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Neurophysiology, Neurotransmitters, and the Nervous System

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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. Some of these cells, called *glial cells*, are not excitable; they provide structural and metabolic functions in the nervous system. The other cells, called *neurons*, are excitable, and they function to 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.

Nerve cells come in many shapes and sizes, but they all have a number of identifiable parts. A typical nerve cell is shown in Figure 4-1. Like all other cells in the body, it has a *nucleus* that contains genetic information. The cell is covered by a *membrane* and is filled with a fluid called *cytoplasm*. All nerve cells have a *cell body*, which is the largest part of the cell and contains the nucleus. Arising from the cell body are several structures. At one end are projections called *dendrites*. These divide into smaller and smaller fibers. 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 is usually 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 itself around the axon.

As we have seen in Chapter 1, cell membranes are made up of two layers of *lipid* molecules (see Figure 1-5) with large protein molecules embedded in them. In nerve cells, these large protein molecules have special functions that make the cells excitable and capable of conveying, storing, and integrating information. These actions are accomplished by controlling the flow of ions through the membrane. These proteins are often a target of behaviorally active drugs.

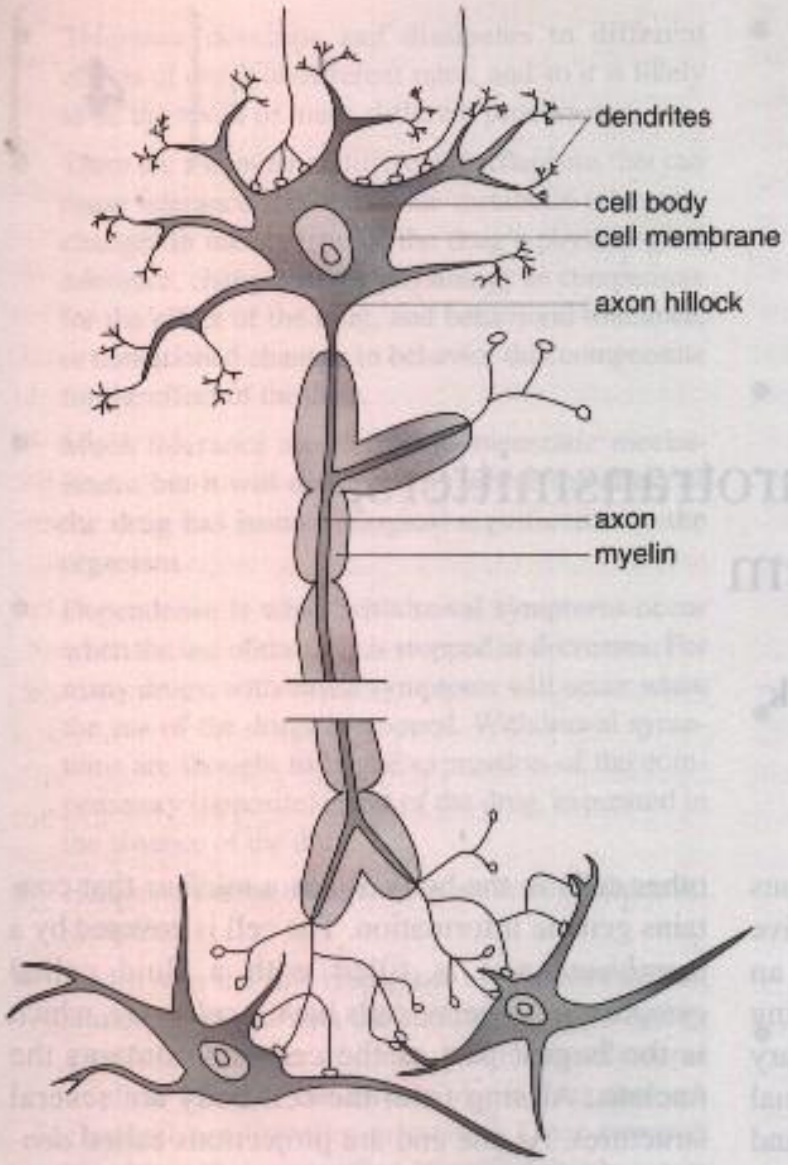

Figure 4-1 A typical nerve cell. Note that the neuron receives input from synapses from several other nerve cells at its dendrites and cell body and that it also has synapses on other nerve cells.

Resting Potential

If we take two very fine wires, insert one inside a neuron and place the other just outside the membrane, and then attach the wires to a voltmeter, we will see that there is a difference in electrical charge; the inside is slightly negatively charged compared to the outside. A *voltmeter* is a device that measures differences in electrical potential between two places; the same sort of instrument is used to test batteries. The potential difference across the membrane is called the *resting potential*. The resting potential varies from cell to cell but is usually about −70 millivolts. (One millivolt is 1/1,000 volt. A standard flashlight battery has a charge of 1.5 volts.)

The reason for this potential difference is that there is an uneven distribution of ions between the inside and the outside of a cell. *Ions* are particles that possess an electrical charge. The ions described in Chapter 1 were usually large drug molecules; the ions that are responsible for the resting potential of a cell are ionized molecules of the elements potassium (K^+), sodium (Na^+), chlorine (Cl^-), and calcium (Ca^{++}), although some larger molecules of amino acids 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 and the outside of the membrane—and (b) the outside of the membrane is always considered equal to zero. The resting potential exists because there are more positively charged ions than negatively charged ions outside the cell. Because there are fewer positively charged ions inside the cell, the inside of the cell is negative with respect to the outside.

Three processes are responsible for this uneven distribution of ions. The most important process is an *active transport mechanism* known as an *ion pump*. Ion pumps are specialized molecules of protein that selectively move ions from one side of a membrane to another. In nerve cells, an ion pump, known as the Na^+/K^+ pump, moves Na^+ ions to the outside and K^+ ions to the inside, but it moves three Na^+ ions out for every two K^+ ions it moves in, thereby creating an excess of positive ions outside the membrane (see Figure 4-2).

Two other processes are also at work. One is simple diffusion, the tendency for a substance to move from an area of high concentration to an area of lower concentration. The other is *electrostatic charge*, the tendency for similar electrical charges to repel each other and for opposite electrical charges to attract each other. Positive ions are repelled by the net positive charge outside the membrane and attracted to the negative charge inside. The reverse is true for negative ions.

If the membranes were completely permeable to ions, diffusion and electrostatic charge would drive ions unevenly distributed by the ion pumps back across the membrane as fast as the pumps could move them. But membranes are not permeable to ions. The only way that ions can move across the membrane is through specialized holes, or channels, in the membrane. These are called *ionophores* or *ion channels*. Like ion pumps, ion channels are large protein molecules embedded in the cell membrane. They are specialized so that they will allow only certain ions to pass through, and then only at a particular rate. There are ion channels for K^+, Na^+, and Cl^-. (There are also channels for Ca^{++} ions, but these are not involved in the resting potential and have a special function, described later.) There are two types of ion channels: those that are always open (*nongated*), and those that are *gated*. Gated ion channels open and close in response to specific stimuli (see Figure 4-2).

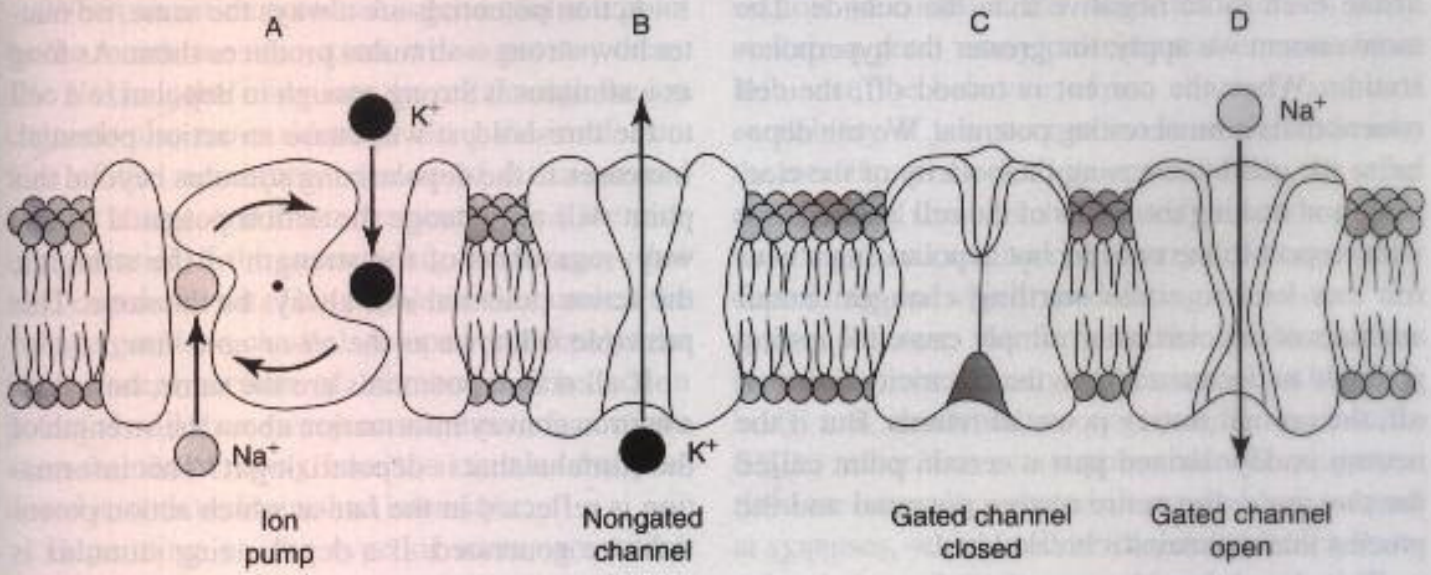

Figure 4-2 (A) An ion pump moving potassium ions (K^+) into a cell and moving sodium ions (Na^+) out of a cell through a membrane. (B) A nongated ion channel that is always open and allows particular ions (in this case, K^+) to move back out of the cell. (C) A closed gated Na^+ ion channel. (D) The open configuration of the same channel shown in C. Note how it allows Na^+ back into the cell.

Normally, the nongated channels do not permit ions to flow through the membrane fast enough to neutralize the ion pumps, so a net positive charge remains outside. This fact explains the resting potential. 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.

Stimulation of the Axon

Action Potential. The resting potential of a neuron describes the distribution of ions in the absence of stimulation. In fact, the 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 a *depolarization*. When the membrane potential becomes more negative (i.e., moves further away from zero), it is called a *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 fine electrode (a fine wire similar to the one used to measure the resting potential) 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. We can depolarize the cell by reversing the polarity of the electrode 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 past a certain point called the *threshold*, the entire resting potential and the process that maintains it break down.

This breakdown occurs because of special gated ion channels that are sensitive to the number of positive charges inside the cell. These *voltage gated ion channels* open when the potential difference is reduced beyond the threshold. When they open, they allow the free flow of ions across the membrane. First, sodium channels open, and Na^+ ions rush into the cell driven by their concentration gradient (there are many more outside than inside) and their electrostatic charge (they are positively charged, and the outside has a net positive charge). As a result, the resting potential of the membrane is neutralized. In fact, the polarity is actually reversed slightly. When this condition occurs, the sodium ion channels close and potassium channels open. Potassium (K^+) ions rush out of the neuron, driven by their concentration gradient and the transient positive charge created by all the Na^+ ions that just entered. Along with the ion pumps, this process restores the resting potential. The process is illustrated in Figure 4-3.

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 many hundreds of 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.

The All-or-None Law

Action potentials are always the same, no matter how strong a stimulus produces them. As long as a stimulus is strong enough to depolarize a cell to the threshold, it will cause an action potential. Increases in the depolarizing stimulus beyond this point will not change the action potential in any way; regardless of the strength of the stimulus, the action potential will always be the same. 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 that is 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. Weak stimuli that produce low levels of depolarization will permit the membrane a bit of time to recover between action potentials, but more

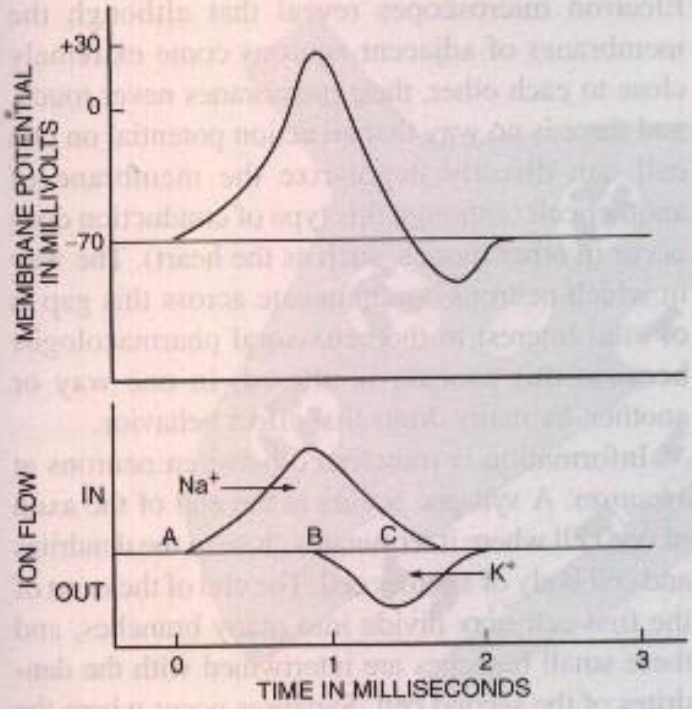

Figure 4-3 The flow of ions during an action potential. The top panel shows a typical action potential. Starting at point A, the resting potential begins to break down. It reaches a peak at B and then returns toward normal. After briefly overshooting −70 mV, the resting potential is restored. The bottom panel shows what happens to ions during the action potential. At point A, sodium channels open, and Na^+ ions rush in. At point B, the sodium channels close, the potassium channels open, and K^+ ions rush out. At point C, the potassium ion channels close, and normal resting potential is restored by ion pumps.

intense depolarization caused by stronger stimuli permits less recovery time between action potentials. As a result, the stronger the depolarizing stimulus, the faster the membrane will fire.

Conduction of Action Potentials along the Membrane

When an action potential is generated at a point on the membrane of an axon, it does not stay there. The Na^+ ions that move into the cell through the ion channels also move sideways along the inside surface of the membrane because of diffusion and electric charge, and this movement reduces the resting potential of the surrounding membrane—that is, it depolarizes it. This depolarization causes the voltage gated ion channels to open and depolarizes the adjacent section of membrane. The action potential will then sweep across the surface of the axon membrane, away from the stimulus that produced it, with undiminished intensity.

Depending on the type of axon, an action potential can move as fast as 100 meters a second. The presence of the myelin coating on the axon greatly speeds the conduction of action potentials along the axon. Myelinated axons can conduct much faster than unmyelinated ones.

Stimulation of the Dendrites and Cell Body

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 an electrode into the membrane of a dendrite or a cell body, the same depolarizing stimulus that caused an action potential in an axon can give rise to very different events, depending on which modulating influences are active. Because the form of the depolarization is variable, we refer to depolarization in the cell body and dendrites as *postsynaptic potentials* (PSPs) rather than action potentials. (These potentials are normally created in membranes located at synapses, which will be discussed later.) Postsynaptic potentials are created by the same type of ion flows as action potentials, and they spread across the membrane in a similar manner except that the intensity of PSPs decreases as the distance from the site of stimulation lengthens. The region of

the cell known as the axon hillock, where the axon joins the cell body, is the place where variable PSPs are converted to unvarying action potentials. Thus, if the membrane of the cell body and dendrites is highly depolarized, a high rate of action potentials will be produced at the axon hillock.

We will return to the behavior of PSPs in the section on synapses, in which we will discuss how one neuron communicates with another.

Action Potentials from Sensory Neurons

We have seen how action potentials are created when a section of a neuron's membrane is depolarized past its threshold and how the action potential moves along an axon. But the action potentials we have discussed have been artificially created by inserting a stimulating electrode 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 the 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. 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 the behavioral pharmacologist 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 occurs at the end of the axon of one cell where it terminates close to the dendrites and cell body of another cell. The end of the axon of the first cell may divide into many branches, and these small branches are intertwined with the dendrites of the second cell. Synapses occur where the axons and dendrites come close to each other.

Figure 4-4 is a schematic drawing of a typical synapse. It is characterized by (a) a swelling called the *terminal bouton* at the termination of the branch of the axon of the *presynaptic cell* (the cell sending the information) and (b) a thickening on the membrane of the cell body or dendrite of the postsynaptic cell (the cell receiving the information) immediately beneath the bouton. Between the terminal bouton and the postsynaptic cell is a gap called the *synaptic cleft*. Another feature of the synapse is a number of spherical structures in the terminal bouton called *synaptic vesicles*.

Action at a Synapse

When an action potential arrives at the terminal bouton, calcium (Ca^{++}) channels open, and the flow of calcium ions into the cell causes a chemical called a *neurotransmitter* to be released from the synaptic vesicles into the synaptic cleft. The neurotransmitter is stored in the *vesicles*. When the calcium enters the cell, the vesicles move to the membrane at the synaptic cleft and release the neurotransmitter through the cell wall into the cleft. The neurotransmitter diffuses across the cleft, where it comes in contact with the membrane of the postsynaptic cell.

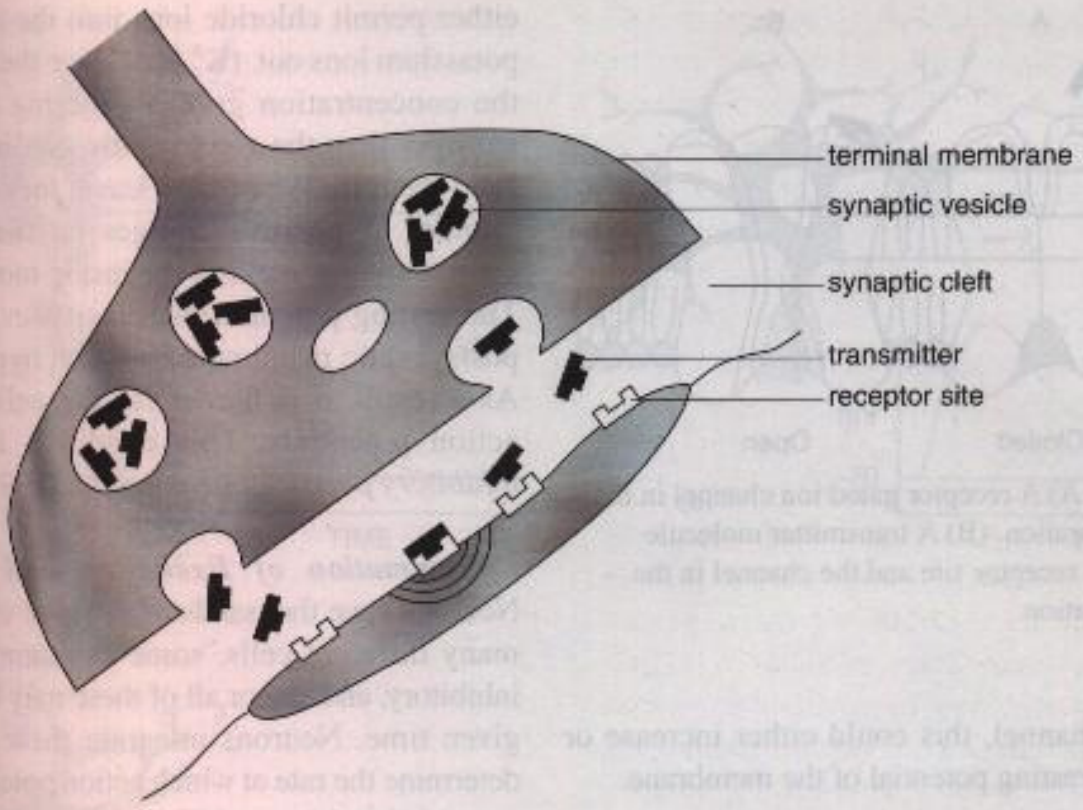

Figure 4-4 Schematic drawing of a synapse. The molecules of transmitter normally stored in vesicles are released into the cleft in response to the arrival of an action potential. The transmitter molecules diffuse across the cleft and occupy receptor sites on the membrane of the postsynaptic cell. These events cause changes in the excitability of the postsynaptic cell membrane, making it either easier (excitation) or more difficult (inhibition) to fire.

Embedded in the membrane of the postsynaptic cell are specialized molecules called *receptor sites* or *recognition sites*. Receptor sites are designed so that molecules of the neurotransmitter will briefly *bind* to (become attached to) them, much like a key fitting into a lock. When a neurotransmitter with the right configuration (the key) attaches to a receptor site (the lock), it causes certain changes to occur in the postsynaptic cell—changes that can result in a shift in its resting potential or a change in its biochemistry. Such changes can be brought about in a number of direct and indirect ways.

Proteins. It has been mentioned that much of the machinery needed to make a neuron operate, such as ion channels, ion pumps, and receptors, are molecules of *protein*. A protein is actually a long chain of fairly simple molecules called *amino acids*. There are only 20 different amino acids in your body, and every protein is made of these 20 amino acids chained together in a different order. These proteins can be hundreds of amino acids long. What allows proteins to have such special properties is that these chains of amino acids do not remain in a line; rather, they fold up into very complex three-dimensional shapes, allowing them to have the sophisticated mechanical properties they need to function as ion pumps, and so on.

Receptors are proteins, and their configuration means that they can bind to a particular transmitter with the correct complementary shape. When a neurotransmitter of the correct shape binds to a receptor, the receptor changes its shape (we sometimes say the receptor has been activated). This activated receptor has the capacity to alter the functioning of the cell in many different ways.

In some synapses, receptor sites are connected to a gated ion channel and cause it to open or close. This process is illustrated in Figure 4-5. Depending

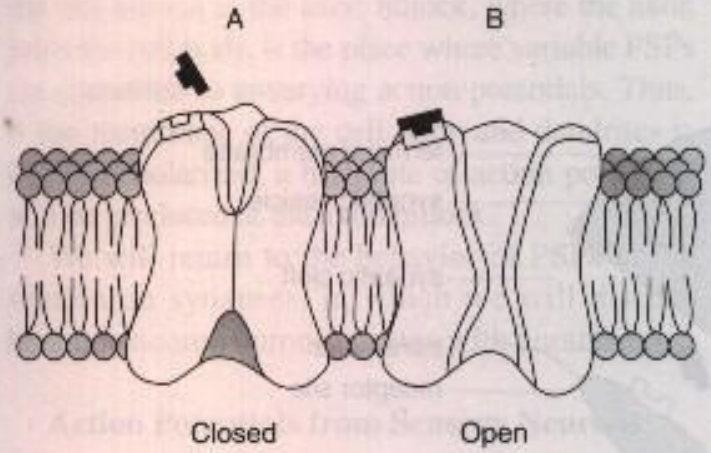

Figure 4-5 (A) A receptor gated ion channel in the closed configuration. (B) A transmitter molecule occupying the receptor site and the channel in the open configuration.

on the ion channel, this could either increase or decrease the resting potential of the membrane.

Excitation. If the presynaptic cell is producing action potentials at a high rate and it has many synapses on the cell body and dendrites of the postsynaptic cell, the resting potential of the postsynaptic cell will be strongly affected.

When the transmitter causes the receptor sites to open gated ion channels that permit Na^+ into the cell, the resting potential will move closer to the action potential threshold. In other words, the membrane will be depolarized. Depolarization of the postsynaptic membrane has a special name: *excitatory postsynaptic potential* (EPSP). The faster a presynaptic cell fires, the more neurotransmitter it will release at its synapses and the greater the EPSP it will cause. If enough EPSPs are being produced at the same time at many synapses, the postsynaptic cell may be depolarized past its threshold at its axon hillock, and it will create action potentials in its axon. As described in the earlier section on the all-or-none law, the more the postsynaptic cell is depolarized past its threshold, the faster the cell will fire.

Inhibition. There are also synapses at which the neurotransmitter will inhibit the firing of the postsynaptic cell. In this case the neurotransmitter causes the receptor site to open ion channels that either permit chloride ions into the cell or allow potassium ions out. (K^+ ions leave the cell because the concentration gradient forcing them out is stronger than the electrostatic gradient trying to keep them in. When they leave, they increase the number of positive charges on the outside of the membrane, making the inside more negative.) The resting potential then increases; that is, the postsynaptic membrane becomes hyperpolarized. As a result, it is harder for the cell to produce action potentials. This condition is called an *inhibitory postsynaptic potential* (IPSP).

Summation of Excitation and Inhibition. Neurons have thousands of synaptic contacts from many different cells, some excitatory and some inhibitory, and any or all of these may be active at a given time. Neurons integrate these signals and determine the rate at which action potentials will be generated at the axon hillock or whether any will be generated at all. There are two major types of integration: (a) *spatial summation* and (b) *temporal summation.* Spatial summation occurs when two or more neurons release transmitters onto the same target neuron. The target neuron will have Na^+ ions entering in some regions (excitation) and K^+ ions leaving at 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. The sum of these effects must be able to depolarize the cell beyond the threshold if an action potential is to occur (see Figure 4-6.) Temporal summation occurs when a neuron produces several action potentials closely in time. Although each one may be too small to initiate an action potential, if they arrive closely together, their EPSPs may summate and reach threshold (see Figure 4-6).

Terminating Synaptic Action

The arrival of action potentials at the terminal bouton initiates the release of a transmitter into the synaptic cleft that causes changes in the membrane of the postsynaptic cell, but it is important to have some mechanism to get rid of the transmitter when the presynaptic terminal bouton stops receiving

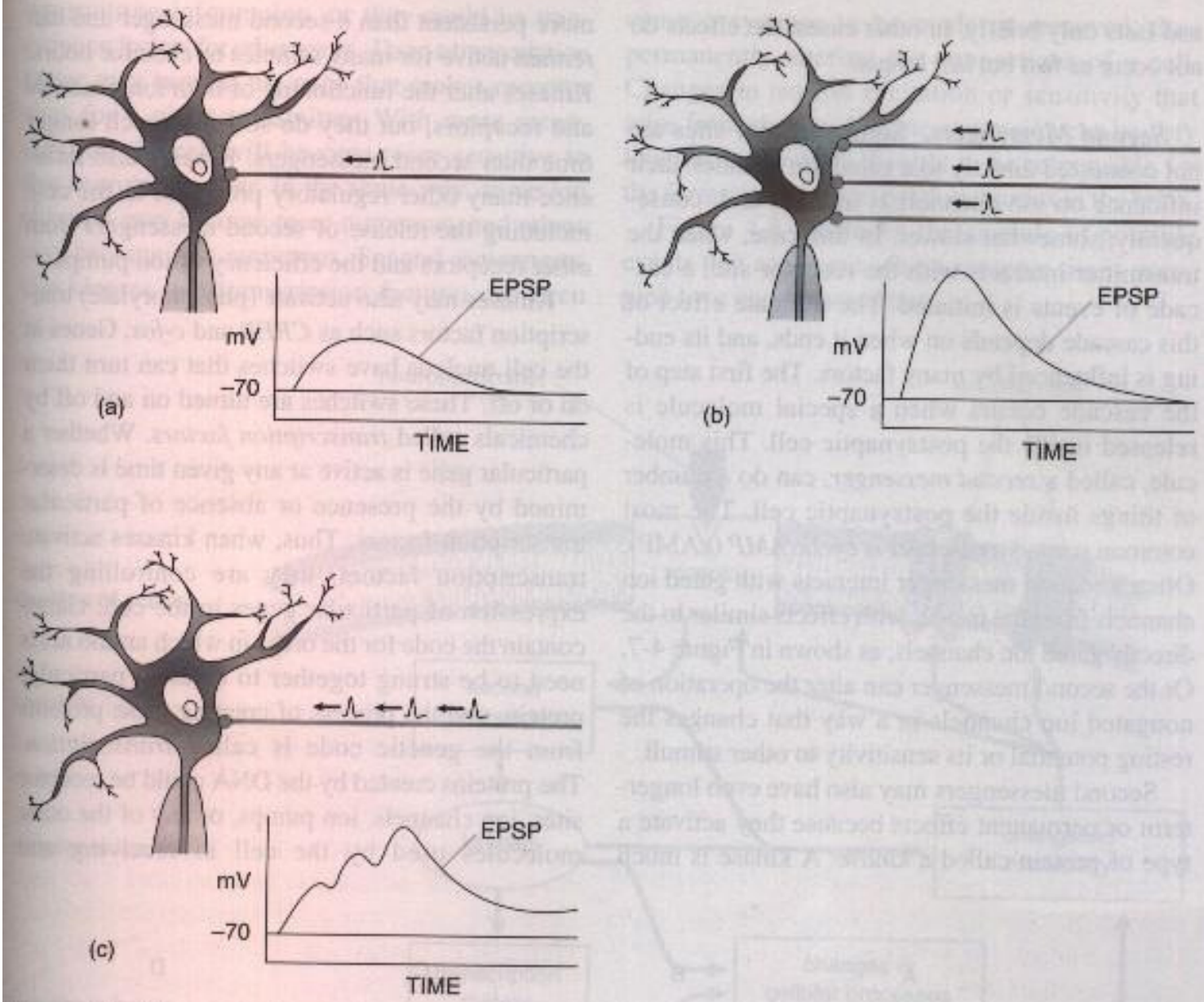

Figure 4-6 Temporal and spatial summation of PSPs on a dendrite. (a) A single impulse arrives at a synapse and causes a PSP. (b) Three impulses arrive at the same time at three different synapses. Their effects summate, causing a much bigger PSP (spatial summation). (c) Three impulses arrive in quick succession at one synapse. Their effects are summed to cause a greater PSP than if only one had arrived (temporal summation).

action potentials. Otherwise, the transmitter would stay in the cleft and continue to influence the postsynaptic cell. Every synapse has some system to accomplish this purpose. It is usually accomplished in one of two ways: (a) The synapse contains an enzyme that destroys the transmitter if it stays in the cleft for any length of time, or (b) the presynaptic cell has a means of reabsorbing the transmitter and then recycling it. The latter process, called *reuptake*, is accomplished by a sort of active transport mechanism embedded in the membrane of the presynaptic cell.

Speed and Duration of the Effects of Neurotransmitters

As we have seen in some synapses, receptor sites are connected to a gated ion channel and cause it to open or close. When this happens the effect occurs very rapidly, in the order of milliseconds,

and lasts only briefly. In other cases, the effects do not occur as fast but last longer.

Second Messengers. Some receptor sites are not connected directly to a gated ion channel; their influence on ion channels is indirect and, consequently, somewhat slower. In this case, when the transmitter interacts with the receptor site, a cascade of events is initiated. The ultimate effect of this cascade depends on when it ends, and its ending is influenced by many factors. The first step of the cascade occurs when a special molecule is released inside the postsynaptic cell. This molecule, called a *second messenger*, can do a number of things inside the postsynaptic cell. The most common second messenger is *cyclic AMP* (cAMP). Often a second messenger interacts with gated ion channels from the inside, with effects similar to the directly gated ion channels, as shown in Figure 4-7. Or the second messenger can alter the operation of nongated ion channels in a way that changes the resting potential or its sensitivity to other stimuli.

Second messengers may also have even longer-term or permanent effects because they activate a type of protein called a *kinase*. 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 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

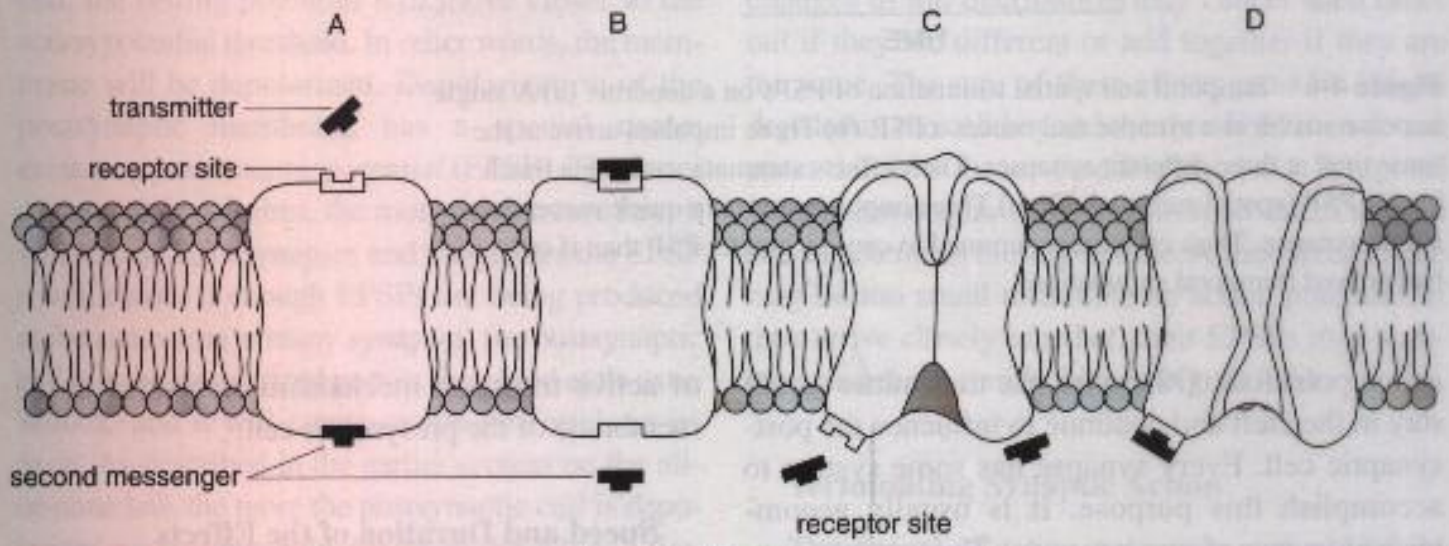

Figure 4-7 How second messengers work. (A and B) When a receptor outside the cell membrane is occupied by a transmitter molecule, it causes the release, inside the cell, of a molecule of a second messenger. (C and D) The second messenger then interacts with a receptor on the inside of a gated ion channel, in this case causing it to open. Second messengers may do a great many other things in the postsynaptic cell.

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.

Figure 4-8 illustrates the cascade of possible events that can occur after a receptor site is occupied by a neurotransmitter.

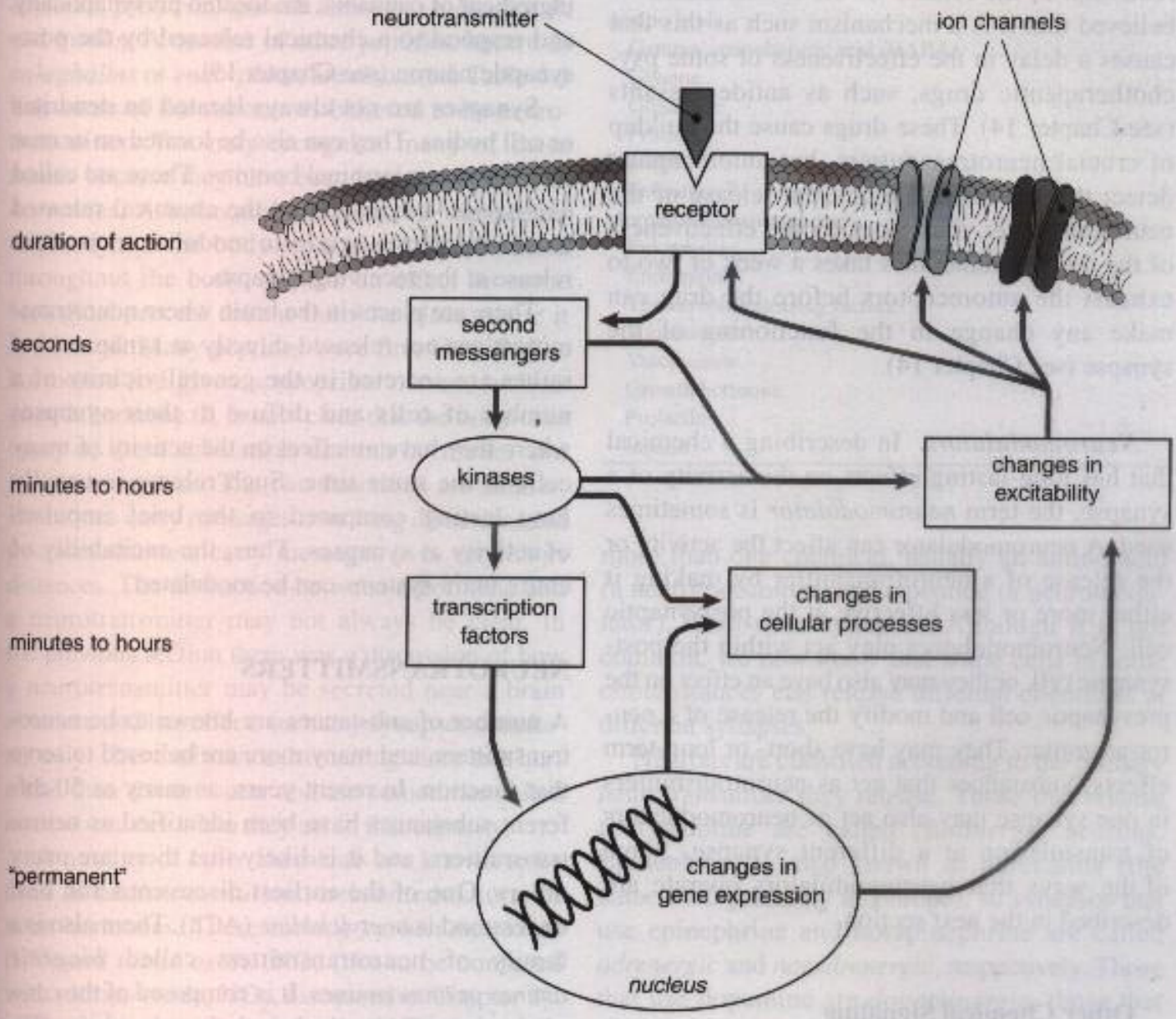

Figure 4-8 The relation between a signal cascade and the resulting effects on cell excitability. As the cascade progresses, the duration of the effect increases. No matter how many steps there are in the cascade and how long those steps are active, all the alterations have common end points. Every change in excitability is the result of alterations to ion channels or receptors or of a change in the biochemical processes of the cell.

Presynaptic Effects of Neurotransmitters

Receptor sites are not located only on the postsynaptic neuron. In fact, there are often many receptor sites for the neurotransmitter located on the presynaptic neuron. These are called *autoreceptors*. They serve to provide feedback on the amount of neurotransmitter in the synaptic cleft and control its release. If levels of the neurotransmitter get too high, the autoreceptors will cause a reduction in the release of the transmitter. It is believed that it is a mechanism such as this that causes a delay in the effectiveness of some psychotherapeutic drugs, such as antidepressants (see Chapter 14). These drugs cause the buildup of crucial neurotransmitters, but autoreceptors detect this excess and block the release of the neurotransmitter, thus blocking the effectiveness of the drug. It sometimes takes a week or two to exhaust the autoreceptors before the drug can make any change in the functioning of the synapse (see Chapter 14).

Neuromodulators. In describing a chemical that has long-lasting effects on the activity of a synapse, the term *neuromodulator* is sometimes used. A neuromodulator can affect the activity or the release of a neurotransmitter by making it either more or less effective at the postsynaptic cell. Neuromodulators may act within the postsynaptic cell, or they may also have an effect on the presynaptic cell and modify the release of a neurotransmitter. They may have short- or long-term effects. Substances that act as neurotransmitters in one synapse may also act as neuromodulators of transmission at a different synapse. Some of the ways that neuromodulators operate are described in the next section.

Other Chemical Signaling Between Neurons

The release of transmitters from the presynaptic cell altering the excitability of a postsynaptic cell is the most common and best-understood mechanism by which cells communicate, but it is not the only one. In addition to autoreceptors, we now know that the presynaptic cell also has receptor sites on the terminal bouton that can respond to chemicals released by the postsynaptic cell or other nearby cells when they become depolarized. 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, the active ingredient of cannabis, are located presynaptically and respond to a chemical released by the postsynaptic neuron (see Chapter 15).

Synapses are not always located on dendrites or cell bodies. They can also be located on or near other axons or terminal boutons. These are called *axo-axonal synapses*, and the chemical released at these synapses serves to modulate transmitter release at the receiving synapse.

There are places in the brain where neurotransmitters are not released directly at synapses, but rather are secreted in the general vicinity of a number of cells and diffuse to their synapses where they have an effect on 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.

NEUROTRANSMITTERS

A number of substances are known to be neurotransmitters, and many more are believed to serve that function. In recent years, as many as 50 different substances have been identified as neurotransmitters, and it is likely that there are many others. One of the earliest discovered and best understood is *acetylcholine* (ACh). There also is a family of neurotransmitters called *biogenic amines* or *monoamines*. It is composed of the *catecholamines* (CA), which include *epinephrine* (E), *norepinephrine* (NE), *dopamine* (DA), and one *indoleamine*, *serotonin*, which is often called *5-hydroxytryptamine* (5-HT).

Some transmitters are amino acids. Three of the most common are (a) *gamma-aminobutyric acid*

(GABA), (b) *glycine*, and (c) *glutamate*. 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.

Peptides consist of a number of amino acids linked together in a chain. As you know, receptor sites are made of long chains of peptides folded into a specific shape. Some neurotransmitters are also peptides. These include *somatostatin, vasopressin, oxytocin, prolactin, growth hormone, substance P*, and *insulin*. A number of other peptides, known as *enkephalins* or *endorphins*, are also used. Table 4-1 lists some of the substances believed to be neurotransmitters. You may recognize many of these names because they have been known for years as *hormones*. A hormone is a chemical messenger released into the body by a gland. It circulates throughout the body and has an effect on some biological process distant from the place where it is released. 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. The two functions are similar: Hormones carry messages over long distances, and neurotransmitters carry messages over very short distances. The distinction between a hormone and a neurotransmitter may not always be clear. In the previous section there was a discussion of how a neurotransmitter may be secreted near a brain structure and has 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 that capacity.

A number of other chemicals are known to be used as neurotransmitters, neuromodulators, or neurohormones. These include *carbon monoxide* (CO) and *nitric oxide* (NO) (not to be confused with nitrous oxide, NO_2, discussed in Chapter 8).

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 release more than one chemical, usually an amino acid (a neurotransmitter) and a peptide (a neuromodulator), from their synapses. Although it is not common, we now know that some cells in some circumstances can release different chemicals at different synapses.

TABLE 4-1 Neurotransmitters in the Central Nervous System

Acetylcholine (Ach)
Biogenic amines (monoamines)
Catecholamines
Norepinephrine (NE)
Dopamine (DA)
Epinephrine (E)
Indoleamine
Serotonin (5-hydroxytryptamine, 5-HT)
Others
Histamine
Amino acids
Gamma-aminobutyric acid (GABA)
Glycine
Glutamate
Proline
Peptides
Substance P
Morphine-like substances
Enkephalins
Endorphins
Thyrotropin-releasing factors
Somatostatin
Vasopressin
Growth hormone
Prolactin
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. 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 it binds to. Because any transmitter may have a number of

different receptor sites, activity at its synapses may have 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 the vesicles 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

The transmission between nerves is a chemical process, and it is primarily at synapses that drugs have the opportunity to interfere with the process. Substances administered from outside the body can find their way to synapses and alter their function in many different ways. Externally administered drugs can mimic neurotransmitters by occupying some or all of the receptor sites that cause the drugs' effect (*agonism*). Drugs sometimes occupy receptor sites but have no effect. This action blocks the transmitter from having its normal effect (*antagonism*), as illustrated in Figure 4-9. Other ways that drugs can alter synaptic transmission include (a) decreasing the activity of enzymes that either create or destroy a transmitter, (b) altering the reuptake of a transmitter, (c) altering the activity of a second messenger, (d) interfering with the operation of ion channels, or (e) changing the amount of transmitter that a neuron releases in response to an action potential.

Modulating all this is the function of autoreceptors. If a drug is given that blocks receptors, both the postsynaptic receptor site and the autoreceptors will be blocked. There is, consequently, a decrease in neurotransmission to the postsynaptic cell, but there is also a decrease in activity in the autoreceptor. This decrease in autoreceptor activity stimulates the cell to produce more neurotransmitter that can 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 the postsynaptic receptor, then the net result might be an increase in transmission across the synapse because the presynaptic cell will overcompensate by releasing too much transmitter.

As you can see, things can get very complicated.

Acetylcholine

Acetylcholine (ACh) is synthesized in cholinergic cells and stored in the synaptic vesicles. When an action potential arrives at the terminal bouton, the vesicle releases the ACh into the synaptic cleft, where it interacts with receptor sites on the surface of the postsynaptic cell. The synaptic cleft also contains an enzyme called *acetylcholinesterase* (AChE), which breaks down the ACh whenever it comes in contact with it. Thus, the ACh does not remain in the synaptic cleft for very long. Several drugs interfere with the activity of the 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.

Some drugs alter the functioning of cholinergic synapses by acting at the ACh receptor sites. Although all ACh receptor sites are stimulated by ACh, they can be classified according to other

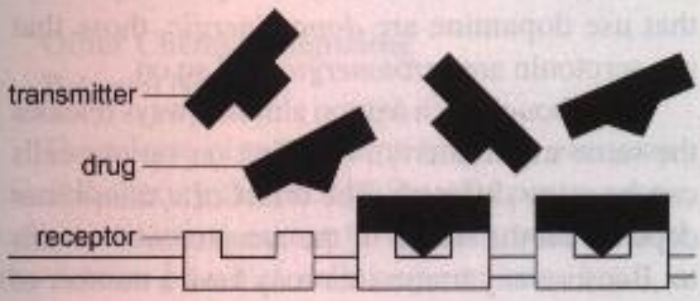

Figure 4-9 Drug transmitter molecules compete for the transmitter's receptor sites. A receptor site may be occupied by the drug molecule, keeping the transmitter molecule out, but the drug is not the correct shape to activate the receptor in the same way the transmitter would. Therefore, the drug blocks the receptor, and the effectiveness of the transmitter is minimized.

substances that can affect them. *Nicotinic* cholinergic receptors are stimulated by nicotine and blocked by a drug called *curare*, a poison that some South American Indians place on the point of their spears and arrows. *Muscarinic* cholinergic receptors are stimulated by muscarine and blocked by drugs like atropine and scopolamine (see Chapter 8).

Interestingly, muscarinic and nicotinic receptor sites differ in the way they alter the postsynaptic cell. Nicotinic receptors are directly connected to a gated ion channel; muscarinic receptors use a second messenger.

Biogenic Amines (Monoamines)

The catecholamines—E, NE, and DA—and the indoleamine 5-HT all work in a similar way, so we will consider them together. The catecholamine neurotransmitters are made by the body from *tyrosine*, a substance found in food. The tyrosine is converted into *L-dopa*, which is then converted to DA and used by dopaminergic neurons. Some DA is converted into NE, and E is created from the NE by another step. Each step in the conversion of tyrosine to E is controlled by a special enzyme. 5-HT is converted from *tryptophan*, another substance found in food, in two steps, using two enzymes.

The biogenic amines—E, NE, DA, and 5-HT—are stored in vesicles in the terminal bouton, where they are protected from two enzymes that destroy them: *monoamine oxidase* (MAO) and *catechol-O-methyltransferase* (COMT). Like ACh, these neurotransmitters are released into the cleft when an action potential arrives, but they are deactivated by a slightly more complex mechanism. After the neurotransmitters diffuse across the synapse and interact with receptor sites, they are reabsorbed into the terminal bouton, where they are again stored in the vesicles and recycled. Any transmitter not protected in this way is destroyed by MAO and COMT.

Other drugs, such as the amphetamines, stimulate these synapses by causing a leakage of the neurotransmitter into the cleft and increasing the amount of neurotransmitter released when an action potential arrives. Drugs such as cocaine and some antidepressants block reuptake so that the transmitter stays in the cleft longer. Activity at synapses that use monoamines as neurotransmitters are also stimulated by drugs that block the activity of MAO (see Chapter 13).

Each biogenic amine can have a number of different receptor sites. Epinephrine and norepinephrine work at two types of receptors: *alpha* (α) and *beta* (β) adrenergic receptors. Each of these has two subtypes, α_1 and α_2 and β_1 and β_2. Dopamine has at least six receptor types; the two main ones, D_1 and D_2, are found in different dopaminergic brain systems. 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 13).

Serotonin has four main types of receptors: 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4. In addition, there are four subtypes of the 5-HT_1 receptor (known as 5-HT_{1a}, 5-HT_{1b}, and so on). The 5-HT_3 receptors are connected to a gated ion channel, but the rest use a second messenger system.

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). Don't be confused—these refer to the same thing.

Gamma-Aminobutyric Acid (GABA)

Most of the neurotransmitters mentioned so far are either excitatory or inhibitory, depending on the nature of the receptor site; GABA, however, is believed to be a universal inhibitory neurotransmitter in all parts of the brain. It produces its inhibitory effect by directly opening a Cl^- ion channel, permitting negatively charged chloride ions to flow inward along their concentration gradient. This action stabilizes the membrane and makes it more difficult to create an action potential. Like the other amino acid transmitters, GABA is removed from the cleft by a reuptake mechanism.

Depressant drugs like the barbiturates and the benzodiazepines (e.g., Valium; see Chapter 7) enhance these inhibitory properties of GABA by increasing its ability to open the chloride ion channel. Convulsant drugs like bicuculline block GABA by occupying its receptor.

There are two classes of GABA receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are directly linked to an ion channel and have immediate inhibitory effects, but $GABA_B$ receptors use a second messenger and are slower acting. 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, and this makes it possible for different benzodiazepines to have different effects in 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, & Radolph, 2004).

Glutamate

Glutamate is the major excitatory transmitter in the brain. It has a number of receptor sites that work in a complex fashion and are dependent on the presence of several other substances. The best-understood glutamate receptor is the *NMDA receptor*. One of its receptors operates through a second messenger system, but glutamate causes excitation primarily using the NMDA receptor by directly opening ion channels that allow positively charged ions to cross the membrane. This channel can be blocked by alcohol, solvents, and the hallucinogenic drug phencyclidine (PCP; see Chapter 16).

Peptides

Neurotransmitter peptides are chains of amino acid molecules attached in a specific order. They can be as short as four or five amino acids or as long as 30 or more. Because most other neurotransmitters are built around a single amino acid precursor, peptide molecules are physically much larger than traditional neurotransmitters. Unlike other neurotransmitters that can be synthesized directly in the terminal bouton, these transmitters are formed in the cell body and transported to the synapse before they are stored in vesicles. Peptides are often released with other transmitters; for instance, a neuron may release glutamate and a peptide.

Peptides can be classified into several groups. One group is the *opioid-type* peptides. These are generally formed from a chain of amino acids manufactured elsewhere in the body. Some chains, varying in length from 16 to 30 amino acids, are known as *endorphins*, and shorter chains of five amino acids are called *enkephalins*. There are known receptor sites for these peptides in the brain and elsewhere in the body. Opiates such as morphine activate these same receptors. Opioid peptides have several types of receptors: *mu* (m), *kappa* (κ), and *delta* (δ) receptors. Most of the analgesic and reinforcing effects of morphine are mediated by the mu receptor, although some analgesia is associated with all of the opioid receptor types.

Almost all peptide receptors generate their effects through second messenger systems. In some cases, the peptide/receptor complex may be taken inside the cell (*endocytosis*) where it activates kinases directly. Sometimes the peptide/receptor complex can act directly as a transcription factor. The ways in which these actions are accomplished are very different from traditional neurotransmitters, but the end results are similar.

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, and the axons from these cells also tend to stay together. They form a bundle of axons, which connects to other clusters of cell bodies. We, therefore, find that the nervous system is made up of groups of cell bodies and bundles of axons running between these groups of cell bodies. 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 usually appear white and are called *white matter*. The unmyelinated cell bodies are called *gray matter*.

The PNS

Somatic Nervous System. The PNS may be divided into two functional units: (a) the *somatic nervous system* and (b) the *autonomic nervous system*. The somatic system is made up of all the sensory nerves from most of the conscious senses, such as the nerves running from the sensory receptors in the eyes, ears, and skin to the CNS. The somatic nervous system also contains the motor nerves, which have their cell bodies in the spinal cord and send axons directly to the *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 is the transmitter at most neuromuscular junctions, and the receptor sites are of the nicotinic cholinergic type.

Autonomic Nervous System. Whereas the somatic system usually carries information into the CNS from our conscious senses, the autonomic nervous system is concerned with sensory systems that we are not usually aware of: information about blood pressure and blood gases, the functioning of the intestines, and levels of hormones. The somatic system controls the muscles over which we have voluntary control; the autonomic nervous system controls 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 really has two divisions. The one that is dominant most of the time and generally keeps the internal functioning of the body operating smoothly is called the *parasympathetic nervous system*. The other autonomic system, called the *sympathetic nervous system*, is connected to the same internal organs as the parasympathetic system, but at times of stress and danger, it comes into operation and takes over from the parasympathetic system. Its function is 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 the heart rate and breathing rate increase. This series of changes is called the *fight-or-flight response*.

The parasympathetic and sympathetic nervous systems are anatomically, functionally, and neurochemically distinct. Both systems are influenced by a number of drugs. 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 of the eye can be examined. When atropine is placed in the eye, it blocks the receptor sites at the parasympathetic neuromuscular junctions. Because the parasympathetic system can no longer control the size of the pupils, they dilate. The muscles that control the lens are also under parasympathetic control, so the atropine makes vision blurry as well. Some drugs, such as tricyclic antidepressants and antipsychotics (see Chapters 13 and 14), have anticholinergic side effects that include blurred vision and a dry mouth.

The primary transmitter in the sympathetic system is epinephrine (adrenaline). In times of stress, the adrenal gland secretes epinephrine into the

blood, directly stimulating receptors in the sympathetic system and causing the fight-or-flight response. Drugs such as amphetamine and cocaine that stimulate adrenergic synapses will also cause sympathetic arousal.

The CNS

Spinal Cord. The CNS has two basic parts: the *brain* and the *spinal cord*. Some integration of information and reflex activity goes on within the spinal cord, but it functions primarily as a relay station. It transmits information from the sensory nerves into 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 4-10. It is made up of cell bodies and synapses. Axons from sensory nerves enter the gray matter of the spinal cord from the side nearest the back (dorsal side), and motor axons leaving the spinal cord do so from the side nearest the front (ventral side), as illustrated in Figure 4-10. 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 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. Not all areas of the brain grow new neurons, however. In humans, a region of the hippocampus (see the section "Limbic System" later in this chapter) is the only area known to give rise to new brain cells (Eriksson et al., 1998).

The brain is a complicated structure made up of numerous nuclei and complex fiber tracts that connect the nuclei in many ways. For this reason, the brain has been called a "great raveled knot."

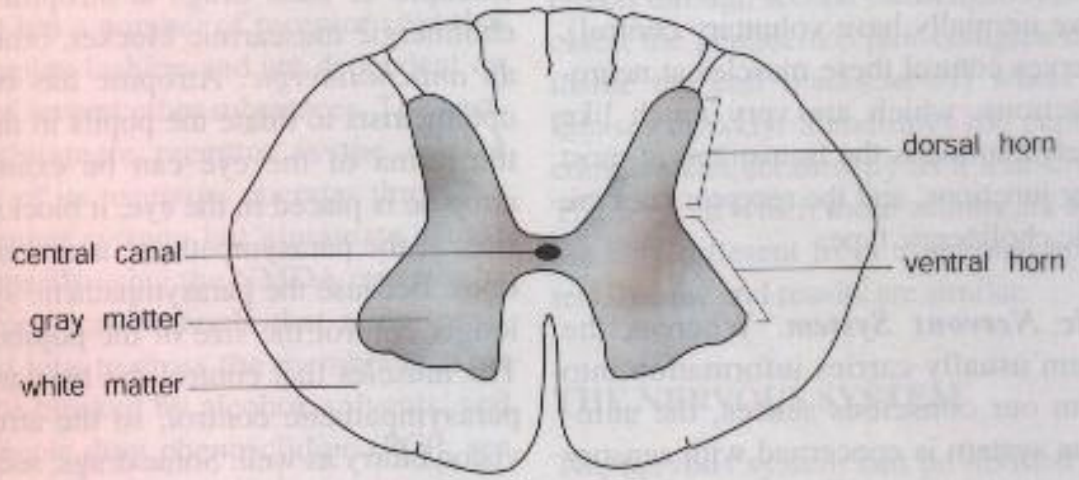

Figure 4-10 A cross section of the spinal cord, showing the white matter and gray matter. Axons of sensory nerves come in through the dorsal horn (toward the back) and form synapses in the gray matter. Cell bodies in the ventral horn (toward the front) send axons to the muscles out the ventral side of the cord. The white matter consists of bundles or tracts of myelinated axons running between the brain and different parts of the body.

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 4-11 represents the brain and identifies some of its structures.

Medulla. The area at the base of the brain, where the spinal cord arises, is called the *medulla*. For the most part, it is made up of fiber tracts running to and from the spinal cord and connecting it to higher centers in the brain. A number of nerves of the autonomic nervous system enter and leave the brain at the medulla, and many of them have control centers located there. The proper functioning of these centers depends on the general level of arousal in this area of the brain. The respiratory center, which controls breathing, is very sensitive to many drugs. Barbiturates, opiates, 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. If you are ever in a position to help someone who has taken an overdose of a drug, it is important to stimulate or maintain breathing, either by keeping the person aroused and awake or by artificial respiration.

Another center that is located in this part of the brain and is sensitive to drugs is the *vomiting center*. This center is able to monitor the blood 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.

Reticular Activating System and Raphé System. Two diffuse projection systems originate in the medulla and run forward into the higher parts of the brain: the *reticular activating system* (RAS) and the *Raphé system*.

The RAS is a complicated interconnection of diffuse centers and branching fiber tracts connected in such a way that when one part is excited, the entire system becomes activated. The RAS receives input from axons of sensory nerves that run past the RAS on their way from a sense organ

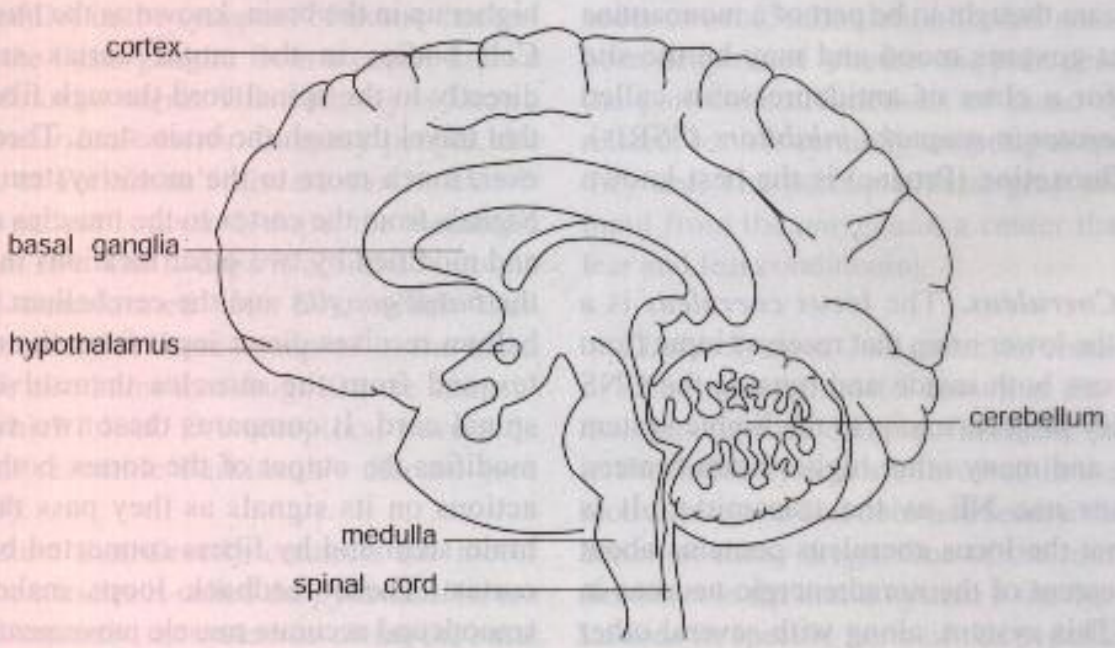

Figure 4-11 A cross section of a human brain. Note the locations of some of the structures mentioned in the text.

to the sensory areas of the cortex. Thus, the RAS is activated by incoming stimulation and projects a diffuse net of 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. 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.

Unlike the RAS, which causes arousal, parts of the Raphé system cause sleep. The Raphé system is also made up of a number of nuclei, but they are not interconnected in the same way as the RAS. Artificial stimulation of some Raphé 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. The Raphé nuclei use serotonin as a neurotransmitter, and drugs that alter serotonin activity also seem to interfere with sleep.

A number of centers in the Raphé system send axons forward to the limbic system and the forebrain through the *medial forebrain bundle*. These projections are thought to be part of a monoamine system that governs mood and may be the site of action for a class of antidepressants called *selective serotonin reuptake inhibitors* (SSRIs), of which fluoxetine (Prozac) is the best-known example.

Locus Coeruleus. The *locus coeruleus* is a nucleus in the lower brain that receives input from many sources both inside and outside the CNS and diffusely projects axons to the limbic system and cortex and many other higher-brain centers. Its synapses use NE as the transmitter. It is believed that the locus coeruleus contains about 50 to 70 percent of the noradrenergic neurons in the brain. This system, along with several other similar systems (such as the serotonergic forebrain projections of the Raphé system), projects to the higher-brain centers through the medial forebrain bundle and is known to be involved in the control of mood. Depression is believed to be a result of abnormal functioning of these systems.

The activity of the locus coeruleus is controlled by a large inhibitory input of synapses that releases GABA. In addition to mood, activity in the locus coeruleus is believed to be associated with fear, panic, and anger. *Positron emission tomography* (PET) shows that the locus coeruleus and the places in the brain where it sends its axons become highly active when people are having panic attacks. Drugs like the benzodiazepines (e.g., Valium), which increase the inhibitory effect of GABA, are known to relieve anxiety (see Chapter 7), and drugs like amphetamine and cocaine, which stimulate adrenergic synapses, can cause anxiety (see Chapter 12).

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. Just inside the skull, above the medulla, is a structure known as the *cerebellum*. The cerebellum functions as part of the motor system. Voluntary actions are initiated and controlled by an area of the cortex (discussed later) higher up in the brain, known as the *motor cortex*. Cell bodies in the motor cortex send axons directly to the spinal cord through fiber bundles that travel through the brain stem. There is, however, much more to the motor system than this. Signals from the cortex to the muscles are refined and modified by two other locations in the brain: the *basal ganglia* and the cerebellum. The cerebellum receives direct input from the motor cortex and from the muscles themselves via the spinal cord. It compares these two signals and modifies the output of the cortex both by direct actions on its signals as they pass through the brain stem and by fibers connected back to the cortex. These feedback loops make possible smooth and accurate muscle movements. Another function of the cerebellum is control of the movement of the eye from one fixation point to

another. The cerebellum also seems to be involved in learning.

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.

Basal Ganglia. The basal ganglia, located just under the cortex, are important in controlling voluntary movement. Although they contain several nuclei, in a broad sense the basal ganglia can be divided into an input side and an output side. The *striatum* is the input side; it receives axons from the cortex and *thalamus*. The striatum includes the *caudate nucleus* and *putamen*. Projections from the striatum are sent to the *globus pallidus* (or *pallidum*), which is the output side of the basal ganglia. The globus pallidus sends projections back to the cortex via the thalamus. Together, the basal ganglia, the thalamus, and the cortex make up the "motor loop" and control all voluntary movement.

Parkinson's disease is a result of a malfunction of the basal ganglia. People suffering from Parkinson's disease have tremors, rigidity in the limbs, and difficulty initiating movement. It has been demonstrated that Parkinson's is caused by a depletion of DA in the synapses of axons that terminate in the basal ganglia from a center known as the *substantia nigra*. This pathway is known as the *nigrostriatal system*. In many people, the symptoms of Parkinson's disease can be alleviated if the patient is given L-dopa, the metabolic precursor of DA. The L-dopa is absorbed into the brain and transformed into DA, 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 13).

The system that directly connects the motor cortex to the muscles is called the *pyramidal motor system*; consequently, the system involving the basal ganglia is sometimes called the *extrapyramidal motor system*.

In addition to motor control, the basal ganglia have other functions. They include control of eye movement, memory for locations in space, and some thought processes.

Periaqueductal Gray. Another system that runs through the central part of the brain is the *periaqueductal gray* or *central gray*. It has two functions of interest. The first is involved in the perception of pain. The periaqueductal gray serves as one of several relays for axons that carry pain signals from the dorsal horn of the spinal cord to the cortex. This area is rich in receptor sites for opiate drugs (e.g., morphine) and their endogenous counterparts, endorphins and enkephalins. These neurons send axons to the spinal cord, where they inhibit the neurons that convey pain signals from the body to higher levels of the brain. They do so both by direct inhibition and by stimulating other neurons that release endogenous opiates in the spinal cord. Thus, opiate drugs can block pain by stimulating cells in the periaqueductal gray and the spinal cord.

Also located in the periaqueductal gray 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 periaqueductal gray also receives input from the *amygdala*, a center that mediates fear and fear conditioning.

Limbic System. Just under the cortex is a series of interconnected nuclei known as the *limbic system*. Among other complex functions, the structures in the limbic system are involved in the control of motivations and emotions and seem to be the site of action of many drugs. One of the more complex structures in the limbic system is the *hypothalamus*. Lesions in specific parts of the hypothalamus can either induce excessive eating or drinking or abolish eating or drinking in experimental animals.

Some reinforcement or pleasure centers are also located in the hypothalamus. Humans and nonhumans will learn to press levers or engage in activities that are followed by electrical stimulation in these areas of the brain. It is thought that the reinforcement centers are stimulated 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. They have been called *pleasure centers* because humans sometimes report experiencing pleasure when these areas of the brain are stimulated electrically.

Many reinforcement centers of the brain are associated with the fiber tract called the *medial forebrain bundle*, which carries axons that run in both directions between lower centers in the brain and the hypothalamus and other limbic system structures.

One important reinforcement system, the *mesolimbic dopamine system*, has been identified as a fiber tract whose cell bodies are located in the *ventral tegmental area* (VTA) in the midbrain. The axons of these neurons run through the medial forebrain bundle and terminate in synapses in the limbic system, forebrain, and other structures. In the limbic system, many fibers from the VTA have synapses in the *nucleus accumbens*. Because these fibers use DA as a neurotransmitter and some are known to have receptor sites for morphine-like transmitters on their cell bodies in the VTA, drugs like amphetamine, cocaine, and morphine can stimulate them. This stimulation is probably the source of the *rushes* or intense feelings of pleasure that these drugs cause as well as the powerful tendency to repeat actions that lead to the administration of the drug (see Chapter 5). Malfunctions of the mesolimbic dopamine system also appear to be an important cause of schizophrenia (see Chapter 13).

The *hippocampus* is a large limbic structure that has been implicated in learning and memory. Removal of the hippocampus in humans (as was done years ago to treat epilepsy) causes amnesia. In rats, the hippocampus is important for spatial memory, and destruction of the hippocampus will prevent an animal from learning even a very simple maze consisting of an open field with no walls. 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 state dependency and long-term effects rather than acute effects. Place preference, created by associating a place with a drug (discussed in Chapter 5), is also probably mediated, at least in part, by the hippocampus.

Other limbic system structures include the amygdala and the *septum*. Among other connections, these centers receive serotonergic input from the Raphé nuclei. Lesions in the amygdala cause normally aggressive experimental animals to become calm and placid, but when the amygdala is stimulated, animals become aggressive and attack other animals. The amygdala also is active in fear and fear conditioning and is known to be active when people are afraid or have panic attacks. Lesions in the septum also cause emotional changes.

Although it is not known how drugs affect neurotransmitters in the limbic system, it appears that many benzodiazepine receptors are located in this region. 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* makes up the uppermost surface of the brain and virtually covers the rest of the brain. It is convoluted and gives the brain the appearance of a walnut. Because of its convolutions, most of the cortex cannot be seen. If it were flattened out, it would cover an area of 2.5 square feet.

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 prominent excitatory and inhibitory transmitters. Dissociative anesthetics like PCP and ketamine (see Chapter 16) are known to act at these NDMA receptors for glutamate, and

these drugs probably have their effects directly on the cortex.

One of the functions of the cortex is to handle the integration of sensory information. Information from each sense is projected to a different part of the cortex, where it is analyzed. Visual information is processed in the *visual cortex* at the back of the brain, and hearing is processed in the *temporal lobes*, as in language and speech. The *somatosensory cortex* handles sensory input from the body. The motor cortex is the area that is responsible for voluntary motor control and is located close to the somatosensory cortex. The motor cortex sends axons directly to the interneurons in the spinal cord that control the motor neurons and, consequently, the muscles (pyramidal motor system). Other axons from this area go to the basal ganglia and the cerebellum, which modify the direct output of the motor cortex and coordinate bodily movement (extrapyramidal motor system). Many of these areas of the cortex are shown in Figure 4-12.

While sensory and motor functions are handled by the central and posterior parts of the cortex, higher mental processes of thought and cognition are carried out in areas of the *frontal cortex* and the *prefrontal cortex*. The frontal cortex monitors the relationship between stimuli and reinforcer availability (including cues that predict the availability of drugs), provides inhibition or control over actions, and appears to regulate expression of emotional behavior. Located ventral to (below) the frontal cortex is the *orbitofrontal cortex*, which is involved in the learning and relearning of stimulus–reward associations and in behavioral control following rewarding or punishing feedback. The prefrontal cortex is the most rostral (toward the front) region of the cortex and is involved in working memory functions, including directing attention, decision making, task switching, deductive reasoning, planning, judgment, and memorization. The *dorsolateral prefrontal cortex* (higher and to the side) has been implicated in the representation, manipulation, and maintenance of attentional demands of a task. The *anterior cingulate* is part of the medial prefrontal cortex that is thought to mediate attention, response competition and selection, suppression of prepotent response tendencies, conditioned drug seeking, and craving.

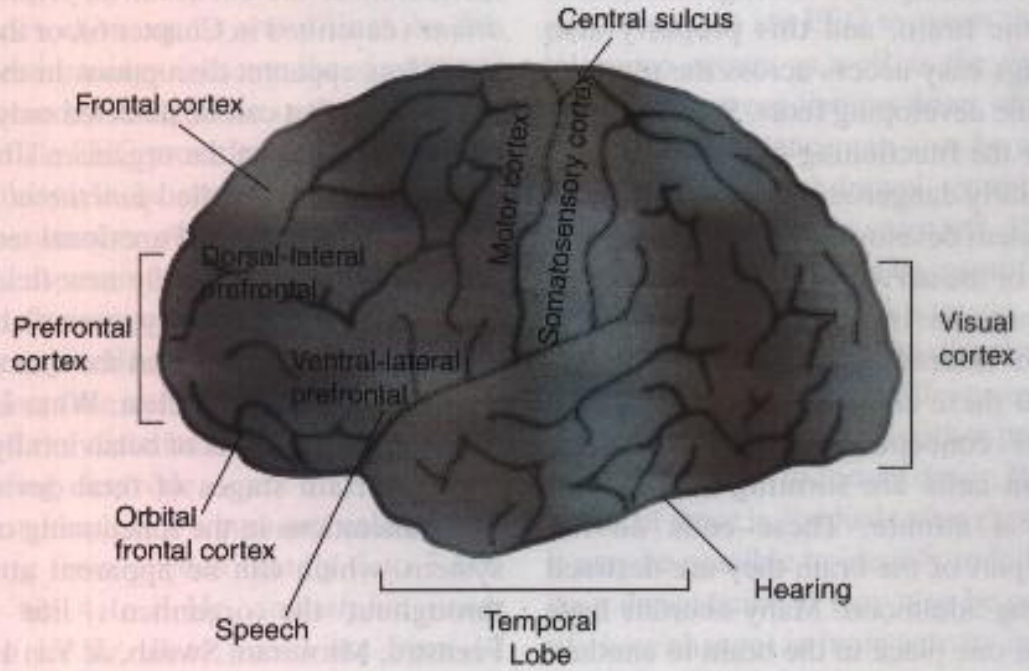

Figure 4-12 The cortex showing the major areas.

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

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 a 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. Most functional teratology research has been done on laboratory animals, and the exact significance for humans is still not clear. 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, Feenstra, Mirmiran, Swaab, & Van Haaren, 1988; Spear, 1997).

BRAIN IMAGING OF DRUG EFFECTS

Electroencephalography and Event-Related Potentials

Electroencephalography. In Chapter 2, we discussed how changes in level of arousal, from alertness to sleep, correspond to variations in brain wave activity. These changes are measured using a device called an *electroencephalograph* (EEG). Invented in 1929 by a German neuropsychiatrist named Hans Berger, the EEG is the oldest technique used to monitor brain activity.

The EEG works by measuring electrical activity originating in the cerebral cortex and subcortical nuclei. Generally, 21 electrodes are adhered to the scalp at specific locations that are determined using standard landmarks on the skull, and a reference electrode is attached to a neutral part of the body, usually the earlobe or cheek, where there is very little electrical activity. This electrode provides an electrically neutral point against which to measure the electrical potential differences at the other 21 electrodes. The potential differences between the points on the scalp and the neutral part of the body are amplified and recorded by pens on a roll of paper that moves at a constant rate. The changes in the potential detected by these electrodes show up as wavy lines on the paper, and these tracings indicate the simultaneous firing of neurons in the brain in the vicinity of the electrode. The EEG provides a direct measure of brain activity. It is analyzed in terms of *frequency* (the number of oscillations or waves per second, measured in hertz [Hz]) and *amplitude* (or the magnitude of waves in millivolts). Frequency reflects the rate of firing, and amplitude reflects the number of neurons firing in synchrony and the distance between the neurons and the recording electrode.

The slowest-frequency waves are called *delta waves*, ranging from approximately 1 to 3 Hz. *Theta waves* are 4 to 8 Hz, and *alpha waves* are from 8 to 13 Hz. *Beta waves* are from 12 to 35 Hz.

EEG is a very useful tool in psychopharmacology. In addition to being a direct measure of arousal, EEG changes can also be correlated with changes in subjective state or mood. By asking participants to report their mood while under the influence of a particular drug, their subjective state can be correlated with EEG recordings.

EEG recordings can also be used to compare alterations in brain activity during a drug-free baseline measure or in a control group versus participants under the influence of a particular drug. Such alterations may include the appearance of a new waveform that differs from that of the control state, spikes in amplitude of waveforms (characteristic of seizure activity), or stabilization of normal waveform fluctuations that occur between varying levels of arousal.

Classification of newly developed drugs can also be accomplished using EEG by comparing electrophysiological characteristics of known drugs and categorizing new drugs according to similarities in frequency and amplitude of waveforms. Drug tolerance and drug dependence (discussed in Chapter 3) can also be quantified by assessing changes in EEG recordings over repeated sessions. Decreases in drug-induced changes in the amplitude or frequency of EEG waves across repeated drug sessions indicate tolerance to the neurophysiological effects of a drug. Similarly, researchers can use EEG to assess the rate at which tolerance occurs as well as the degree of cross-tolerance between various drugs of the same class. Physical dependence can also be assessed by the appearance of withdrawal symptoms once the effects of a drug have worn off. Physical dependence, like tolerance, can be quantified by correlating EEG recordings with somatic and autonomic withdrawal symptoms. Finally, there is evidence that the EEG can detect differences in brain wave patterns between people with a predisposition to become addicted to certain drugs. By analyzing the EEGs of these individuals after exposure to a drug, it may be possible to identify individuals at risk of drug dependence. It may also be possible to identify how changes in brain activity in high-risk individuals can cause addiction to certain drugs.

Event-Related Potentials. To assess genetic vulnerabilities to drug addiction, researchers most commonly analyze *evoked potentials*, also referred to as *event-related potentials* (ERP), within an EEG paradigm. Commonly occurring events, such as visual or auditory stimuli presented by an experimenter, evoke characteristic deflections in the waveform being plotted on the EEG recording. An unexpected stimulus evokes a very different ERP with a characteristic positive deflection in amplitude at approximately 300 milliseconds (ms) but ranging from 250 to 500 ms following stimulus presentation. This ERP is known as the *P300* (a positive deflection at approximately 300 ms post-stimulus). The paradigm used to evoke the P300 is called the *oddball paradigm*, in which a participant is presented with two stimuli that differ along some dimension, such as the color of visual stimuli or the tone of auditory stimuli. One of these stimuli is rarely presented (the low-probability stimulus), whereas the other occurs frequently (the high-probability stimulus). The participant is instructed to ignore the high-probability stimulus and to attend only to the low-probability stimulus (the oddball). Presentation of the oddball evokes the P300 potential. The amplitude of the P300 provides an index of the amount of cognitive energy or resources the participant is devoting to perception of the stimulus. Decreases in P300 amplitude, therefore, indicate a reduced capacity or an impairment in the ability to pay attention to the stimulus. The latency of the P300 (i.e., the amount of time that elapses between presentation of the oddball and the occurrence of the P300 potential) provides an index of the time required for the participant to evaluate and recognize the stimulus as the oddball. Longer P300 latencies, therefore, indicate that the participant needs more time to process the stimulus. There is some evidence that the P300 wave is different in those who have a high genetic susceptibility to become an alcoholic.

The P300 is also useful in assessing the acute effects and duration of action of different classes of drugs on participants' cognitive capacity. These measures can be more sensitive than behavioral or neuropsychological assessments and are useful in discovering some of the more subtle impairments in the cognitive processing of events. ERP can also be used to measure tolerance and dependence in drug-using participants. Intoxicated participants with a history of drug abuse often display P300 amplitudes and latencies similar to control participants who are naive to the particular drug, This suggests that the brain of a drug abuser can compensate for the effects of the drug (i.e., that the participant has developed tolerance to the drug-induced cognitive impairments). When the same participants stop using the drug, however, reductions in P300 amplitude and increases in latency appear, suggesting the development of drug dependence.

Problems with EEG and ERP. Both EEG and ERP are useful techniques that continue to inform researchers of the effects of drug intoxication. These techniques are extremely reliable when testing conditions are strictly maintained but are sensitive to factors such as time of day, season of the year, age of the participant, and the recency of food intake. These factors must, therefore, be carefully controlled when performing EEG or ERP techniques. It has been suggested that EEG and ERP have limited diagnostic ability given that the distinctiveness of drug effects can be very small. For example, increases in alpha activity is common to many classes of drugs and is similarly observed in participants practicing transcendental meditation. Similarly, decreases in P300 amplitude that indicate drug withdrawal are also evident in individuals diagnosed with dementia, schizophrenia, depression, and borderline personality disorder. These similarities could possibly lead to misinterpretation of EEG or ERP data because these changes in brain activity may be caused by some factor other than the drug effect under investigation.

Positron Emission Techniques

Positron Emission Tomography. *Positron emission tomography* (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 that is 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 such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are short lived, with half-lives ranging from 2 to 110 minutes, and decay by emitting positrons. The emitted positrons are antimatter that travel a distance of less than 1 mm before meeting an electron, which is matter. As a result, they annihilate each other, and this produces high-energy *gamma rays* that pass out of the brain in exactly opposite directions, at which point they are detected by special cameras.

Radiation detector cameras used in PET imaging are comprised of a ring of *scintillator crystals* that fluoresce momentarily when struck by high-energy gamma rays. Bursts of light produced by gamma rays that hit the ring of crystals at exactly 180 degrees apart and at exactly the same time are detected and amplified by photomultiplier tubes. This information is then transmitted to a computer. Gamma rays detected even slightly off of 180 degrees apart or at a difference of nanoseconds are ignored. 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, by measuring changes in metabolic activity and blood flow to these areas. Using the glucose-mimicking radiotracer 2-deoxy-2-[^{18}F]fluoro-D-glucose (abbreviated ^{18}FDG), changes that occur in regional glucose metabolism as neurons are activated and deactivated can be traced to particular brain regions that are active during drug craving, and changes in 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 radio-label 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, such as EEG, 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. Ideally, a PET scanner would be able to isolate the location of gamma ray emission within 0.5 mm, something that has not yet been achieved. The most state-of-the-art PET scanners achieve a reconstructed image resolution of 4 to 4.5 mm because of the necessary size of scintillator crystals, which measure approximately 3 to 4 mm in width. PET scanning also poses a health risk in that radioactive agents are administered into a patient's body. The total dose of radiation during a scanning session is usually 7 millisieverts (mSv), comparable to 70 chest X-rays. This amount seems relatively large. However, when we consider that 7 mSv is approximately equal to 1 year of radiation exposure for the aircrew of a commercial jetliner, the risk can be put in better perspective. Nevertheless, the health costs and benefits of radiation exposure inherent in conducting 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 (at a price of $2.5 million to $4.6 million, plus an additional $1 million setup cost) 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 that detect rays that project from the brain in parallel. This information is then amplified by photomultiplier tubes and transmitted to a computer. Nonparallel gamma rays are undetected and are absorbed by the lead. Compared to PET scanning, SPECT uses radioisotopes that are much longer lasting, 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 coincident detection of gamma rays in PET, detection of parallel rays in 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) 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. Although they are aligned with the magnetic field, this does not mean that hydrogen nuclei 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. Two units of measurement are commonly used to describe the intensity of a magnetic field within the bore: *gauss* and *tesla* (where 1 tesla = 10,000 gauss). The magnetic pull of the earth is 0.5 gauss, whereas the magnetic field that runs through the bore of the MRI machine measures 1.5 to 2.0 tesla, or 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*. It consists of many coils of wire, wrapped around the bore of the magnet, that conduct an electric current and create the magnetic field. You can imagine that the amount of electricity required to generate and maintain a magnetic field of 1.5 tesla would be prohibitively expensive. To overcome this obstacle, the coils of wire are bathed in liquid helium, bringing the temperature of the wire to more than 452 degrees Fahrenheit (269 degrees Celsius) below zero. This extreme cold eliminates the electrical resistance of the wire and makes using the MRI scanner much more economically feasible.

Once the participant is placed within the *isocenter* (exact 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*. For the hydrogen proton, the Larmor frequency in a magnetic field of 1.5 tesla is 63.9 megahertz (MHz), where 1 MHz equals 1 million Hz, or 1 million cycles per second. 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 their 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've 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've ever rubbed a moist fingertip around the rim of a crystal wine glass, you'll 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 a 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 coils of 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's 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 coil of 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 percent 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.

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 or mood 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 data acquisition. 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 through the coil, a gradient magnet, much weaker in intensity compared to the superconducting magnet (ranging in strength from 180 to 270 gauss), 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 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 certain individuals. People weighing more than 134 kg (295 pounds) cannot be handled by most MRI machines, although newer machines are being constructed to accommodate heavier individuals. Furthermore, a significant number of participants (approximately 10 percent) also report feeling high levels of discomfort or anxiety, with 1 percent of participants exhibiting severe claustrophobic or panic attacks inside the small confinement of the MRI bore. 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 (e.g., newly inserted staples or fragments of metal in the eye, which does not form 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 life-monitoring equipment that contain metal cannot enter the MRI room.

fMRI is also affected by issues that do not apply to MRI. Changes in blood flow and volume measured by fMRI BOLD imaging are interpreted to result from experimentally controlled stimuli or induction of a particular mood or emotional state. However, activation of certain brain regions could represent noise in the data created by 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 4-2 provides a comparison of the advantages and disadvantages of these brain imaging techniques, and Color Plates A to D give examples of the images they can produce.

TABLE 4-2 Summary of the Advantages and Disadvantages of Different Brain Imaging Techniques

EEG and ERP

Advantages

- Provides a direct measure of brain activity and thereby records timing of activity very precisely
- Noninvasive
- Inexpensive

Disadvantages

- Poor spatial resolution
- Does not directly record interior of brain
- Susceptible to noise from head movements
- Susceptible to variations in testing condition

PET and SPECT

Advantages

- Ability to radio-label an almost infinite number of naturally occurring and synthetic chemicals
- Can be completed very quickly
- Good spatial resolution
- Can image any region of the brain

Disadvantages

- Uses radioactive chemicals
- High cost of cyclotron, scanner, and numerous medical personnel
- Provides an indirect measure of brain function, thereby reducing temporal resolution

MRI and fMRI

Advantages

- Superior spatial resolution
- Can be completed very quickly
- Can image any region of the brain
- Thought to be noninvasive

Disadvantages

- Cannot accommodate individuals with metallic implants
- Increases in regional blood flow may be altered by mood or even daydreaming
- Only a moderate level of temporal resolution in fMRI

CHAPTER SUMMARY

- Nervous tissue is made up of nerve cells called neurons, which are excitable. Their excitability depends on the breakdown of the resting potential, which is the difference in electrical charge between the inside and the outside of the membrane of each cell. The resting potential is a result of uneven distribution of ions on either side of the membrane.
- There are more positively charged ions outside the neuron than inside. This uneven distribution of ions is created by the K^+/Na^+ ion pump. Ion channels permit the flow of specific ions across the cell membrane at a specific rate. Some ion channels may be opened either by the presence of a chemical or by a change in the resting potential.
- When the cell membrane on an axon is depolarized to a certain point (called the threshold), ion channels open, and the resting potential can no longer be maintained and breaks down. This condition is called an action potential. The resting potential then quickly restores itself.
- Action potentials are not generated when the resting potential of the dendrites and cell body are depolarized. Instead, an excitatory postsynaptic potential is generated that passively spreads over the surface of the membrane.
- Action potentials move away from the cell body, along the cell's axon, to synapses very near the cell body and dendrites of another neuron. They stimulate the second neuron by releasing a chemical called a neurotransmitter into the tiny gap between the cells.
- The transmitter interacts with receptor sites on the membrane of the postsynaptic cell. Depending on the nature of the receptor site, the effect will be to cause either depolarization (an increase in the excitability of the postsynaptic cell called an EPSP) or hyperpolarization (a decrease in the excitability of the postsynaptic cell called an IPSP).
- Neurotransmitters may cause other longer-acting effects on the postsynaptic cell by causing the release of second messengers and by modifying the expression of genes that create receptor sites and ion channels.
- Production of action potentials at a cell's axon depends on the sum of the excitation and inhibition at all the synapses on its dendrites and cell body at any given time.
- Autoreceptors are located on the presynaptic membrane and regulate the concentration of neurotransmitter, and sometimes the postsynaptic cell and other nearby cells release chemical messengers that can modify the release of neurotransmitters.
- Acetylcholine, epinephrine, norepinephrine, dopamine, serotonin, GABA, glutamate, and some peptides can act as neurotransmitters. Some can also act as neuromodulators and neurohormones.
- Drugs have their effect by interfering with some aspect of synaptic transmission. Among other things, they can block receptor sites, stimulate receptor sites, block the metabolism or reuptake of neurotransmitters, and interfere with second messengers.
- Each neurotransmitter can have a number of different receptor sites and the effect of the neurotransmitter is determined by the type of neurotransmitter.
- The nervous system has two major divisions. The central nervous system is made up of all the neurons in the brain and spinal cord; all other neurons make up the peripheral nervous system, which is further divided into the somatic and the autonomic nervous systems. The autonomic nervous system also has two parts: the parasympathetic system, which controls the vegetative involuntary functions of the body on an ongoing basis, and the sympathetic nervous system, which prepares the body for the sudden expenditure of energy, or the fight-or-flight response.
- The central part of the spinal cord is gray matter (cell bodies) surrounded by white matter (myelinated axons), which consists of fiber bundles of axons running to and from the brain.
- The medulla, located at the base of the brain, controls breathing and other autonomic functions. The cerebellum controls the smooth movement of muscles. The reticular activating system controls arousal. The Raphé system, conversely, is important in causing sleep.
- The locus coeruleus is a center in the lower brain that sends norepinephrine projections to the limbic system and the cortex. It is associated with anxiety and panic, and it seems to be responsible for withdrawal from opiates. The central gray is important in mediating responses to pain. It contains opiate receptors and is one site of action for the analgesic effects of the opiates.

- The basal ganglia form part of the extrapyramidal motor system. The striatum is the input side of the basal ganglia, and the pallidum is the output side. Together with the cortex, they form a loop that controls motor activity.
- The limbic system controls emotions and motivation. It is made up of a number of centers, including the hypothalamus, which controls eating and drinking and contains reinforcement centers.
- The nucleus accumbens receives dopaminergic input from the ventral tegmental area. This is the mesolimbic dopamine system, which is important in motivation and reinforcement of natural motivations and drug self-administration.
- The cortex makes up the uppermost surface of the brain and receives direct input from many senses. It also has direct control over voluntary movement. The cortex contains centers that permit us to recognize speech and written language and enable us to speak and write.
- The frontal and prefrontal cortex are important in thinking and decision making, attention, and working memory.
- The development of the brain is a complex process that involves the formation, migration, and connection of billions of neurons. Because migration and synapse formation are controlled by substances that resemble neurotransmitters, drugs that affect the functioning of the central nervous system can be teratogens and can severely disrupt the development of the nervous system.
- A number of neuroimaging techniques are now widely used to study the effects of drugs. These include EEG and ERP, PET, and its variation SPECT, and MRI and fMRI.