The monoamines are produced by several systems of neurons in the brain. Most of these systems consist of a relatively small number of cell bodies located in the brain stem, whose axons branch repeatedly and give rise to an enormous number of terminal buttons distributed throughout many regions of the brain. Monoaminergic neurons thus serve to modulate the function of widespread regions of the brain, increasing or decreasing the activities of particular brain functions.

Dopamine

The first catecholamine in Table 4.1, dopamine (DA), produces both excitatory and inhibitory postsynaptic potentials, depending on the postsynaptic receptor. Dopamine is one of the more interesting neurotransmitters because it has been implicated in several important functions, including movement, attention, learning, and the reinforcing effects of drugs that people tend to abuse; therefore, it is discussed in Chapters 8, 9, 13, and 18.

The synthesis of the catecholamines is somewhat more complicated than that of ACh, but each step is a simple one. The precursor molecule is modified slightly, step by step, until it achieves its final shape. Each step is controlled by a different enzyme, which causes a small part to be added or taken off. The precursor for the two major catecholamine neurotransmitters (dopamine and norepinephrine) is tyrosine, an essential amino acid that we must obtain from our diet. Tyrosine receives a hydroxyl group (OH—an oxygen atom and a hydrogen atom) and becomes L-DOPA (1,3,4-dihydroxyphenylalanine). The enzyme that adds the hydroxyl group is called tyrosine hydroxylase. L-DOPA then loses a carboxyl group (COOH—one carbon atom, two oxygen atoms, and one hydrogen atom) through the activity of the enzyme DOPA decarboxylase and becomes dopamine. Finally, the enzyme dopamine β-hydroxylase attaches a hydroxyl group to dopamine, which becomes norepinephrine. These reactions are shown in Figure 4.12.

The brain contains several systems of dopaminergic neurons. The three most important of these originate in the midbrain: in the substantia nigra and in the ventral tegmental area. (The substantia nigra was shown in Fig-

The Monoamines

Dopamine, norepinephrine, epinephrine, and serotonin are four chemicals that belong to a family of compounds called monoamines. Because the molecular structures of these substances are similar, some drugs affect the activity of all of them to some degree. The first three—dopamine, norepinephrine, and epinephrine—belong to a subclass of monoamines called catecholamines. It is worthwhile learning the terms in Table 4.1, because they will be used many times throughout the rest of this book. (See Table 4.1.)

curare (kuhr ree) A drug that blocks nicotinic acetylcholine receptors.

monoamine (mahm o o men) A class of amines that includes indolamines such as serotonin and catecholamines such as dopamine, norepinephrine, and epinephrine.

catcholamine (kat a kohl a men) A class of amines that includes the neurotransmitters dopamine, norepinephrine, and epinephrine.

dopamine (DA) (dope a men) A neurotransmitter; one of the catecholamines.

L-DOPA (ell dope a) The levorotatory form of DOPA; the precursor of the catecholamines; often used to treat Parkinson’s disease because of its effect as a dopamine agonist.
solving. These three systems of dopaminergic neurons are shown in Figure 4.13.

Degeneration of dopaminergic neurons that connect the substantia nigra with the caudate nucleus causes Parkinson's disease, a movement disorder characterized by tremors, rigidity of the limbs, poor balance, and difficulty in initiating movements. The cell bodies of these neurons are located in a region of the brain called the substantia nigra ("black substance"). This region is normally stained black with melanin, the substance that gives color to skin. This compound is produced by the breakdown of dopamine. (The brain damage that causes Parkinson's disease was discovered by pathologists who observed that the substantia nigra of a deceased person who had had this disorder was pale rather than black.) People with Parkinson's disease are given L-DOPA, the precursor to dopamine. Although dopamine cannot cross the blood-brain barrier, L-DOPA can. Once L-DOPA reaches the brain, it is taken up by dopaminergic neurons and is converted to dopamine (step 1 of Figure 4.5). The increased synthesis of dopamine causes more dopamine to be released by the surviving dopaminergic neurons in patients with Parkinson's disease. As a consequence, the patients' symptoms are alleviated.

Another drug, AMPT (or α-methyl-p-tyrosine), inactivates tyrosine hydroxylase, the enzyme that converts tyrosine to L-DOPA (step 2 of Figure 4.5). Because this drug interferes with the synthesis of dopamine (and of norepinephrine, as well), it serves as a catecholamine antagonist. The drug is not normally used medically, but it has been used as a research tool in laboratory animals.

The drug reserpine prevents the storage of monoamines in synaptic vesicles by blocking the transporters in the membrane of vesicles of monoaminergic neurons (step 3 of Figure 4.5). Because the synaptic vesicles remain empty, no neurotransmitter is released when an action potential reaches the terminal button. Reserpine, then, is a monoamine antagonist. The drug, which comes from the root of a shrub, was discovered over

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**nigrostriatal system** (nigh groh stry ay tal) A system of neurons originating in the substantia nigra and terminating in the neostriatum (caudate nucleus and putamen).

**mesolimbic system** (mees al um bik) A system of dopaminergic neurons originating in the ventral tegmental area and terminating in the nucleus accumbens, amygdala, and hippocampus.

**mesocortical system** (mees ahr kor ti kul) A system of dopaminergic neurons originating in the ventral tegmental area and terminating in the prefrontal cortex.

**Parkinson's disease** A neurological disease characterized by tremors, rigidity of the limbs, poor balance, and difficulty in initiating movements; caused by degeneration of the nigrostriatal system.

**AMPT** A drug that blocks the activity of tyrosine hydroxylase and thus interferes with the synthesis of the catecholamines.

**reserpine** (ree sur pen) A drug that interferes with the storage of monoamines in synaptic vesicles.
three thousand years ago in India, where it was found to be useful in treating snakebite and seemed to have a calming effect. Pieces of the root are still sold in markets in rural areas of India. In Western medicine, reserpine was previously used to treat high blood pressure, but it has been replaced by drugs with fewer side effects.

Several different types of dopamine receptors have been identified, all metabotropic. Of these, two are the most common: D₁ receptors and D₂ receptors. It appears that D₁ receptors are exclusively postsynaptic, whereas D₂ receptors are found both presynaptically and postsynaptically in the brain. Stimulation of D₁ receptors increases the production of the second messenger cyclic AMP, whereas stimulation of D₂ receptors decreases it, as does stimulation of D₃ and D₄ receptors. Several drugs stimulate or block specific types of dopamine receptors.

Autoreceptors are found in the dendrites, soma, and terminal buttons of dopaminergic neurons. Activation of the autoreceptors in the dendritic and somatic membrane decreases neural firing by producing hyperpolarizations. The presynaptic autoreceptors located in the terminal buttons suppress the activity of the enzyme tyrosine hydroxylase and thus decrease the production of dopamine—and ultimately its release. Dopamine autoreceptors resemble D₂ receptors, but there seem to be some differences. For example, the drug apomorphine is a D₂ agonist, but it seems to have a greater affinity for presynaptic D₂ receptors than for postsynaptic D₂ receptors. A low dose of apomorphine acts as an antagonist, because it stimulates the presynaptic receptors and inhibits the production and release of dopamine. Higher doses begin to stimulate postsynaptic D₂ receptors, and the drug begins to act as a direct agonist. (See Figure 4.14.)

Several drugs inhibit the reuptake of dopamine, thus serving as potent dopamine agonists (step 10 of Figure 4.5). The best known of these drugs are amphetamine, cocaine, and methylphenidate. Amphetamine has an interesting effect: It causes the release of both dopamine and norepinephrine by causing the transporters for these neurotransmitters to run in reverse, propelling DA and NE into the synaptic cleft. Of course, this action also blocks reuptake of these neurotransmitters. Cocaine and methylphenidate simply block dopamine reuptake. Because cocaine also blocks voltage-dependent sodium channels, it is sometimes used as a topical anesthetic, especially in the form of eye droplets for eye surgery.

**Apomorphine** (ap o more feen) A drug that blocks dopamine autoreceptors at low doses; at higher doses, blocks postsynaptic receptors as well.

**Methylphenidate** (meth ul fen i date) A drug that inhibits the reuptake of dopamine.

**Monoamine Oxidase** (MAO) (mahn o a meen) A class of enzymes that destroy the monoamines: dopamine, norepinephrine, and serotonin.

**Deprenyl** (depp na nil) A drug that blocks the activity of MAO-B; acts as a dopamine agonist.

**Chlorpromazine** (klor prob ma seen) A drug that reduces the symptoms of schizophrenia by blocking dopamine D₂ receptors.
Methylphenidate (Ritalin) is used to treat children with attention deficit disorder.

The production of the catecholamines is regulated by an enzyme called monoamine oxidase (MAO). This enzyme is found within monoaminergic terminal buttons, where it destroys excessive amounts of neurotransmitter. A drug called deprenyl destroys the particular form of monoamine oxidase (MAO-B) that is found in dopaminergic terminal buttons. Because deprenyl prevents the destruction of dopamine, more dopamine is released when an action potential reaches the terminal button. Thus, deprenyl serves as a dopamine agonist. (See Figure 4.15.)

MAO is also found in the blood, where it deactivates amines that are present in foods such as chocolate and cheese; without such deactivation these amines could cause dangerous increases in blood pressure.

Dopamine has been implicated as a neurotransmitter that might be involved in schizophrenia, a serious mental disorder whose symptoms include hallucinations, delusions, and disruption of normal, logical thought processes. Drugs such as chlorpromazine, which block $D_2$
receptors, alleviate these symptoms (step 7 of Figure 4.5). Hence, investigators have speculated that schizophrenia is produced by overactivity of dopaminergic neurons. More recently discovered drugs—the so-called atypical antipsychotics—have more complicated actions, which are discussed in Chapter 16.

As we saw in the case reported at the beginning of this chapter, MPTP can damage the brain and cause the symptoms of Parkinson’s disease. This discovery galvanized researchers interested in this disease. (I recently checked PubMed, a Web site maintained by the U.S. National Institutes of Health, and found that 3,426 publications referred to MPTP.) The first step was to find out whether the drug would have the same effect in laboratory animals so that the details of the process could be studied. It did; Langston et al. (1984) found that injections of MPTP produced parkinsonian symptoms in squirrel monkeys and that these symptoms could be reduced by L-DOPA therapy. And just as the investigators had hoped, examination of the animals’ brains showed a selective loss of dopamine-secreting neurons in the substantia nigra.

It turns out that MPTP itself does not cause neural damage; instead, the drug is converted by an enzyme present in glial cells into another substance, MPP+. That chemical is taken up by dopamine-secreting neurons, by means of the reuptake mechanism that normally retrieves dopamine that is released by terminal buttons. MPP+ accumulates in mitochondria in these cells and blocks their ability to metabolize nutrients, thus killing the cells (Maret et al., 1990). The enzyme that converts MPTP into MPP+ is none other than monoamine oxidase (MAO), which, as you now know, is responsible for deactivating excess amounts of monoamines present in terminal buttons. Because pharmacologists had already developed MAO inhibitors, Langston and his colleagues decided to see whether one of these drugs (pargyline) would protect squirrel monkeys from the toxic effects of MPTP by preventing its conversion into MPP+ (Langston et al., 1984). It worked; when MAO was inhibited by pargyline, MPTP injections had no effects.

These results made researchers wonder whether MAO inhibitors might possibly protect against the degeneration of dopamine-secreting neurons in patients with Parkinson’s disease. No one thought that Parkinson’s disease was caused by MPP+, but perhaps some other toxins were involved. Epidemiologists have found that Parkinson’s disease is more common in highly industrialized countries, which suggests that environmental toxins produced in these societies may be responsible for the brain damage (Tanner, 1989; Veldman et al., 1998). Fortunately, several MAO inhibitors have been tested and approved for use in humans. One of them, deprenyl, was tested and appeared to slow down the progression of neurological symptoms (Tetrud and Langston, 1989).