotropic receptors (mGlu$_1$–mGlu$_8$) expressed throughout the brain that stimulate or inhibit second messenger systems and control functions such as learning, motor activity, and pain sensitivity. Three ionotropic receptors, called *kainate*, *AMPA*, and *NMDA* receptors, open to allow an influx of Na^+ ions and efflux of K^+ ions when stimulated, producing EPSPs. The most complex of these is the NMDA receptor, which is dependent on the presence of several other substances (see Figure 4-16). The NMDA receptor contains four externally located binding sites: one for glutamate and additional sites for zinc (Zn^{2+}), polyamines, and glycine. Inside the NMDA receptor ion channel, there is also a binding site for magnesium (Mg^{2+}) and an additional site to which various substances, including the dissociative drugs ketamine and PCP (see Chapter 15) and alcohol (see Chapter 6), can all bind.

At resting potential, the NMDA receptor ion channel is blocked by Mg^{2+} sitting in its binding site, preventing the movement of ions through the channel. As the postsynaptic cell depolarizes (often from the activation of coexisting AMPA receptors), the Mg^{2+} ion becomes dislodged from its binding site, thereby freeing up the ion channel. Thus, NMDA receptor activation is voltage dependent. In addition, NMDA receptor activation is neurotransmitter dependent, meaning that glutamate released from the presynaptic cell must bind to its receptor site. Still, this is not enough to fully activate the NMDA receptor. In addition to glutamate binding, glycine must also bind to its site on the NMDA receptor. When these conditions are met, the NMDA ion channel opens and Na^+ rushes through the channel. In addition, NMDA receptor ion channels admit Ca^{2+} ions into the cell. This is extremely important, not only

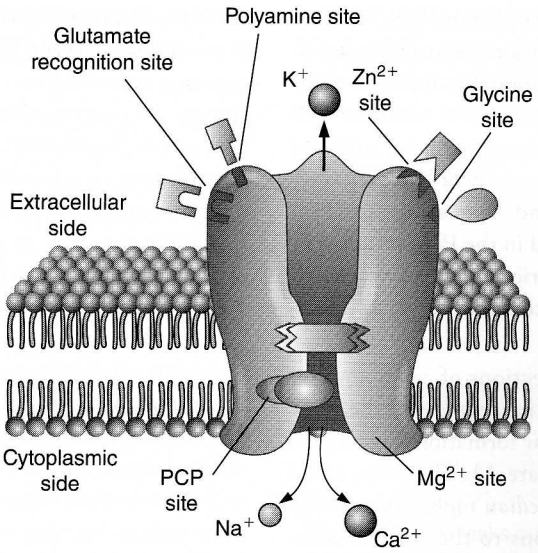


FIGURE 4-16 Glutamate NMDA receptor.

because the presence of additional positive ions further depolarizes the cell, but also because Ca^{2+} serves an important, additional purpose—it acts as a second messenger to active enzymes, protein kinases, and transcription factors to produce long-lasting effects on the cell's excitability.

It is this kind of NMDA-mediated change in the function of glutamate neurons that is thought to underlie learning and memory. Drugs that inhibit NMDA receptor activation also impede learning and memory. Modification of this system, brought about by chronic drug use, has also been linked with craving and addiction (Volkow et al., 2010). Overstimulation of glutamate receptors can be toxic, causing cell death. This is referred to as *excitotoxicity*, which has been linked to NMDA receptor loss in Alzheimer's disease.

GAMMA-AMINOBUTYRIC ACID (GABA). GABA is the most widespread inhibitory neurotransmitter in the brain—an estimated 20–30% of CNS neurons are GABAergic. GABA is synthesized in GABAergic cells from the amino acid glutamine, which you recall is converted to glutamate by the enzyme *glutaminase*. In GABAergic neurons, there is an additional enzyme not present in glutamatergic neurons or in glia; it is called *glutamic acid decarboxylase* (GAD). GAD is the rate-limiting enzyme that converts glutamate to GABA. Interestingly, GAD requires a coenzyme, vitamin B6, to complete this conversion; a diet deficient in vitamin B6 can lead to a decrease in GABA synthesis, resulting in convulsions and possibly death. Following exocytosis, GABA is taken back into the presynaptic cell, via reuptake transporters, and into glial cells where it is converted into glutamate and then glutamine. Glial cells release glutamine back to the axon terminals of GABAergic neurons for resynthesis and packaging into synaptic vesicles. GABA in also broken down into its precursor, glutamate, by the enzyme *GABA aminotransferase*.

Like glutamate, GABA neurons project widely throughout the brain, including the cortex, basal ganglia, hippocampus, hypothalamus, brainstem, and cerebellum.

There are two classes of GABA receptors: $GABA_A$ receptors are ionotropic and control a Cl^- ion channel to permit an influx of negative ions when stimulated; $GABA_B$ receptors are metabotropic; they inhibit Ca^{2+} channels and, through the actions of a second messenger, indirectly control the opening of a K^+ channel to hyperpolarize the neuron. $GABA_B$ receptors also decrease cAMP second messenger activity and act as autoreceptors. The structure of $GABA_A$ receptors, which has

19 known subunit genes, is much more diverse than that of $GABA_B$, which has only three known subunit genes (more about this in Chapters 6 and 7).

Most drugs affect $GABA_A$ receptors, which, like NMDA receptors, are rather complex in that they contain more than one externally located binding site. In addition to the binding site for GABA, the receptor complex contains additional sites to which the tranquilizing drugs barbiturates and benzodiazepines (e.g., Valium; see Chapter 7), steroids (e.g., progesterone), picrotoxin (a poisonous plant compound), anaesthetic gases (e.g., nitrous oxide), and alcohol (see Chapter 6) can all bind. These drugs enhance the inhibitory properties of GABA by prolonging or increasing its ability to open the chloride ion channel. Drugs like bicuculline, which blocks the $GABA_A$ receptor binding site, or allylglycine, which prevents GABA synthesis, lead to neural excitation and convulsions. Drugs that increase GABA neurotransmission are used to treat seizures and other disorders such as anxiety and insomnia.

The $GABA_A$ receptor is made up of five subunits that show considerable variation in configuration in different brain systems. This makes them deferentially sensitive to different benzodiazepines and other drugs. Different benzodiazepines may have different affinities for some of these variations, which makes it possible for different benzodiazepines to have different effects on behavior. Some are more potent tranquilizers, some are better sedatives, and so on. By identifying the variations in the GABA receptor molecule and designing drugs that activate only those receptors, it might be possible to create benzodiazepines with very specific effects (Möhler, Fritschy, Crestani, Hensch, & Rudolph, 2004).

GLYCINE. Glycine is formed in the axon terminal from the amino acid *serine*. Following release, it is taken back into the cell by reuptake transporters. Receptors for glycine exist in the lower brainstem and spinal cord and are always ionotropic, controlling a Cl^- ion channel to produce IPSPs when stimulated. Glycine receptors are antagonized by the drug *strychnine*, which occurs in the seeds of a tree found in India, called the Poison Nut tree. When consumed in even very small doses, strychnine can cause convulsions and death. Glycine receptors are also blocked by caffeine.

Other Small Molecule Neurotransmitters and Neuromodulators

ADENOSINE. Adenosine molecules consist of *adenine* and the sugar *ribose*. All cells contain adenosine, as it is required for some very basic life processes; therefore, there are no major adenosine pathways that have been identified in the brain. When neurons are running low on oxygen or energy, they release adenosine (glia do so also), which causes dilation of blood vessels in the cells' proximity and a consequent increase in blood flow and in fuel and oxygen supply to the neurons. Adenosine binds to four receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3), all of which are metabotropic and coupled to G proteins that influence cAMP activity. In the brain, adenosine receptor binding exerts inhibitory effects via the opening of K^+ ion channels. Adenosine plays a major role in sleep and wakefulness, in large part through its neuromodulatory actions on ACh, NE, 5-HT, DA, and glutamate neurons. Low levels of adenosine correspond with alertness and wakefulness, whereas high levels correspond with sleepiness and fatigue. During wakefulness and heightened neural activity, adenosine levels slowly rise; during sleep and lowered neural activity, they slowly fall. The inhibitory effects of adenosine receptor binding can be antagonized by the A_{2A} and A_1 receptor blockers caffeine and theophylline, found in coffee and tea (see Chapter 9).

ENDOCANNABINOIDS. The endocannabinoids are a group of small lipid molecules that act as neuromodulators within the CNS in a manner similar to THC, the active ingredient in marijuana (see Chapter 14). Two of the well-researched endocannabinoids are called *anandamide* (meaning "internal bliss") and *arachidonylglycerol* (2-AG). These molecules bind to two types of cannabinoid receptors, both of which are metabotropic and coupled to G proteins. CB_2 receptors are found in the PNS and control immune system functions. CB_1 receptors are the most abundant metabotropic receptor subtype in the entire brain and are found in the frontal cortex, anterior cingulate cortex, hypothalamus, hippocampus, basal ganglia, and cerebellum. Endocannabinoids act at CB_1 receptors as *retrograde messengers*. That is, they are released from the dendrites and cell body of the postsynaptic cell in response to the firing of action potentials and bind to heteroreceptors on the terminal button of

the presynaptic cell membrane. CB_1 receptors can be found on axon terminals of neurons releasing ACh, DA, NE, 5-HT, glutamate, and GABA. Endocannabinoids are unconventional neurotransmitters in that they are not synthesized and stored in synaptic vesicles, but are produced from lipid compounds in the cell membrane. Once synthesized, they immediately diffuse across the postsynaptic cell membrane and bind to CB_1 receptors on the presynaptic cell. Here, they stimulate G proteins, which inhibit neurotransmission by inhibiting Ca^{2+} channel opening (recall that the entry of Ca^{2+} into the presynaptic terminal button initiates the movement of synaptic vesicles to the cell membrane and the exocytosis of neurotransmitter molecules into the synaptic cleft). A high rate of action potential firing in the postsynaptic neuron leads to increased release of endocannabinoids and, thereby, greater inhibition of the presynaptic cell. CB_1 receptor activation by endogenous cannabinoids or THC causes sedation, analgesia, stimulates appetite, and impairs concentration and memory. CB_1 receptor activation is also pivotal in the euphoric and addictive properties of opioid drugs, such as heroin, morphine, and oxycodone (see Chapter 11).

NITRIC OXIDE. *Nitric oxide* (NO) is a soluble gas produced in many cells throughout the body where it plays an important role in vasodilation and blood flow. In neurons, NO is synthesized in the cytoplasm from the amino acid *arginine* with the help of the enzyme *nitric oxide synthase* (NOS). Like the endocannabinoids, NO is not stored in vesicles or released by exocytosis in response to an action potential. Instead, it is created on demand and diffuses instantaneously and passively through the cell membrane (it is an uncharged molecule, not an ion), into the extracellular fluid, and penetrates nearby cells—both postsynaptic and presynaptic (i.e., it is a retrograde messenger). NO does not bind to a receptor but instead activates *guanylate cyclase*, the enzyme responsible for the production of the second messenger cGMP, to enhance neurotransmission of the presynaptic neuron. In just a few seconds following its synthesis, NO spontaneously decays into biologically inactive compounds. cGMP activity is much more prolonged, although it too is eventually halted by enzymatic degradation. The drug sildenafil (Viagra), sold primarily as a treatment for erectile dysfunction, works by inhibiting the enzymatic degradation of cGMP, thereby enhancing its vasodilatory effects.

Large Molecule Neurotransmitters: Peptides

More than 100 different neuropeptides have been identified that act as neurotransmitters, neuromodulators, and neurohormones. Neuroactive peptides can be grouped into one of five categories, including a *miscellaneous peptides* category for those (such as insulin) that do not fit neatly into one of the other four. The *brain–gut peptides* (such as substance P) were first discovered in the gut. The *pituitary peptides* and *hypothalamic peptides* were first identified as hormones released from the pituitary (such as vasopressin and ACTH) and hypothalamus (such as somatostatin and CRH), respectively. Finally, the *opioid peptides* are a family of more than 20 endogenous morphine-like molecules that bind to opioid receptors in the brain and spinal cord and throughout the body. Opioid peptides play important roles in regulating blood pressure and temperature, food and fluid intake, stress responsiveness, sensitivity to pain, aggression, emotion, sexual behavior, and the euphoric and reinforcing value of natural and drug rewards.

Opioid peptides are synthesized within the neuron's cell body as much larger protein chains (*polypeptides*) that are hundreds of amino acids in length. Polypeptides serve as precursor molecules that get packaged, along with enzymes, into vesicles where they are cleaved (chopped) into their smaller, active form during transport from the cell body to the axon terminal. Peptides often coexist in the axon terminal with small molecule neurotransmitters (such as 5-HT, glutamate, or GABA), and both are released in response to an action potential.

One kind of endogenous opioid peptide is called *beta-endorphin*. It is synthesized in the hypothalamus and pituitary from the precursor polypeptide *proopiomelanocortin*. An additional active peptide produced from proopiomelanocortin is *adrenocorticotropic hormone* (ACTH), which is an important stress hormone. Additional endogenous opioid peptides are called the *enkephalins* (*met-enkephalin* and *leu-enkephalin*; *enkephalin* means "in the head"), which are five amino acids long, cleaved from the polypeptide *proenkephalin A*. *Dynorphin* is the product of the polypeptide *prodynorphin*, synthesized in the pituitary. Less is known about the more recently discovered opioid peptides *nociceptin* and the *endomorphins*. Nociceptin is the product of the polypeptide *pronociceptin*; the precursor for the endomorphins is unknown.

Opioid peptides have several types of receptors that are widely distributed throughout the brain, including the cortex, thalamus, hypothalamus, amygdala, hippocampus, ventral tegmental area, nucleus accumbens, and periaqueductal gray, and in the spinal cord. All receptor subtypes are metabotropic. Receptor activation stimulates G proteins that regulate ion channels for K^+ or Ca^{2+} or second messenger systems to inhibit cell excitability. Beta-endorphin acts on all three main receptor types: *mu* (μ), *delta* (δ), and *kappa* (κ). The enkephalins act mainly on delta receptors, the endomorphins on mu receptors, the dynorphins on kappa receptors, and nociceptin binds to its own ORL_1 receptor. Most of the analgesic and reinforcing effects of morphine and other opiate drugs are mediated by the mu receptor, although some analgesia is associated with all of the opioid receptor types.

Following release from the cell, neurotransmitter peptides are broken down by enzymes called *peptidases*; they are not taken back into the presynaptic cell for recycling. Hormone peptides released into the circulatory system are too large to pass through the blood–brain barrier and remain outside the CNS. For this reason, the same peptide can produce different effects when released as a neurotransmitter or neuromodulator compared to when it is released as a neurohormone.

BRAIN IMAGING OF DRUG EFFECTS

In the next chapter, you will learn that addiction is a brain disease; chronic drug use changes the structure and function of the brain. We know this thanks to technology that allows researchers to image the brains of addicts. Some of the most common brain imaging techniques used in addictions research are outlined next.

Positron Emission Techniques

POSITRON EMISSION TOMOGRAPHY (PET). PET makes use of the unstable, chemical properties of *radioactive tracer isotopes* (*radiotracers*) to produce three-dimensional images of the brain. Radioisotopes most commonly used in PET imaging of the brain include ^{15}oxygen (^{15}O), ^{13}nitrogen (^{13}N), ^{11}carbon (^{11}C), and ^{18}fluorine (^{18}F). Participants ingest a radiotracer made up of a metabolically active agent, such as glucose, water, or a drug of abuse, that has been made radioactive by being combined with a radioactive isotope. For example, when a stable carbon atom in a molecule of cocaine is replaced by the unstable isotope of carbon, ^{11}C, the result is the radiotracer [^{11}C]-cocaine, which can be detected in the brain. A machine called a *cyclotron* is needed to create these radiotracers.

Radiotracers can be given by injection, inhalation, or orally, depending on the agent being administered. Participants must wait for a short period while the radiotracer becomes concentrated in brain areas where the metabolically active agent or drug is distributed. They are then placed in the PET imaging scanner, which is shaped like a cylinder and contains a series of connected radiation detector cameras. Radioisotopes are short-lived, with half-lives ranging from 2 to 110 minutes, and decay by emitting positrons. An emitted positron travels less than 1 mm before colliding with an electron. The collision produces high-energy *gamma rays* that pass out of the brain and are detected by radiation detector cameras comprised of a ring of *scintillator crystals* that fluoresce momentarily when struck by high-energy gamma rays. This information is then transmitted to a computer. By measuring where gamma rays hit the scintillator crystals, researchers can plot the origin of positron emission to create an image of exactly where the radiotracer activity is within the brain.

PET scans can be used for a wide range of purposes. First, they allow researchers to directly measure the brain distribution and activity of stimulant drugs such as cocaine, methamphetamine, and amphetamine; opioids such as heroin and morphine; hallucinogens such as PCP and ketamine; and other commonly used drugs, such as nicotine, alcohol, and marijuana.

Second, local concentrations of drug receptor sites can be determined by administering tiny doses of radiotracers that contain pharmacologically inactive amounts of a drug and occupy only a small fraction of available receptor sites. This allows researchers to estimate drug receptor density in specific brain areas and to keep track of changes in the number of receptors that might occur over time, for example, because of tolerance.

Third, PET scanning can be used to assess competition for receptor binding sites, as when molecules of a drug or radiotracer compete with a neurotransmitter for binding on the same receptor site. Competition between a drug and a radiotracer that occupies the same receptor site but produces no changes in mood can provide an index of the degree of drug binding required to produce subjective feelings of drug-induced euphoria. This

method can also be used to measure the actions of naturally occurring chemicals, such as neurotransmitters, or to assess potential treatments (antagonists) that might block or reverse the effects of an abused drug.

Fourth, PET scanning can be used to isolate areas of the brain that are active during a mental activity, such as drug craving. Changes in brain glucose metabolism that occur as neurons are activated and deactivated can be pinpointed using a glucose-mimicking radiotracer, and regional cerebral blood flow (which is correlated with glucose metabolism) can be assessed using [^{15}O]-water.

Finally, PET scanners for laboratory animals, such as rats and apes, aid in the preclinical assessment of newly developed drug treatments. Animal researchers use this technology to radiolabel and monitor drug absorption, distribution, and excretion more efficiently compared to the time and cost involved in sacrificing multiple animals and analyzing brain tissue.

PET scanning of the human brain was developed in 1973 by researchers at Washington University in St. Louis, Missouri. It was superior to other techniques used at that time because PET could isolate areas of drug activity and glucose and oxygen use deep within the brain and could be completed in as little as 30 seconds. Currently, radiolabeling allows researchers to locate the sites of action of a virtually unlimited number of biologically active compounds.

PROBLEMS WITH PET. PET imaging does have its limitations. Compared to newer technologies, such as *magnetic resonance imaging*, PET offers a low degree of spatial resolution, and it is sometimes difficult to distinguish between two structures very close together in the brain. Because of the necessary size of scintillator crystals, which measure approximately 3 to 4 mm in width, PET scanners achieve a reconstructed image resolution of 4 to 4.5 mm, which makes it difficult to distinguish between small structures in the brain. PET scanning also poses some health risk in that radioactive agents are administered into a patient's body. The health costs and benefits of radiation exposure associated with PET scans must be weighed carefully, especially if multiple scans are to be performed on a single patient.

Finally, the expense of PET scanning, in terms of medical personnel and equipment required, limits its use. Because the radioisotopes used to create radiotracers decay so quickly, they must be produced on-site. This means that a cyclotron, which produces the radioisotopes, must be bought or located very nearby.

SPECT. As an alternative to PET, brain imaging can be completed using its sister technique, *single photon emission computed tomography* (SPECT). SPECT uses a *collimator*, consisting of lead blocks containing many tiny holes that allow gamma rays to pass through and hit scintillator crystals. This information is then transmitted to a computer. Compared to PET scanning, SPECT uses radioisotopes such as ^{99m}technetuim (^{99m}Tc), ^{123}iodine (^{123}I), and ^{133}xenon (^{133}Xe) with half-lives ranging from 6 hours to 5 days. This allows for more long-lasting brain functions to be measured and also eliminates the need for having a cyclotron on-site, greatly reducing the cost of scanning. However, compared to PET, SPECT can be technically challenging and more susceptible to error. Furthermore, the spatial resolution of SPECT is even less than that of PET, generating an even less precise image of active brain regions.

Magnetic Resonance Techniques

MAGNETIC RESONANCE IMAGING (MRI). MRI is a technique that takes advantage of the magnetic charge of billions of hydrogen atoms that exist in the body. The nucleus of the hydrogen atom has a single proton (which has a positive electrical charge) and a large *magnetic moment*, making it ideal for the purposes of MRI. Having a large magnetic moment means that when hydrogen atoms are placed within a magnetic field, they will align with the field, similar to the way in which iron filings scattered randomly on a sheet of paper will align parallel to a bar magnet placed beneath the paper. Just because hydrogen nuclei are aligned with the magnetic field does not mean they stand still. In fact, the atoms are in constant movement, each spinning on its axis like a child's toy top. It is this spinning of positively charged protons that produces the magnetic property of hydrogen nuclei.

The most fundamental component of an MRI machine is the very powerful magnet that creates an external magnetic field, forcing the alignment of hydrogen nuclei within the body. The MRI machine looks like a giant cube, typically measuring 2 meters tall by 2 meters wide and 3 meters long. It contains a horizontal tube, called the *bore* of the magnet, in which a participant is

placed. The magnetic field that runs through the bore of the MRI machine is up to 40,000 times more intense than the magnetic field of the earth. The type of magnet most commonly used to create this amazingly powerful field is called a *superconducting magnet.*

Once the participant is placed within the center of the bore and the magnetic field is turned on, the spinning hydrogen protons within the participant's body align in the direction of the field, which, running from head to toe, is called the *z-axis*. Because of the complex laws of quantum mechanics, approximately half the protons will line up in the direction of the participant's feet and half in the direction of the participant's head. However, they largely cancel each other out and produce a net magnetization *angle of alignment* (a) of 0 degrees. While they are aligned, spinning hydrogen protons also rotate, or *precess*, around the axis of the externally created magnetic field, somewhat similar to how the earth revolves around the sun. The precession frequency of an atom (how quickly the protons precess) is specific to the type of atom and is known as the *Larmor frequency*. Although all hydrogen nuclei precess at this frequency, at any given time the protons may be at any *phase* of their precession around the axis of the externally created magnetic field. It helps to think of phase in terms of an analog clock. Imagine that multiple clocks are purchased in an airport shop and taken by the purchasers to various parts of the world. Once they arrive in their particular time zone, each purchaser sets the clock to the proper time of day. The second hand, minute hand, and hour hand on each of the clocks should move (precess) around the center (axis) of the clock at the same speed. However, each of the clocks would be at a different phase of its precession since each time zone is different. So while the frequency of precession for each clock is identical, each clock would be at a different phase of its precession around the axis of the clock at any given time. Phase is an important component in obtaining an MRI image, which we will review shortly.

So far we have discussed the *magnetic* component of MRI, but what about *resonance?* Resonance is defined as the transfer of energy, at a particular frequency, between two systems. Every material has a natural frequency at which it resonates. If you have ever rubbed a moist fingertip around the rim of a crystal wine glass, you will have noticed that the glass seems to "sing." This phenomenon is produced by the transfer of energy from the friction generated by the contact of your moving fingertip with the glass, causing the molecules of the crystal to vibrate at their natural resonant frequency. If a singer could produce a tone of the exact resonant frequency of crystal and of great enough amplitude (volume), the glass would absorb enough energy from the sound waves produced by the singer that it would shatter under the strain. In MRI, electromagnetic energy in the form of *radiofrequency* (RF) *waves* is directed into the body. Electromagnetic energy is a combination of electric and magnetic fields that travel at the speed of light. In addition to RF waves, other forms of electromagnetic energy include X-rays, microwaves, gamma rays, and all forms of light, including ultraviolet and infrared. When directed into the body, pulses of RF energy that are at the precise Larmor frequency of hydrogen protons cause the protons to absorb the energy and resonate. As the protons resonate, their net magnetization, or angle of alignment (a) with the z-axis (the external magnetic field), diverges from 0 degrees and, if enough energy is applied, approaches 90 or even 180 degrees. When a = 90 degrees, the RF pulse is referred to as a 90-degree pulse; at 180 degrees, it is referred to as a 180-degree pulse. As RF waves are applied through the MRI machine, hydrogen protons not only increase their angle of alignment from the z-axis but also acquire the same phase of precession around the axis of the external magnetic field. Thinking back to our clock analogy, it is as if all clocks all over the world suddenly began to display the same time of day and rotate in step with each other. When the RF pulse is turned off, the protons begin to return to their 0-degree alignment with the z-axis and also begin the process of *dephasing*, or rotating out of step. As they do so, the protons release the excess of energy (in the form of RF waves) that was stored during resonation, creating a signal that is picked up by the MRI machine and sent to a computer.

It is these two components of relaxation—proton realignment with the z-axis and proton dephasing—that are used to create an MRI image of the body. These two components of proton relaxation are characterized by *relaxation times* that will be used to describe MRI data. The first is called *spin–lattice relaxation time* (T1) and is the amount of time in milliseconds for the strength of the net magnetization (e.g., a = 90 or 180 degrees) to return to 63% of its value before RF waves were applied. This measure will vary according to the type of tissue being resonated. The second component of proton relaxation

is called *spin–spin relaxation time* (T2) and is the amount of time required for protons to complete their dephasing (or to stop rotating in step) once the RF waves have been stopped. A T1-weighted image (where spin–lattice relaxation is the dominant source of the MR signal) produces a clear image of neuroanatomy in which gray matter appears gray, white matter appears white, and cerebrospinal fluid is dark. A T2-weighted image (where spin–spin relaxation is the dominant source of the MR signal) highlights areas of pathology in which gray matter appears dark, white matter appears bright, and cerebrospinal fluid is even brighter.

When an MRI exam is being administered, the most widely used methodology is called the *spin echo sequence*, which allows researchers to construct three-dimensional images of the body. A series of 90-degree RF pulses are repeatedly applied to the participant at a constant repetition time. As protons relax following the cessation of the 90-degree RF pulse, a 180-degree RF pulse is applied that reverses proton relaxation, causing an increase in the angle of alignment and a rephasing of protons, thereby increasing the emitted signal. The images created have a high spatial resolution in the order of 0.5 to 2.0 mm, making the produced image visually superior to that produced in PET imaging.

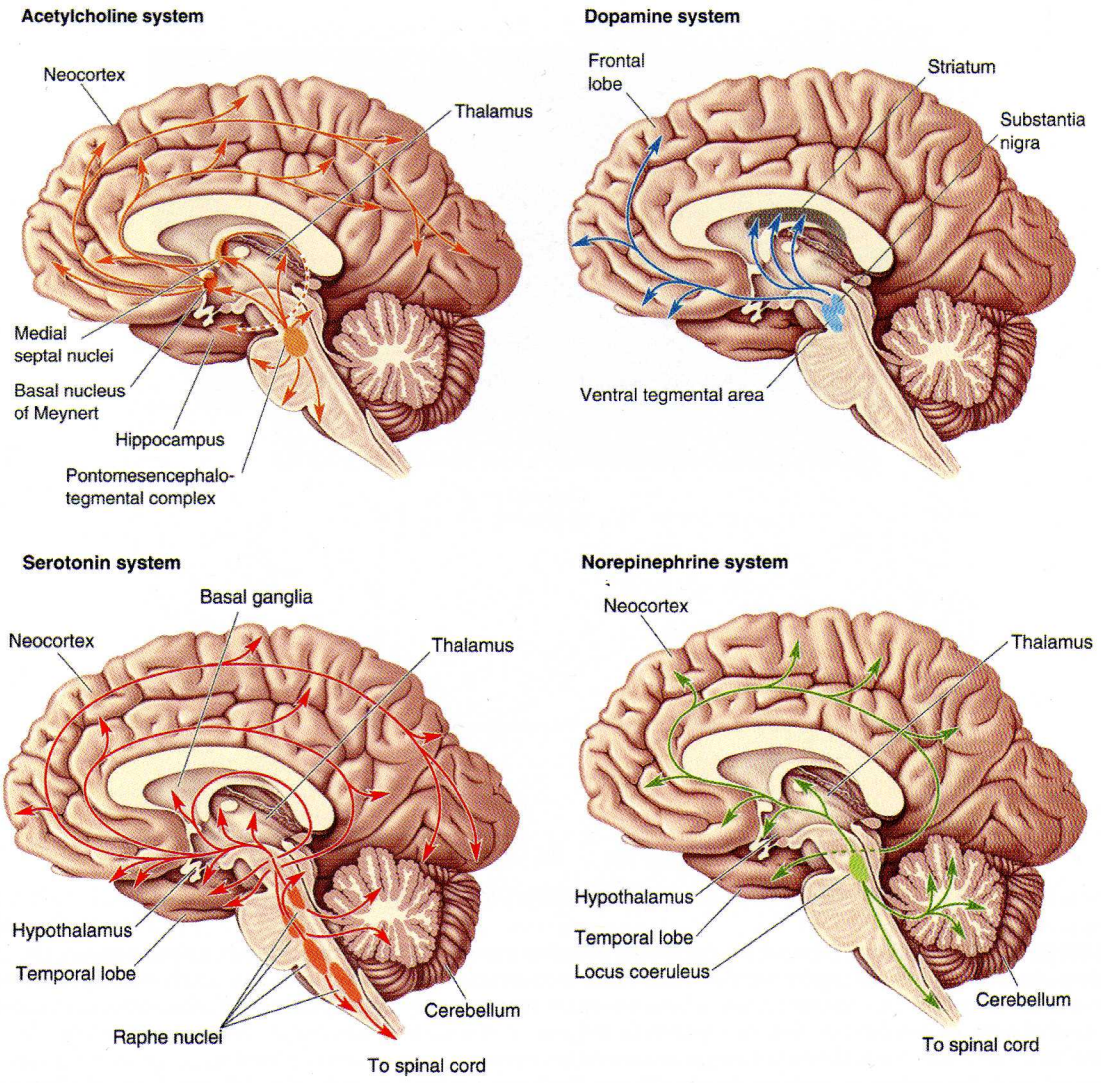
The MRI room must be specially constructed with a reinforced floor and a magnetic shield not only to block the effects of the superconducting magnet but also to prevent interference from other sources of radiofrequency waves (such as FM radio) that can be picked up and sent by the machine and interfere with data acquisition.

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI). Like PET scanning, magnetic resonance can also be used to link changes in cerebral blood flow with activity in specific areas of the brain using a technique called *functional magnetic resonance imaging* (fMRI). Rather than injecting radioactive tracers, however, fMRI relies on the intravenous injection of a magnetic agent (the *contrast technique*) or the magnetic properties of iron-rich deoxygenated hemoglobin (the *noncontrast technique*). A commonly used contrast technique requires the injection of gadolinium, a silvery-white metal that is highly magnetic. Injection of gadolinium increases the strength of the magnetic field only in those regions of the brain that are activated by a particular stimulus (such as a word, picture, or sound broadcast to the participant in the MRI machine) or a particular emotional state. The change in magnetic field strength alters spin–spin (T2) relaxation time, thereby producing a visually contrasting image in active versus inactive areas of the brain.

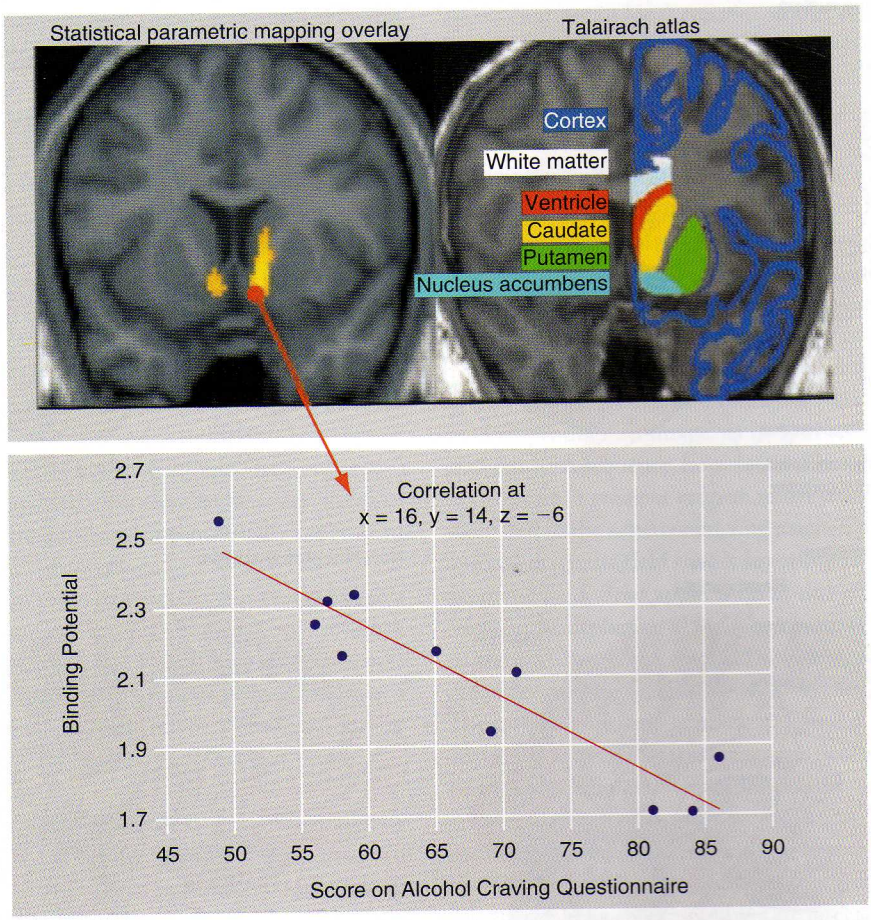
The most commonly used noncontrast fMRI technique is referred to as *blood oxygen level-dependent* (BOLD) *imaging*, which uses T2-weighted images to assess changes in local concentrations of deoxygenated hemoglobin. During brain activation, changes in blood flow and volume exceed the speed at which oxygen is consumed from the blood. This leads to increased quantities of oxygenated hemoglobin (and a reduction in the ratio of deoxygenated to oxygenated hemoglobin) in the brain, thereby producing changes in fMRI signal intensity.

fMRI frequently uses a methodology called *gradient echo sequence*, which is very similar to spin echo sequence used in MRI. In fact, both spin echo and gradient echo sequences can be used in both MRI and fMRI. In gradient echo sequence, series of RF pulses are applied at the Larmor frequency of hydrogen, and T1 and T2 relaxation times are used to produce an image, as in spin echo sequence. In gradient echo sequence, however, as RF pulses are applied to the brain, a *gradient magnet*, much weaker in intensity compared to the superconducting magnet, produces an additional magnetic field that is superimposed on the main magnetic field. Brief application of this gradient field accelerates the dephasing of hydrogen protons (i.e., spin–spin relaxation). A second gradient is then applied to reverse the process of dephasing, causing rephasing of protons. The purpose of using gradient magnets is to cause brief disturbances in the external magnetic field rather than administering additional RF pulses, as is the case in spin echo imaging. The gradient magnets excite only a small slice of tissue rather than the entire volume and are thereby used to alter the resonance of hydrogen protons at very precise areas of the brain that researchers are interested in imaging. As such, multiple gradients can be applied to different regions of the brain in succession, thereby significantly reducing the amount of time required for scanning.

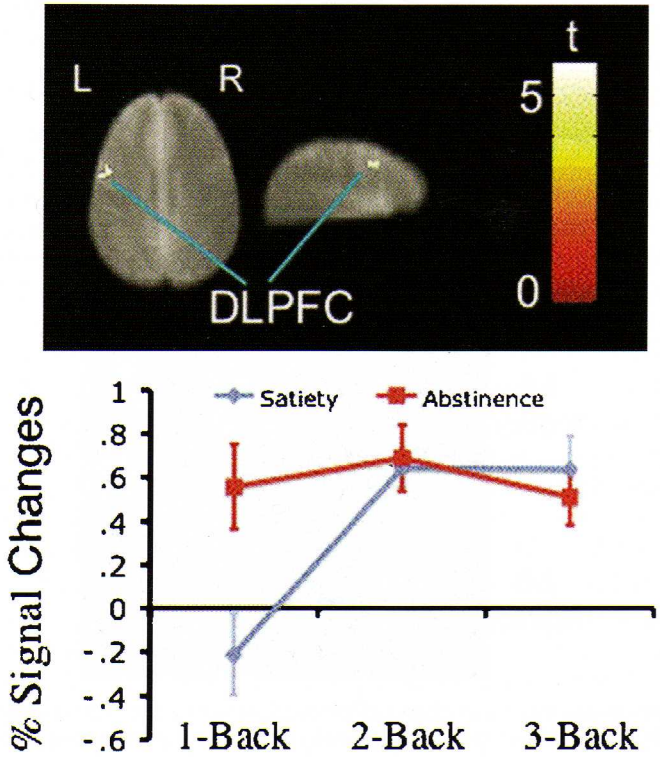
ADVANTAGES AND PROBLEMS WITH MRI. Magnetic resonance techniques are superior to many other forms of brain imaging because they produce images with very high contrast resolution (the ability to distinguish two similar but not identical tissues in a very small area) and spatial resolution in relatively little time. They are also quite safe in that they do not require the injection of radioactive materials, as does PET



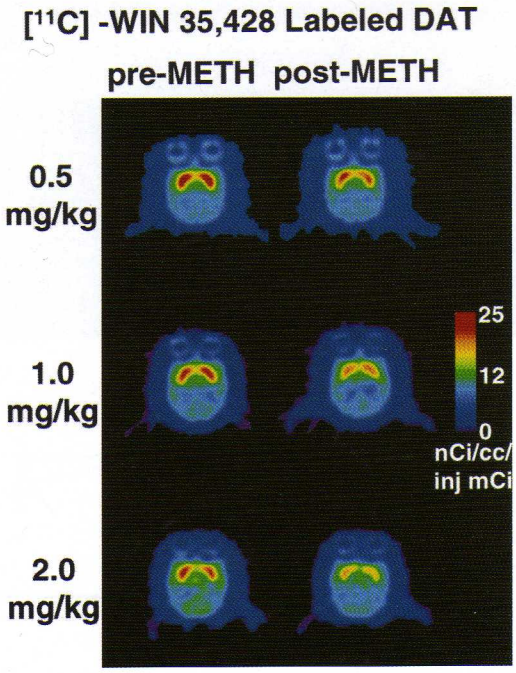
COLOR PLATE A Four major neurotransmitter systems (Adapted from Bear, Connors, & Paradiso, 2007; figures 15-12 [p. 500], 15-13 [p. 501], 15.14 [p. 503], 15.15 [p. 504]; reprinted with permission).



COLOR PLATE B This figure shows the relationship between activity in the ventral striatum (the location of the nucleus accumbens) and craving for alcohol caused by exposure to alcohol-related cues in long-term alcoholics. The yellow brain image at the right shows the area of the brain that was activated when the participants were exposed to the alcohol cues. As you can see, this corresponds to the area of the nucleus accumbens, as shown in the brain image on the left. The lower panel shows the negative correlation between craving and the binding potential for dopamine D_2 receptors in the nucleus accumbens. As you can see, the lower the binding potential at D_2 receptors, the higher the craving induced by the alcohol-related cues. (Heinz et al., 2004; reprinted with permission)



COLOR PLATE C The top panel of this figure shows the BOLD image of the brain. The location of the dorsal lateral prefrontal cortex (DLPC) is indicated. The color bar at the right indicates the level of activity in the DLPC during the task. The lower panel shows the amount of activity in the DLPFC during the 1-, 2-, and 3-back tests when subjects had smoked within the previous 1.5 hours (Satiety) and when they were deprived of nicotine for 14 hours (Abstinence). (Adapted from Xu et al., 2005, fig. 3, p. 147; reprinted with permission)



COLOR PLATE D This figure shows the effect of giving various doses of methamphetamine to baboons four times at 2-hour intervals. These PET images were taken 2 to 3 weeks after the drug treatment. The color bar in the left panel shows the color associated with the amount of binding to the dopamine transporter (DAT), with red showing many transporter molecules and blue showing fewer. The images show the pre- and postmethamphetamine activity in the brain. The yellow and red areas are in the caudate nucleus. You can see a dose-related decrease in DAT binding, indicating that there has been death of some dopamine cells in the area. (Adapted from Villemagne et al., 1998, fig. 1, p. 421; reprinted with permission)

TABLE 4-3 Summary of the Advantages and Disadvantages of Different Brain Imaging Techniques

PET and SPECT	MRI and fMRI
Advantages	***Advantages***
• Ability to radiolabel an almost infinite number of naturally occurring and synthetic chemicals	• Superior spatial resolution
• Can be completed very quickly	• Can be completed very quickly
• Good spatial resolution	• Can image any region of the brain
• Can image any region of the brain	• Thought to be noninvasive
Disadvantages	***Disadvantages***
• Uses radioactive chemicals	• Cannot accommodate individuals with metallic implants
• High cost of cyclotron, scanner, and numerous medical personnel	• Increases in regional blood flow may be altered by mood or even daydreaming
• Provides an indirect measure of brain function, thereby reducing temporal resolution	• Only a moderate level of temporal resolution in fMRI

scanning. However, MRI and fMRI are not without shortcomings. Like PET scanning equipment, MRI equipment is very expensive to purchase and use. In addition, the physical setup of the MRI machine can be problematic for heavier individuals. Furthermore, a significant number of people feel highly anxious, uncomfortable, and claustrophobic within the small confines of the MRI machine. The loud clanking noise created by the scanner and scanning sessions ranging from 20 to 90 minutes only exacerbate this problem. An additional problem is the need for participants to remain entirely motionless throughout the session, which is especially difficult if they are feeling anxious or uncomfortable. Even very slight head movements can create significant loss of spatial resolution and distortion in the created image.

Because of the extreme intensity of the superconducting magnet, participants and medical personnel are checked carefully for any metal objects they may be carrying before they enter the MRI room. Paper clips, keys, hemostats, stethoscopes, hair clips, and any other small magnetic objects can be pulled off the body and become dangerous flying projectiles, getting sucked into the bore of the MRI where the participant is lying. In addition to external objects, metallic objects inside the body, such as aneurysm clips in the brain, some dental implants, heart pacemakers, and metal objects not secured in place by the growth of scar tissue can be dislodged or heated to scalding temperatures by the magnet, causing severe internal damage. Pacemakers are particularly sensitive and can malfunction even if the wearer goes near the scanning room. In addition, heart monitors, oxygen tanks, IV poles, and many other forms of lifesaving and monitoring equipment that contain metal cannot enter the MRI room.

Additional caveats apply to fMRI. Changes in blood flow and volume measured by fMRI BOLD imaging that are thought to result from experimental stimuli or manipulation may be the result of boredom, anxiety, or simply thinking about something outside the experimental context. Standard lag times of 4 to 8 seconds between stimulus onset and signal acquisition, dictated by the relationship between neuronal activation and changes in blood flow and volume, make it all the more difficult to correlate the presentation of stimuli with changes in regional blood flow.

Table 4-3 provides a comparison of the advantages and disadvantages of these brain imaging techniques, and Color Plates B to D give examples of the images they can produce.