expression of presynaptic Ca^{2+} channels and synaptotagmins. At some synapses, vesicles and Ca^{2+} channels appear aligned by an intricate structural network.

14. Transmitter release can be modulated intrinsically or extrinsically as an aspect of synaptic plasticity. Synaptic strength can be strongly influenced intrinsically by the pattern of firing in phenomena known as "depression" and "facilitation." In addition, extrinsic neuromodulators can alter the dynamics of release by regulation of Ca^{2+} channels or events downstream of Ca^{2+} entry.

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16

Neurotransmitters

A Chemical Messenger Must Meet Four Criteria to Be Considered a Neurotransmitter

Only a Few Small-Molecule Substances Act as Transmitters

- Acetylcholine
- Biogenic Amine Transmitters
- Amino Acid Transmitters
- ATP and Adenosine

Small-Molecule Transmitters Are Actively Taken Up Into Vesicles

Many Neuroactive Peptides Serve as Transmitters

Peptides and Small-Molecule Transmitters Differ in Several Ways

Peptides and Small-Molecule Transmitters Can Be Co-released

Removal of Transmitter From the Synaptic Cleft Terminates Synaptic Transmission

Highlights

Chemical synaptic transmission can be divided into four steps: (1) synthesis and storage of a transmitter substance, (2) release of the transmitter, (3) interaction of the transmitter with receptors at the postsynaptic membrane, and (4) removal of the transmitter from the synapse. In the previous chapters, we considered steps 2 and 3. We now turn to the initial and final steps of chemical synaptic transmission: the synthesis and storage of transmitter molecules and their removal from the synaptic cleft after synaptic action.

A Chemical Messenger Must Meet Four Criteria to Be Considered a Neurotransmitter

Before considering the biochemical processes involved in synaptic transmission, it is important to make clear what is meant by a chemical transmitter. The concept is empirical and has changed over the years with increased understanding of synaptic transmission and a corresponding expansion of signaling agents. The concept that a released chemical could act as a transmitter was introduced by the British physician George Oliver and his colleague Edward Albert Schaefer, who in 1894 reported that injection of an adrenal gland extract increases blood pressure (Sir Henry Dale claimed that Oliver discovered this by injecting the extract into his own son). The constituent responsible was independently identified by three laboratories in 1897, and competing claims for priority provide one reason that this transmitter has 38 different names in the Merck Index, including adrenaline (as it was obtained from the adrenal gland) and epinephrine.

Experiments reported in 1904 by Thomas Elliott, a student in the lab of the physiologist John Langley, are generally credited as the first report of chemical neurotransmission. Elliott concluded that "adrenaline might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery." Not incidentally, Elliott also proposed as early as 1914 that nerves could accumulate transmitter by an uptake system, suggesting that adrenal gland signaling might "depend on what could be picked up from the circulating blood and stored in its nerve endings," although uptake mechanisms were not demonstrated until more than 40 years later.

In 1913, Arthur Ewins, working with Henry Dale, discovered acetylcholine (ACh) as a component of the ergot fungus. In 1921, Otto Loewi demonstrated that stimulation of the vagus nerve terminals in frog hearts released "vagustoff," which was later shown to be ACh. Dale and Loewi later shared the Nobel Prize in 1946. The terms *cholinergic* and *adrenergic* were introduced to indicate that a neuron makes and releases ACh or norepinephrine (or epinephrine), respectively, the two substances first recognized as neurotransmitters. The term *catecholaminergic*, encompassing dopamine and the adrenergic transmitters, was derived from one of many natural sources, the catechu tree of India. Since that time, many other substances have been identified as transmitters.

The first secretory vesicles shown to accumulate and release neurotransmitters were the chromaffin vesicles of the adrenal gland, named in 1902 by Alfred Kohn due to their colorimetric reaction with chromate. William Cramer later showed that these organelles accumulate epinephrine. More recently, Mark Wightman provided direct evidence that these vesicles released epinephrine using carbon fiber electrodes as an electrochemical detector to measure catecholamine molecules released following fusion of chromaffin vesicles with the plasma membrane.

As a first approximation, a neurotransmitter can be defined as a substance that is released by a neuron that affects a specific target in a specific manner. A target can be either another neuron or an effector organ, such as muscle or gland. As with many other operational concepts in biology, the concept of a transmitter is not precise. Although the actions of hormones and neurotransmitters are quite similar, neurotransmitters usually act on targets that are close to the site of transmitter release, whereas hormones are released into the bloodstream to act on distant targets.

Neurotransmitters typically act on a target other than the releasing neuron itself, whereas substances termed autacoids act on the cell from which they are released. Nevertheless, at many synapses, transmitters activate not only postsynaptic receptors but also autoreceptors at the presynaptic release site. Autoreceptors usually modulate synaptic transmission that is in progress, for example, by limiting further release of transmitter or inhibiting subsequent transmitter synthesis. Receptors can also exist on presynaptic release sites that receive synaptic input from another neuron. These receptors function as heteroreceptors that regulate presynaptic excitability and transmitter release (Chapters 13 and 15).

Following release, the interaction of neurotransmitters with receptors is typically transient, lasting for periods ranging from less than a millisecond to several seconds. Nevertheless, neurotransmitter actions can result in long-term changes within target cells lasting hours or days, often by activating gene transcription. Moreover, nonneural cells, including astrocytes and microglia, can also synthesize, store, and release neurotransmitters, as well as express receptors that modulate their own function.

A limited number of substances of low molecular weight are generally accepted as classical neurotransmitters, and these exclude many neuropeptides, as well as other substances that are not released by exocytosis. Even so, it is often difficult to demonstrate that a specific neurotransmitter operates at a particular synapse, particularly given the diffusion and rapid reuptake or degradation of transmitters at the synaptic cleft.

A classical neurotransmitter is considered to meet four criteria:

1. It is synthesized in the presynaptic neuron.
2. It is accumulated within vesicles present in presynaptic release sites and is released via exocytosis in amounts sufficient to exert a defined action on the postsynaptic neuron or effector organ.
3. When administered exogenously in reasonable concentrations, it mimics the action of the endogenous transmitter (for example, it activates the same ion channels or second-messenger pathway in the postsynaptic cell).
4. A specific mechanism usually exists for removing the substance from the extracellular environment. This may be the synaptic cleft in the case of "wired" or "private" neurotransmission (in which the action of the substance is limited to a single synapse) or the extrasynaptic space in the case of "volume" or "social" neurotransmission (in which the substance diffuses to multiple synapses).

The nervous system makes use of two main classes of chemical substances that fit these criteria for signaling: small-molecule transmitters and neuropeptides. Neuropeptides are short polymers of amino acids processed in the Golgi apparatus, where they are packaged in large dense-core vesicles (approximately 70–250 nm in diameter). Small-molecule transmitters are packaged in small vesicles (~40 nm in diameter) that are usually electron-lucent. Vesicles are closely associated with specific Ca^{2+} channels at active zones and release their contents through exocytosis in response to a rise in intracellular Ca^{2+} evoked by an action potential (Chapter 15). Vesicle membrane is retrieved through endocytosis and recycled locally in the axon to produce new synaptic vesicles. Large dense-core vesicles

can contain both small-molecule transmitters and neuropeptides and do not undergo local recycling following full fusion with the plasma membrane.

Both types of vesicles are found in most neurons but in different proportions. Small synaptic vesicles are characteristic of neurons that use ACh, glutamate, γ-aminobutyric acid (GABA), and glycine as transmitters, whereas neurons that use catecholamines and serotonin as transmitters often have both small and large dense-core vesicles. The adrenal medulla—the tissue in which most discoveries on secretion were made and still widely used as a model for studying exocytosis—contains only large dense-core vesicles that contain both catecholamines and neuroactive peptides.

Only a Few Small-Molecule Substances Act as Transmitters

A relatively small number of low-molecular-weight substances are generally accepted as neurotransmitters. These include ACh, the excitatory amino acid glutamate, the inhibitory amino acids GABA and glycine, amine containing amino acid derivatives, and adenosine triphosphate (ATP) and its metabolites (Table 16–1). A small set of small molecules, such as the gas nitric oxide lipid metabolites are not released from vesicles and tend to break all of the classical rules (Chapter 14).

Table 16–1 Small-Molecule Neurotransmitter Substances and Their Precursors

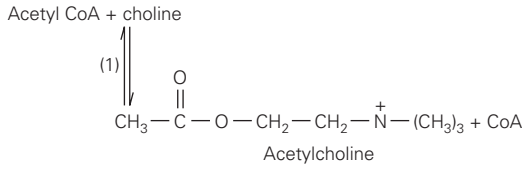
Transmitter	Precursor
Acetylcholine	Choline
Biogenic amines	
Dopamine	Tyrosine
Norepinephrine	Tyrosine via dopamine
Epinephrine	Tyrosine via norepinephrine
Octopamine	Tyrosine via tyramine
Serotonin	Tryptophan
Histamine	Histidine
Melatonin	Tryptophan via serotonin
Amino acids	
Aspartate	Oxaloacetate
γ-Aminobutyric acid	Glutamine
Glutamate	Glutamine
Glycine	Serine
Adenosine triphosphate (ATP)	Adenosine diphosphate (ADP)
Adenosine	ATP
Endocannabinoids	Phospholipids
Nitric oxide	Arginine

The amine messengers share many biochemical similarities. All are charged small molecules that are formed in relatively short biosynthetic pathways and synthesized either from essential amino acids or from precursors derived from the major carbohydrate substrates of intermediary metabolism. Like other pathways of intermediary metabolism, synthesis of these neurotransmitters is catalyzed by enzymes that, with the notable exception of dopamine β-hydroxylase, are cytosolic. ATP, which originates in mitochondria, is abundantly present throughout the cell.

As in any biosynthetic pathway, the overall synthesis of amine transmitters typically is regulated at one rate-limiting enzymatic reaction. The rate-limiting step often is characteristic of one type of neuron and usually is absent in other types of mature neurons. The classical small-molecule neurotransmitters released from a particular neuron are thus determined by their presence in the cytosol due to synthesis and reuptake and to the selectivity of the vesicular transporter.

Acetylcholine

Acetylcholine is the only low-molecular-weight aminergic transmitter substance that is not an amino acid or derived directly from one. The biosynthetic pathway for ACh has only one enzymatic reaction, catalyzed by choline acetyltransferase (step 1 below):



This transferase is the characteristic and limiting enzyme in ACh biosynthesis. Nervous tissue cannot synthesize choline, which is derived from the diet and delivered to neurons through the bloodstream. The co-substrate, acetyl coenzyme A (acetyl CoA), participates in many general metabolic pathways and is not restricted to cholinergic neurons.

Acetylcholine is released at all vertebrate neuromuscular junctions by spinal motor neurons (Chapter 12). In the autonomic nervous system, it is the transmitter released by all preganglionic neurons and by parasympathetic postganglionic neurons (Chapter 41). Cholinergic neurons form synapses throughout the brain; those in the nucleus basalis have particularly

widespread projections to the cerebral cortex. Acetylcholine (together with a noradrenergic component) is a principal neurotransmitter of the reticular activating system, which modulates arousal, sleep, wakefulness, and other critical aspects of human consciousness.

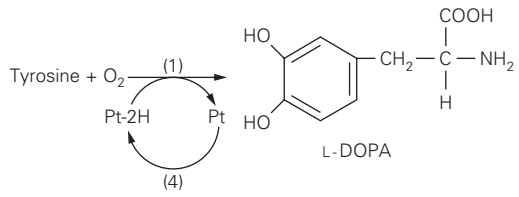
Biogenic Amine Transmitters

The terms *biogenic amine* or *monoamine,* although chemically imprecise, have been used for decades to designate certain neurotransmitters. This group includes the catecholamines and serotonin. Histamine, an imidazole, is also often included with biogenic amine transmitters, although its biochemistry is remote from the catecholamines and the indolamines.

Catecholamine Transmitters

The catecholamine transmitters—dopamine, norepinephrine, and epinephrine—are all synthesized from the essential amino acid tyrosine in a biosynthetic pathway containing five enzymes: tyrosine hydroxylase, pteridine reductase, aromatic amino acid decarboxylase, dopamine β-hydroxylase, and phenylethanolamine-*N*-methyl transferase. Catecholamines contain a catechol nucleus, a 3,4-dihydroxylated benzene ring.

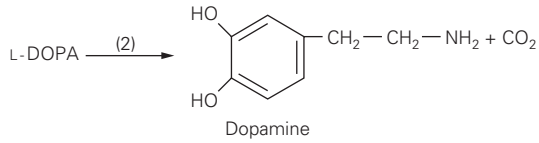
The first enzyme, tyrosine hydroxylase (step 1 below), is an oxidase that converts tyrosine to L-dihydroxyphenylalanine (L-DOPA):



This enzyme is rate-limiting for the synthesis of both dopamine and norepinephrine. A distinct pathway is used to synthesize L-DOPA for production of the melanin pigments found throughout the plant and animal kingdoms, while the neuromelanin pigment found in some dopamine and norepinephrine neurons are metabolites of the oxidized neurotransmitters.

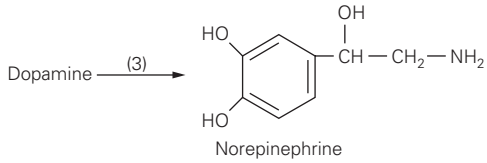
L-DOPA is present in all cells producing catecholamines, and its synthesis requires a reduced pteridine cofactor, Pt-2H, which is regenerated from pteridine (Pt) by another enzyme, pteridine reductase, which uses nicotinamide adenine dinucleotide (NADH) (step 4 above). This reductase is not specific to neurons.

Based on the finding that individuals with Parkinson disease have lost dopamine neurons of the substantia nigra, L-DOPA has been used to restore dopamine and motor function in patients. L-DOPA, whether exogenous or produced by tyrosine hydroxylase, is decarboxylated by a widespread enzyme known as aromatic amino acid decarboxylase, also called L-DOPA decarboxylase (step 2 below), to yield dopamine and carbon dioxide:



Interestingly, dopamine was initially thought to be present in neurons only as a precursor to norepinephrine. That dopamine also functions as a neurotransmitter itself was demonstrated in 1957 by Aarvid Carlsson, who found that rabbits treated with the synaptic vesicle dopamine uptake blocker, reserpine, exhibited floppy ears, but that L-DOPA, under conditions that produced dopamine but not norepinephrine, restored the normal erect ear posture.

In adrenergic neurons, the third enzyme in the sequence, dopamine β-hydroxylase (step 3 below), further converts dopamine to norepinephrine:

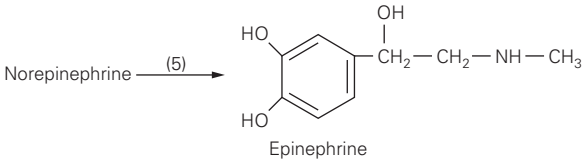


Unlike all other enzymes in the biosynthetic pathways of small-molecule neurotransmitters, dopamine β-hydroxylase is membrane-associated. It is bound tightly to the inner surface of aminergic vesicles as a peripheral protein. Consequently, norepinephrine is the only transmitter synthesized within vesicles.

In the central nervous system, norepinephrine is used as a transmitter by neurons with cell bodies in the locus coeruleus, a nucleus of the brain stem with many complex modulatory functions (Chapter 40). Although these adrenergic neurons are relatively few in number, they project widely throughout the cortex, cerebellum, hippocampus, and spinal cord. In many cases, neurons that release norepinephrine can also release the precursor dopamine, and thus can act at neurons expressing receptors for dopamine or norepinephrine. In the peripheral nervous system, norepinephrine is the transmitter of the postganglionic neurons in the sympathetic nervous system (Chapter 41).

In addition to these four catecholaminergic biosynthetic enzymes, a fifth enzyme, phenylethanolamine-*N*-methyltransferase (step 5 below), methylates

norepinephrine to form epinephrine (adrenaline) in the adrenal medulla:



This reaction requires *S*-adenosyl-methionine as a methyl donor. The transferase is a cytoplasmic enzyme. Thus, for epinephrine to be formed, its immediate precursor norepinephrine must exit from vesicles into the cytoplasm. For epinephrine to be released, it must then be taken back up into vesicles. Only a small number of neurons in the brain use epinephrine as a transmitter.

The production of these catecholamine neurotransmitters is controlled by feedback regulation of the first enzyme in the pathway, tyrosine hydroxylase (Box 16–1). Not all cells that release catecholamines express all five biosynthetic enzymes, although cells that release epinephrine do. During development, the expression of the genes encoding these synthetic enzymes is independently regulated and the particular catecholamine that is produced by a cell is determined by which enzyme(s) in the step-wise pathway is not

Box 16–1 Catecholamine Production Varies With Neuronal Activity

Norepinephrine neurotransmission is far more active during awake states than sleep or anesthesia, with locus coeruleus noradrenergic neurons nearly silenced during rapid eye movement (REM) sleep. The production of catecholamine is able to keep up with wide variations in neuronal activity because catecholamine synthesis is highly regulated. Circadian changes in extracellular dopamine in the striatum have been suggested to result from altered activity of the dopamine uptake transporter.

In autonomic ganglia, the amount of norepinephrine in postganglionic neurons is regulated transsynaptically. Activity in the presynaptic neurons, which are both cholinergic and peptidergic, first induces short-term changes in second messengers in the postsynaptic adrenergic cells. These changes increase the supply of norepinephrine through the cAMP-dependent phosphorylation of tyrosine hydroxylase, the first enzyme in the catecholamine biosynthetic pathway.

Phosphorylation enhances the affinity of the hydroxylase for the pteridine cofactor and diminishes feedback inhibition by end products such as norepinephrine. Phosphorylation of tyrosine hydroxylase lasts only as long as cAMP remains elevated, as the phosphorylated hydroxylase is quickly dephosphorylated by protein phosphatases.

If presynaptic activity is sufficiently prolonged, however, other changes in the production of norepinephrine will occur. Severe stress to an animal results in intense presynaptic activity and persistent firing of the postsynaptic adrenergic neuron, placing a greater demand on transmitter synthesis. To meet this challenge, the tyrosine hydroxylase gene is induced to increase transcription and thus production of the protein. Elevated amounts of tyrosine hydroxylase are observed in the cell body within hours after stimulation and at nerve endings days later.

This induction of increased levels of tyrosine hydroxylase begins with the persistent release of chemical transmitters from the presynaptic neurons and prolonged activation of the cAMP pathway in postsynaptic adrenergic cells, which activates the cAMP-dependent protein kinase (PKA). This kinase phosphorylates not only existing tyrosine hydroxylase molecules but also the transcription factor, cAMP response element binding protein (CREB).

Once phosphorylated, CREB binds a specific DNA enhancer sequence called the cAMP-recognition element (CRE), which lies upstream (5′) of the gene for the hydroxylase. Binding of CREB to CRE facilitates the binding of RNA polymerase to the gene's promoter, increasing tyrosine hydroxylase transcription. Induction of tyrosine hydroxylase was the first known example of a neurotransmitter altering gene expression.

Based on similarity in portions of the amino acid and nucleic acid sequences encoding three of the biosynthetic enzymes—tyrosine hydroxylase, dopamine β-hydroxylase, and phenylethanolamine-*N*-methyltransferase—it has been suggested that the three enzymes may have arisen from a common ancestral protein. Moreover, long-term changes in the synthesis of these enzymes are coordinately regulated in adrenergic neurons.

At first, this discovery suggested that the genes encoding these enzymes might be located sequentially along the same chromosome and be controlled by the same promoter, like genes in a bacterial operon. But in humans, the genes for the biosynthetic enzymes for norepinephrine are not located on the same chromosome. Therefore, coordinate regulation is likely achieved by parallel activation through similar but independent transcription activator systems.

expressed. Thus, neurons that release norepinephrine do not express the methyltransferase, and neurons that release dopamine do not express the transferase or dopamine β-hydroxylase. Some neurons that express tyrosine hydroxylase, and thus produce dopamine, do not express the vesicular monoamine transporter (VMAT), the transporter that accumulates dopamine in synaptic vesicles, and thus do not appear to release dopamine as a transmitter.

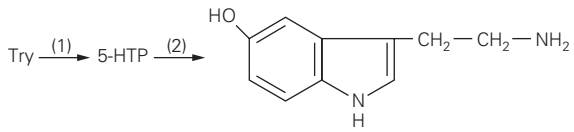
Of the four major dopaminergic nerve tracts, three arise in the midbrain (Chapters 40 and 43). Dopaminergic neurons in the substantia nigra that project to the striatum are important for the control of movement and are affected in Parkinson disease and other disorders of movement, but projections to the associative striatum have also been implicated more recently in dopamine dysfunction in schizophrenia. The mesolimbic and mesocortical tracts are critical for affect, emotion, attention, and motivation and are implicated in drug addiction and schizophrenia. A fourth dopaminergic tract, the tuberoinfundibular pathway, originates in the arcuate nucleus of the hypothalamus and projects to the pituitary gland, where it regulates secretion of hormones (Chapter 41).

The synthesis of biogenic amines is highly regulated and can be rapidly increased. As a result, the amounts of transmitter available for release can keep up with wide variations in neuronal activity. Mechanisms for regulating both the synthesis of catecholamine transmitters and the production of enzymes in the step-wise catecholamine pathway are discussed in Box 16–1.

Trace amines, naturally occurring catecholamine derivatives, may also serve as transmitters. In invertebrates, the tyrosine derivatives tyramine and octopamine (so called because it was originally identified in the octopus salivary gland) play key roles in numerous physiological processes including behavioral regulation. Trace amine receptors also have been identified in mammals, where their functional role is still being characterized. In particular, trace amine-associated receptor 1 (TAAR1) has been shown to modulate aspects of biogenic amine neurotransmission as well as to play a role in the immune system.

Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) and the essential amino acid tryptophan from which it is derived belong to a group of aromatic compounds called indoles, with a five-member ring containing nitrogen joined to a benzene ring. Two enzymes are needed to synthesize serotonin: tryptophan (Trp) hydroxylase (step 1 below), an oxidase similar to tyrosine hydroxylase, and aromatic amino acid decarboxylase, also called 5-hydroxytryptophan (5-HTP) decarboxylase (step 2 below):



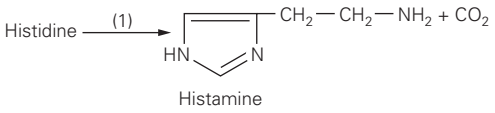
Serotonin

As with the catecholamines, the limiting reaction in serotonin synthesis is catalyzed by the first enzyme in the pathway, tryptophan hydroxylase. Tryptophan hydroxylase is similar to tyrosine hydroxylase not only in catalytic mechanism but also in amino acid sequence. The two enzymes are thought to stem from a common ancestral protein by gene duplication because the two hydroxylases are encoded by genes close together on the same chromosome (tryptophan hydroxylase, 11p15.3-p14; tyrosine hydroxylase, 11p15.5). The second enzyme in the pathway, 5-hydroxytryptophan decarboxylase, is identical to L-DOPA decarboxylase. Enzymes with similar activity, L-aromatic amino acid decarboxylases, are present in nonnervous tissues as well.

The cell bodies of serotonergic neurons are found in and around the midline raphe nuclei of the brain stem and are involved in regulating affect, attention, and other cognitive functions (Chapter 40). These cells, like the noradrenergic cells in the locus coeruleus, project widely throughout the brain and spinal cord. Serotonin and the catecholamines norepinephrine and dopamine are implicated in depression, a major mood disorder. Antidepressant medications inhibit the uptake of serotonin, norepinephrine, and dopamine, thereby increasing the magnitude and duration of the action of these transmitters, which in turn leads to altered cell signaling and adaptations (Chapter 61).

Histamine

Histamine, derived from the essential amino acid histidine by decarboxylation, contains a characteristic five-member ring with two nitrogen atoms. It has long been recognized as an autacoid, active when released from mast cells in the inflammatory reaction and in the control of vasculature, smooth muscle, and exocrine glands (eg, secretion of highly acidic gastric juice). Histamine is a transmitter in both invertebrates and vertebrates. It is concentrated in the hypothalamus, one of the brain centers for regulating the secretion of hormones (Chapter 41). The decarboxylase catalyzing its synthesis (step 1 below), although not extensively analyzed, appears to be characteristic of histaminergic neurons.



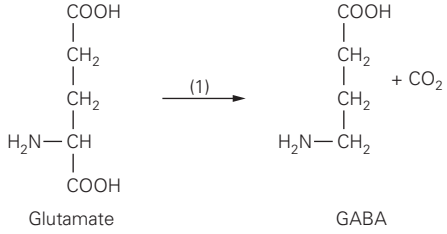
As described in the next section, the biogenic amines are loaded into synaptic and secretory vesicles by two transporters, VMAT1, mostly in peripheral cells, and VMAT2, mostly in the central nervous system. As the transporters are not selective for a given biogenic amine, a mixture of transmitters can be present. Some neurons co-release dopamine with norepinephrine, whereas secretory vesicles from the adrenal medulla can co-release epinephrine and norepinephrine.

Amino Acid Transmitters

In contrast to acetylcholine and the biogenic amines, which are not intermediates in general metabolic pathways and are produced only in certain neurons, the amino acids glutamate and glycine are not only neurotransmitters but also universal cellular constituents. Because they can be synthesized in neurons and other cells, neither is an essential amino acid.

Glutamate, the neurotransmitter most frequently used at excitatory synapses throughout the central nervous system, is produced from α-ketoglutarate, an intermediate in the tricarboxylic acid cycle of intermediary metabolism. After it is released, glutamate is taken up from the synaptic cleft by specific transporters in the membrane of both neurons and glia (see later). The glutamate taken up by astrocytes is converted to glutamine by the enzyme glutamine synthase. This glutamine is transported back into neurons that use glutamate as a transmitter, where it is hydrolyzed to glutamate by the enzyme glutaminase. Cytoplasmic glutamate is then loaded into synaptic vesicles by the vesicular glutamate transporter, VGLUT.

Glycine is the major transmitter used by inhibitory interneurons of the spinal cord. It is also a necessary cofactor for activation of the *N*-methyl-D-aspartate (NMDA) glutamate receptors (Chapter 13). Glycine is synthesized from serine by the mitochondrial form of the serine hydroxymethyltransferase. The amino acid GABA is synthesized from glutamate in a reaction catalyzed by glutamic acid decarboxylase (step 1 below):



GABA is present at high concentrations throughout the central nervous system and is detectable in other tissues. It is used as a transmitter by an important class of inhibitory interneurons in the spinal cord. In the brain, GABA is the major transmitter of a wide array of inhibitory neurons and interneurons. Both GABA and glycine are loaded into synaptic vesicles by the same transporter, VGAT, and thus can be co-released from the same vesicles.

ATP and Adenosine

ATP and its degradation products (eg, adenosine) act as transmitters at some synapses by binding to several classes of G protein–coupled receptors (the P1 and P2Y receptors). ATP can also produce excitatory actions by binding to ionotropic P2X receptors. Caffeine's stimulatory effects depend on its inhibition of adenosine binding to the P1 receptors. Adenine and guanine and their sugar-containing derivatives are called purines; the evidence for transmission at purinergic receptors is especially strong for autonomic neurons that innervate the vas deferens, bladder, and muscle fibers of the heart; for nerve plexuses on smooth muscle in the gut; and for some neurons in the brain. Purinergic transmission is particularly important for nerves mediating pain (Chapter 20).

ATP released by tissue damage acts to transmit pain sensation through one type of ionotropic purine receptor present on the terminals of peripheral axons of dorsal root ganglion cells that act as nociceptors. ATP released from terminals of the central axons of these dorsal root ganglion cells excites another type of ionotropic purine receptor on neurons in the dorsal horn of the spinal cord. ATP and other nucleotides also act at the family of P2Y G protein–coupled receptors to modulate various downstream signaling pathways.

Small-Molecule Transmitters Are Actively Taken Up Into Vesicles

Common amino acids act as transmitters in some neurons but not in others, indicating that the presence of a substance in a neuron, even in substantial amounts, is not in itself sufficient evidence that the substance is used as a transmitter. For example, at the neuromuscular junction of the lobster (and other arthropods), GABA is inhibitory and glutamate is excitatory. The concentration of GABA is approximately 20 times greater in inhibitory cells than in excitatory cells,