

Neurotransmitters and Their Receptors

Overview

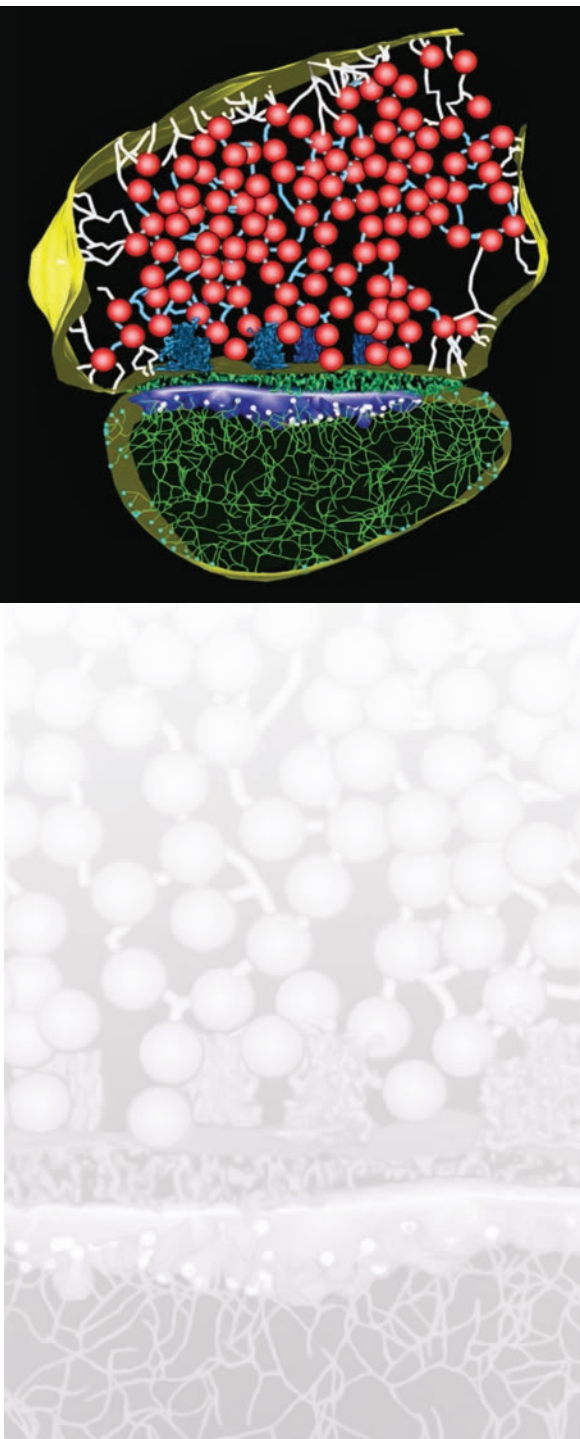
NEURONS IN THE HUMAN BRAIN COMMUNICATE with one another, for the most part, by releasing chemical messengers called neurotransmitters. A large number of neurotransmitters are known. The main excitatory neurotransmitter in the brain is the amino acid glutamate, while the main inhibitory neurotransmitter is γ -aminobutyric acid (GABA). These and all other neurotransmitters evoke postsynaptic responses by binding to and activating neurotransmitter receptors. Most neurotransmitters are capable of activating several different receptors, yielding many possible modes of synaptic signaling. After activating their postsynaptic receptors, neurotransmitters are removed from the synaptic cleft by neurotransmitter transporters or by degradative enzymes. Abnormalities in the function of neurotransmitter systems contribute to a wide range of neurological and psychiatric disorders; thus, many neuropharmacological therapies are based on drugs that affect neurotransmitters, their receptors, or the mechanisms responsible for removing neurotransmitters from the synaptic cleft.

Categories of Neurotransmitters

There are more than 100 different neurotransmitters. This large number of transmitters allows for tremendous diversity in chemical signaling between neurons. It is useful to separate this panoply of transmitters into two broad categories based simply on size (Figure 6.1). **Neuropeptides**, also called **peptide neurotransmitters**, are relatively large transmitter molecules composed of 3 to 36 amino acids. Individual amino acids, such as glutamate and GABA, as well as the transmitters acetylcholine, serotonin, and histamine, are much smaller than neuropeptides and have therefore come to be called **small-molecule neurotransmitters**. Within the category of small-molecule neurotransmitters, the **biogenic amines** (dopamine, norepinephrine, epinephrine, serotonin, and histamine) are often discussed separately because of their similar chemical properties and postsynaptic actions. The particulars of synthesis, packaging, release, and removal differ for each neurotransmitter (Table 6.1). This chapter describes some of the main features of these transmitters and their postsynaptic receptors.

Acetylcholine

As mentioned in Chapter 5, acetylcholine (ACh) was the first substance identified as a neurotransmitter. In addition to its function as the neurotransmitter at skeletal neuromuscular junctions (see Chapter 5), as well as at the neuromuscular synapse between the vagus nerve and cardiac muscle fibers, ACh serves as a transmitter at



enabling Cl^- and other permeant anions to flow through the pore formed by the transmembrane domains of the five subunits (see Figure 6.13, right). This Cl^- flux inhibits the postsynaptic neuron. Blocking these receptors, by binding of strychnine to the same ligand-binding site, closes the pore (see Figure 6.13, left).

Biogenic Amines

Biogenic amine neurotransmitters regulate many brain functions and are also active in the peripheral nervous system. Because biogenic amines are implicated in such a wide variety of behaviors (ranging from central homeostatic functions to cognitive phenomena such as attention), it is not surprising that defects in biogenic amine function are implicated in most psychiatric disorders. The pharmacology of amine synapses is critically important in psychotherapy, with drugs affecting the synthesis, receptor binding, or catabolism of these neurotransmitters being among the most important agents in the armamentarium of modern neuropharmacology (see Clinical Applications, Chapter 7). Many drugs of abuse also act on biogenic amine pathways.

There are five well-established biogenic amine neurotransmitters: the three **catecholamines**—**dopamine**, **norepinephrine (noradrenaline)**, and **epinephrine (adrenaline)**—and **histamine** and **serotonin** (see Figure 6.1). All the catecholamines (so named because they share the catechol moiety) are derived from a common precursor, the amino acid tyrosine (Figure 6.14). The first step in catecholamine synthesis is catalyzed by tyrosine hydroxylase in a reaction requiring oxygen as a co-substrate and tetrahydrobiopterin as a co-factor to synthesize dihydroxyphenylalanine (DOPA). Histamine and serotonin are synthesized via other routes, as described below.

- **Dopamine** is present in several brain regions (Figure 6.15A), although the major dopamine-containing area of the brain is the corpus striatum, which receives major input from the substantia nigra and plays an essential role in the coordination of body movements. In Parkinson's disease, for instance, the dopaminergic neurons of the substantia nigra degenerate, leading to a characteristic motor dysfunction (see Chapter 18). Dopamine is also believed to be involved in motivation, reward, and reinforcement (see Chapter 31); many drugs of abuse work by affecting dopaminergic circuitry in the CNS. In addition to these roles in the CNS, dopamine also plays a poorly understood role in some sympathetic ganglia.

Dopamine is produced by the action of DOPA decarboxylase on DOPA (see Figure 6.14). Following its synthesis in the cytoplasm of presynaptic terminals, dopamine is loaded into synaptic vesicles via a vesicular monoamine transporter (VMAT). Dopamine action in the synaptic cleft is terminated by reuptake of dopamine into nerve terminals or surrounding glial cells by a Na^+ -dependent

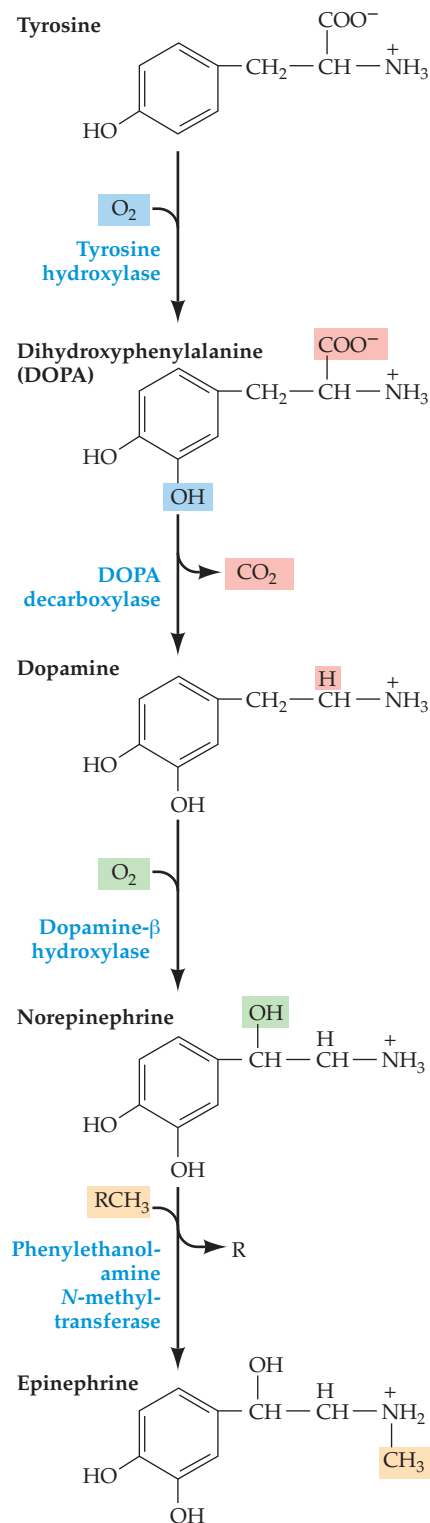


FIGURE 6.14 The biosynthetic pathway for the catecholamine neurotransmitters. The amino acid tyrosine is the precursor for all three catecholamines. The first step in this reaction pathway, catalyzed by tyrosine hydroxylase, is rate-limiting.

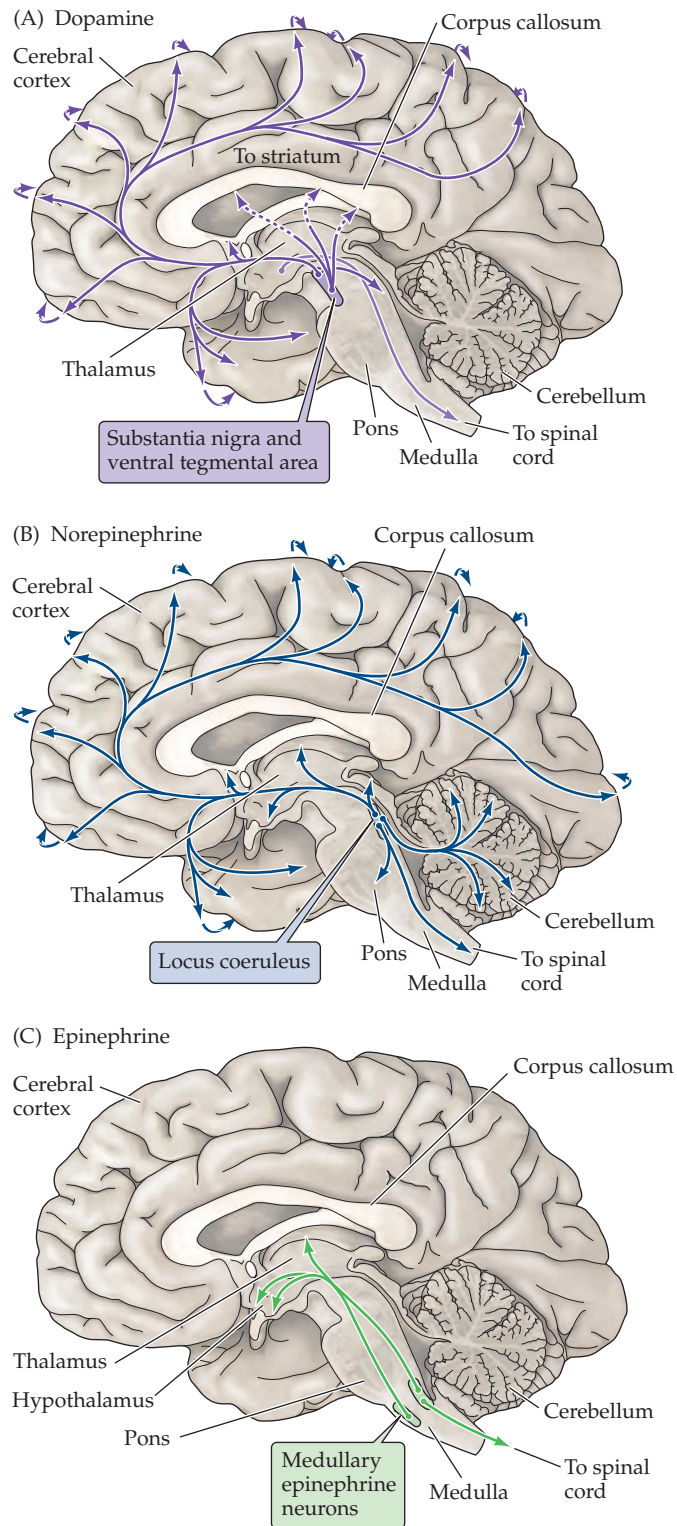


FIGURE 6.15 The distribution of catecholamine neurotransmitters in the human brain. Shown are neurons and their projections (arrows) that contain catecholamine neurotransmitters. Curved arrows along the perimeter of the cortex indicate the innervation of lateral cortical regions not shown in this midsagittal plane of section.

dopamine co-transporter, termed DAT. Cocaine apparently produces its psychotropic effects by inhibiting DAT, thereby increasing dopamine concentrations in the synaptic cleft. Amphetamine, another addictive drug, also inhibits DAT as well as the transporter for norepinephrine (see below). The two major enzymes involved in the catabolism of dopamine are monoamine oxidase (MAO) and catechol O-methyltransferase (COMT). Both neurons and glia contain mitochondrial MAO and cytoplasmic COMT. Inhibitors of these enzymes, such as phenelzine and tranylcypromine, are used clinically as antidepressants (see Clinical Applications, Chapter 7).

Once released, dopamine acts exclusively by activating G-protein-coupled receptors. One of these, the D3 dopamine receptor, is shown in Figure 6.16A. The monomeric structure of this receptor closely parallels that of other metabotropic receptors, such as the mACh receptor (see Figure 6.4A), except that its ligand-binding site is optimized for binding to dopamine. Most dopamine receptor subtypes (see Figure 6.4C) act by either activating or inhibiting adenylyl cyclase (see Chapter 7). Activation of these receptors generally contributes to complex behaviors; for example, administration of dopamine receptor agonists causes hyperactivity and repetitive, stereotyped behavior in laboratory animals. Activation of another type of dopamine receptor in the medulla inhibits vomiting. Thus, antagonists of these receptors are used as emetics to induce vomiting after poisoning or a drug overdose. Dopamine receptor antagonists can also elicit catalepsy, a state in which it is difficult to initiate voluntary motor movement, suggesting a basis for this aspect of some psychoses.

• *Norepinephrine* (also called noradrenaline) is used as a neurotransmitter in the locus coeruleus, a brainstem nucleus that projects diffusely to a variety of forebrain targets (Figure 6.15B) and influences sleep and wakefulness, arousal, attention, and feeding behavior. Perhaps the most prominent noradrenergic neurons are sympathetic ganglion cells, which employ norepinephrine as the major peripheral transmitter in this division of the visceral motor system (see Chapter 21).

Norepinephrine synthesis requires dopamine β -hydroxylase, which catalyzes the production of norepinephrine from dopamine (see Figure 6.14). Norepinephrine is then loaded into synaptic vesicles via the same VMAT involved in vesicular dopamine transport. Norepinephrine is cleared from the synaptic cleft by the norepinephrine transporter (NET), an Na^+ -dependent co-transporter that also is capable of taking up dopamine. As mentioned, NET is a molecular target of amphetamine, which acts as a stimulant by producing a net increase in the release of norepinephrine and dopamine. A mutation in the *NET* gene is a cause of orthostatic intolerance, a disorder that produces lightheadedness while standing up. Like dopamine, norepinephrine is degraded by MAO and COMT.

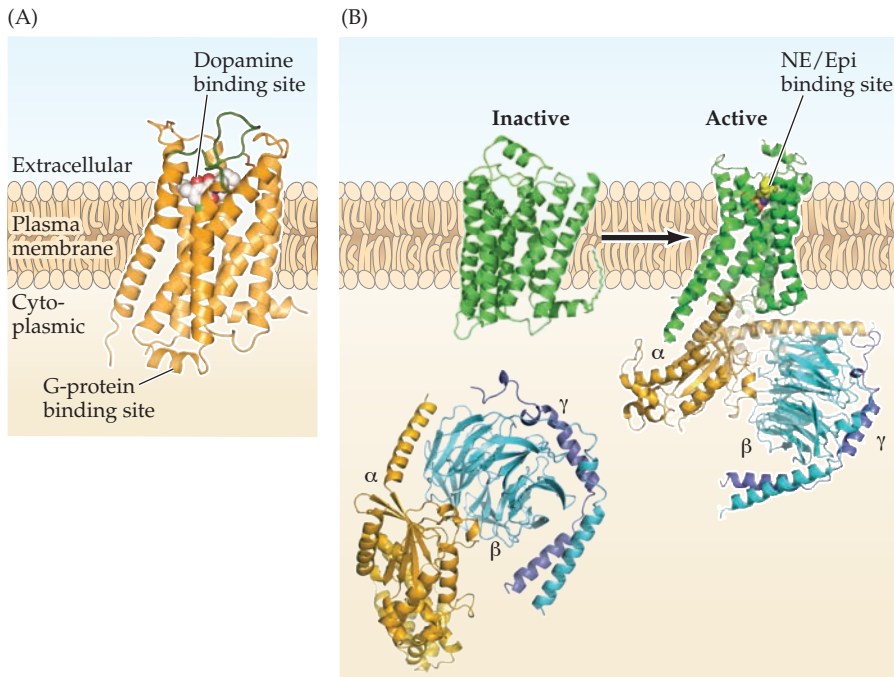


FIGURE 6.16 Metabotropic receptors for catecholamine neurotransmitters.

(A) Structure of the D3 dopamine receptor. Like all metabotropic receptors, the D3 receptor spans the plasma membrane seven times and has a cytoplasmic domain that binds to and activates G-proteins, as well as an extracellular domain that binds dopamine. (B) Structure of the β_2 -adrenergic receptor and its associated G-protein. (Left) In the absence of ligand, the cytoplasmic domain of the β_2 receptor is not bound to the G-protein (α , β , and γ subunits). (Right) Binding of ligand (β agonist, indicated by colored spheres) to the extracellular binding site for norepinephrine (NE) and epinephrine (Epi) causes the β_2 receptor to bind to the α subunit of the G-protein, which in turn induces a dramatic change in the structure of this subunit. (A from Chien et al., 2010; B from Rasmussen et al., 2007, 2011 and Betke et al., 2012.)

Both norepinephrine and epinephrine act on α - and β -adrenergic receptors (see Figure 6.4C). Both types of receptor are G-protein-coupled; in fact, the β -adrenergic receptor was the first identified metabotropic neurotransmitter receptor. As shown in Figure 6.16B, the structure of this receptor is very similar to that of other metabotropic receptors (such as the dopamine receptor in Figure 6.16A). Binding of norepinephrine or epinephrine causes small changes in the structure of this receptor, which permits the G-protein to bind (see Figure 6.16B, right). This, in turn, causes larger changes in the shape of the α subunit of the G-protein, the first step in a series of reactions that allow the G-protein to regulate intracellular signaling cascades (see Chapter 7).

Two subclasses of α -adrenergic receptors have been identified. Activation of α_1 receptors usually results in a slow depolarization linked to the inhibition of K^+ channels, while activation of α_2 receptors produces a slow hyperpolarization due to the activation of a different type of K^+ channel. There are three subtypes of β -adrenergic receptors, two of which are expressed in many types of neurons. Agonists and antagonists of adrenergic receptors, such as the β -blocker propranolol (Inderol), are used clinically for a variety of conditions ranging from cardiac arrhythmias to migraine headaches. However, most of the actions of these drugs are on smooth muscle receptors, particularly in the cardiovascular and respiratory systems (see Chapter 21).

- **Epinephrine** (also called adrenaline) is found in the brain at lower levels than the other catecholamines and also is present in fewer brain neurons than other catecholamines. Epinephrine-containing neurons in the CNS are primarily in the lateral tegmental system and in the

medulla and project to the hypothalamus and thalamus (Figure 6.15C). These epinephrine-secreting neurons regulate respiration and cardiac function.

The enzyme that synthesizes epinephrine, phenylethanolamine-*N*-methyltransferase (see Figure 6.14), is present only in epinephrine-secreting neurons. Otherwise, the metabolism of epinephrine is very similar to that of norepinephrine. Epinephrine is loaded into vesicles via the VMAT. No plasma membrane transporter specific for epinephrine has been identified, although the NET is capable of transporting epinephrine. As already noted, epinephrine acts on both α - and β -adrenergic receptors.

- **Histamine** is found in neurons in the hypothalamus that send sparse but widespread projections to almost all regions of the brain and spinal cord (Figure 6.17A). The central histamine projections mediate arousal and attention, similar to central ACh and norepinephrine projections. Histamine also controls the reactivity of the vestibular system. Allergic reactions or tissue damage cause release of histamine from mast cells in the bloodstream. The close proximity of mast cells to blood vessels, together with the potent actions of histamine on blood vessels, raises the possibility that histamine may influence brain blood flow.

Histamine is produced from the amino acid histidine by a histidine decarboxylase (Figure 6.18A) and is transported into vesicles via the same VMAT as the catecholamines. No plasma membrane histamine transporter has been identified yet. Histamine is degraded by the combined actions of histamine methyltransferase and MAO.

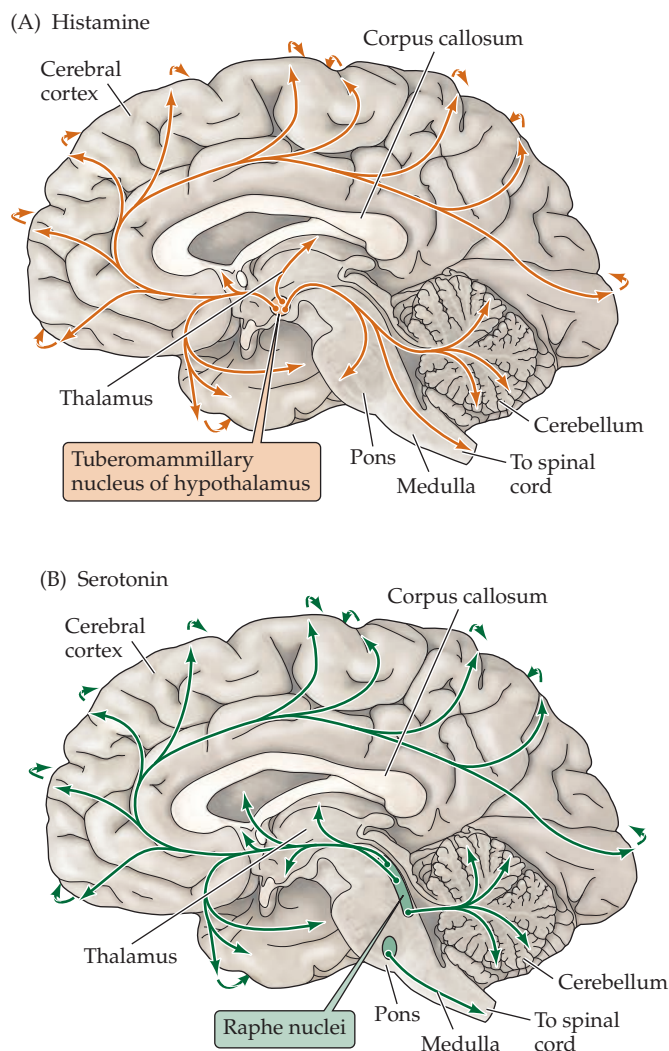


FIGURE 6.17 The distribution of histamine and serotonin neurotransmitters in the human brain. Diagrams show the distribution of neurons and their projections (arrows) containing histamine (A) or serotonin (B). Curved arrows along the perimeter of the cortex indicate the innervation of lateral cortical regions not shown in this midsagittal plane of section.

The four known types of histamine receptors are all metabotropic receptors (see Figure 6.4C). Because of the role of histamine receptors in mediating allergic responses, many histamine receptor antagonists have been developed as antihistamine agents. Antihistamines that cross the blood-brain barrier, such as diphenhydramine (Benadryl), act as sedatives by interfering with the roles of histamine in CNS arousal. Antagonists of the H_1 receptor also are used to prevent motion sickness, perhaps because of the role of histamine in controlling vestibular function. H_2 receptors control the secretion of gastric acid in the digestive system, allowing H_2 receptor antagonists to be used in treating a variety of upper gastrointestinal disorders (e.g., peptic ulcers).

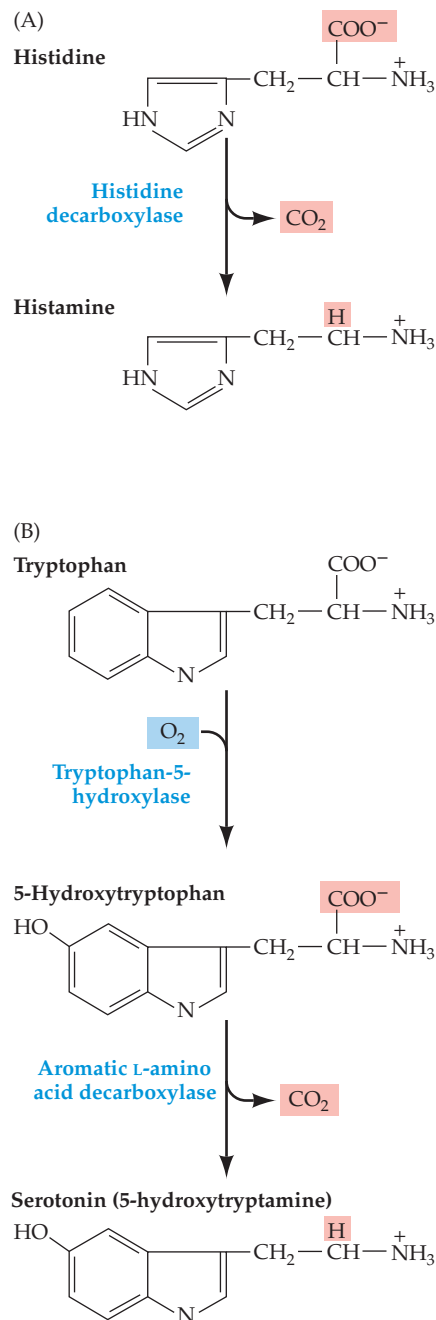
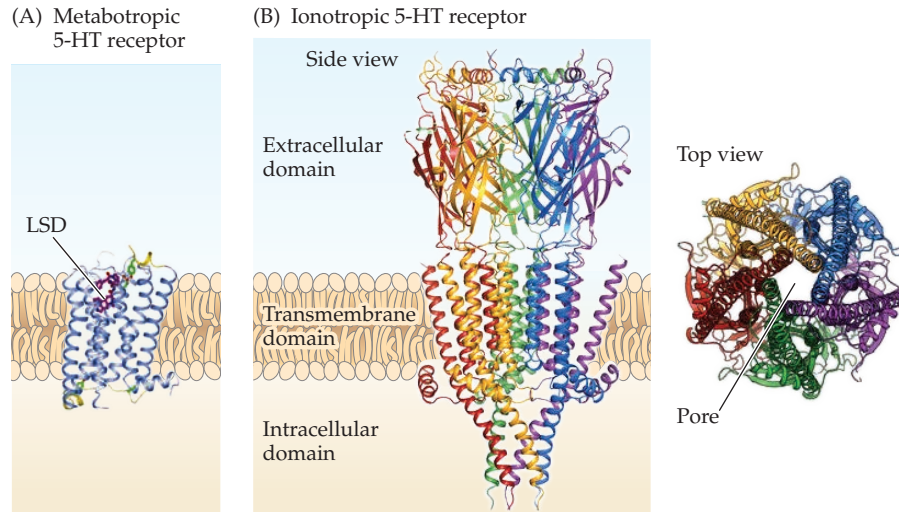


FIGURE 6.18 Synthesis of histamine and serotonin.

(A) Histamine is synthesized from the amino acid histidine. (B) Serotonin is derived from the amino acid tryptophan by a two-step process that requires the enzymes tryptophan-5-hydroxylase and a decarboxylase.

- *Serotonin*, or 5-hydroxytryptamine (5-HT), was initially thought to increase vascular tone by virtue of its presence in blood serum (hence the name serotonin). Serotonin is found primarily in groups of neurons in the raphe region of the pons and upper brainstem, which have widespread projections to the forebrain (Figure 6.17B) and regulate sleep and wakefulness (see Chapter 28). 5-HT occupies a place of prominence in neuropharmacology because a large number of antipsychotic drugs that are valuable in

**FIGURE 6.19 Serotonin receptors.**

(A) Structure of the human 5-HT_{2B} receptor, a metabotropic 5-HT receptor. The pink structure indicates LSD bound to the 5-HT binding site of the receptor. (B) Structure of the human 5-HT₃ receptor, an ionotropic 5-HT receptor consisting of five subunits (each in a different color), each of which has an extracellular domain, transmembrane domain, and intracellular domain. An ion channel is formed by the transmembrane domains of the five subunits (right). (A from Wacker et al., 2017; B from Hassaine et al., 2014.)

the treatment of depression and anxiety act on serotonergic pathways (see Clinical Applications, Chapter 7).

5-HT is synthesized from the amino acid tryptophan, which is an essential dietary requirement. Tryptophan is taken up into neurons by a plasma membrane transporter and hydroxylated in a reaction catalyzed by the enzyme tryptophan-5-hydroxylase (Figure 6.18B), the rate-limiting step for 5-HT synthesis. Loading of 5-HT into synaptic vesicles is done by the VMAT that is also responsible for loading other monoamines into synaptic vesicles. The synaptic effects of serotonin are terminated by transport back into nerve terminals via a specific serotonin transporter (SERT) that is present in the presynaptic plasma membrane and is encoded by the 5HTT gene. Many antidepressant drugs are **selective serotonin reuptake inhibitors (SSRIs)** that inhibit transport of 5-HT by SERT. Perhaps the best-known example of an SSRI is the antidepressant drug Prozac (see Clinical Applications, Chapter 7). The primary catabolic pathway for 5-HT is mediated by MAO.

A large number of 5-HT receptors (encoded by HTR genes) have been identified. Most 5-HT receptors are metabotropic (see Figure 6.4C), with a monomeric structure typical of G-protein-coupled receptors (Figure 6.19A). Metabotropic 5-HT receptors have been implicated in a wide range of behaviors, including circadian rhythms, motor behaviors, emotional states, and state of mental arousal. Impairments in the function of these receptors have been implicated in numerous psychiatric disorders, such as depression, anxiety disorders, and schizophrenia (see Chapter 31), and drugs acting on serotonin receptors are effective treatments for several of these conditions. The psychedelic drug LSD (lysergic acid diethylamide) presumably causes hallucinations by activating multiple types of metabotropic 5-HT receptors (see Figure 6.19A). Activation of 5-HT receptors also mediates satiety and decreased food consumption, which is why serotonergic drugs are sometimes useful in treating eating disorders.

One group of serotonin receptors, the 5-HT₃ receptors, are ligand-gated ion channels formed from combinations of the five 5-HT₃ subunits (see Figure 6.3F). Their pentameric structure is very similar to that of other ionotropic receptors, with functional channels formed by the transmembrane domains of the five subunits (Figure 6.19B). 5-HT₃ receptors are nonselective cation channels and therefore mediate excitatory postsynaptic responses. Ligand-binding sites reside within the extracellular domains of these receptors and serve as targets for a wide variety of therapeutic drugs, including ondansetron (Zofran) and granisetron (Kytril), which are used to prevent postoperative nausea and chemotherapy-induced emesis.

ATP and Other Purines

All synaptic vesicles contain ATP, which is co-released with one or more “classic” neurotransmitters. This observation raises the possibility that ATP acts as a co-transmitter. It has been known since the 1920s that the extracellular application of ATP (or its breakdown products AMP and adenosine) can elicit electrical responses in neurons. The idea that some purines (so named because all these compounds contain a purine ring; see Figure 6.1) are also neurotransmitters is now well established. ATP acts as an excitatory neurotransmitter in motor neurons of the spinal cord, as well as in sensory and autonomic ganglia. Postsynaptic actions of ATP have also been demonstrated in the CNS, specifically for dorsal horn neurons and in a subset of hippocampal neurons. Extracellular enzymes degrade released ATP to adenosine, which has its own set of signaling actions. Thus, adenosine cannot be considered a classic neurotransmitter because it is not stored in synaptic vesicles or released in a Ca²⁺-dependent manner. Several enzymes, including apyrase, ecto-5′ nucleotidase, and nucleoside transporters, are involved in the rapid catabolism and removal of purines from extracellular locations.