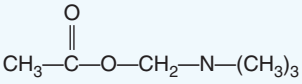
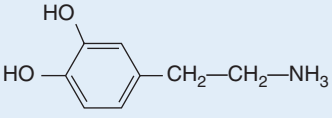
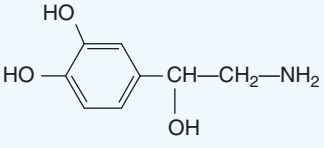
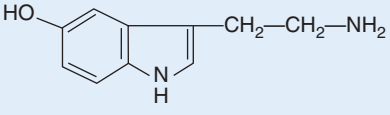
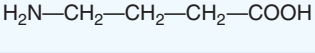
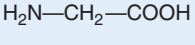
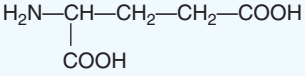
Peptide neurotransmitters are synthesized in the cell body rather than the nerve terminal and may colocalize with classic neurotransmitters in single neurons. A number of neuropeptides are important in pain modulation including substance P and calcitonin gene-related peptide (CGRP), which causes migraine-like headaches in patients. As a consequence, CGRP receptor antagonists have been developed and shown to be effective in treating migraine headaches. Nitric oxide and carbon monoxide are gases that appear also to function as neurotransmitters, in part by signaling in a retrograde fashion from the postsynaptic to the presynaptic cell.

Neurotransmitters modulate the function of postsynaptic cells by binding to specific neurotransmitter receptors, of which there are two major types. *Ionotropic receptors* are direct ion channels that open after engagement by the neurotransmitter. *Metabotropic receptors* interact with G proteins, stimulating production of second messengers and activating protein kinases, which modulate a variety of cellular events. Ionotropic receptors are multiple subunit structures, whereas metabotropic receptors are composed of single subunits only. One important difference between ionotropic and metabotropic receptors is that the kinetics of ionotropic receptor effects are fast (generally <1 ms) because neurotransmitter binding directly alters the electrical properties of the postsynaptic cell, whereas metabotropic receptors function over longer time periods. These different properties contribute to the potential for selective and finely modulated signaling by neurotransmitters.

Neurotransmitter systems are perturbed in a large number of clinical disorders, several of which are highlighted in **Table 444e-2**. One example is the involvement of dopaminergic neurons originating in the substantia nigra of the midbrain and projecting to the striatum (nigrostriatal pathway) in Parkinson's disease and in heroin addicts after the ingestion of the toxin MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine).

A second important dopaminergic system arising in the midbrain is the mediocorticolimbic pathway, which is implicated in the pathogenesis of addictive behaviors including drug reward. Its key components include the midbrain ventral tegmental area (VTA), median forebrain bundle, and nucleus accumbens **(see Fig. 465e-2)**. The cholinergic pathway originating in the nucleus basalis of Meynert plays a role in memory function in Alzheimer's disease.

**TABLE 444e-2 PRINCIPAL CLASSIC NEUROTRANSMITTERS**

| Neurotransmitter | Anatomy | Clinical Aspects |
|---|---|---|
| Acetylcholine (ACh)<br>  | Motor neurons in spinal cord → neuromuscular junction | Acetylcholinesterases (nerve gases)<br>Myasthenia gravis (antibodies to ACh receptor)<br>Congenital myasthenic syndromes (mutations in ACh receptor subunits)<br>Lambert-Eaton syndrome (antibodies to Ca channels impair ACh release)<br>Botulism (toxin disrupts ACh release by exocytosis) |
| | Basal forebrain → widespread cortex | Alzheimer disease (selective cell death)<br>Autosomal dominant frontal lobe epilepsy (mutations in CNS ACh receptor) |
| | Interneurons in striatum | Parkinson's disease (tremor) |
| | Autonomic nervous system (preganglionic and postganglionic parasympathetic; preganglionic sympathetic) | |
| Dopamine<br>  | Substantia nigra → striatum (nigrostriatal pathway)<br>Substantia nigra → limbic system and widespread cortex<br>Arcuate nucleus of hypothalamus → anterior pituitary (via portal veins) | Parkinson's disease (selective cell death)<br>MPTP parkinsonism (toxin transported into neurons)<br>Addiction, behavioral disorders<br>Inhibits prolactin secretion |
| Norepinephrine (NE)<br>  | Locus coeruleus (pons) → limbic system, hypothalamus, cortex<br>Medulla → locus coeruleus, spinal cord<br>Postganglionic neurons of sympathetic nervous system | Mood disorders (MAOA inhibitors and tricyclics increase NE and improve depression)<br>Anxiety<br>Orthostatic tachycardia syndrome (mutations in NE transporter) |
| Serotonin<br>  | Pontine raphe nuclei → widespread projections<br>Medulla/pons → dorsal horn of spinal cord | Mood disorders (SSRIs improve depression)<br>Migraine pain pathway<br>Pain pathway |
| γ-Aminobutyric acid (GABA)<br>  | Major inhibitory neurotransmitter in brain; widespread cortical interneurons and long projection pathways | Stiff person syndrome (antibodies to glutamic acid decarboxylase, the biosynthetic enzyme for GABA)<br>Epilepsy (gabapentin and valprocic acid increase GABA) |
| Glycine<br>  | Major inhibitory neurotransmitter in spinal cord | Spasticity<br>Hyperekplexia (myoclonic startle syndrome) due to mutations in glycine receptor |
| Glutamate<br>  | Major excitatory neurotransmitter; located throughout CNS, including cortical pyramidal cells | Seizures due to ingestion of domoic acid (a glutamate analogue)<br>Rasmussen's encephalitis (antibody against glutamate receptor 3)<br>Excitotoxic cell death |

***Abbreviations:*** CNS, central nervous system; MAOA, monoamine oxidase A; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SSRI, selective serotonin reuptake inhibitor.