Biochemistry of Nerve Transmission

Table of Neurotransmitters

Transmitter Molecule	Derived From	Site of Synthesis
Acetylcholine	Choline	CNS, parasympathetic nerves
Serotonin 5-Hydroxytryptamine (5-HT)	Tryptophan	CNS, chromaffin cells of the gut, enteric cells
GABA	Glutamate	CNS
Glutamate		CNS
Aspartate		CNS
Glycine		spinal cord
Histamine	Histidine	hypothalamus
Epinephrine (adrenalin)synthesis pathway	Tyrosine	adrenal medulla, some CNS cells
Norepinephrine (noradrenalin) synthesis pathway	Tyrosine	CNS, sympathetic nerves
Dopamine synthesis pathway	Tyrosine	CNS
Adenosine	ATP	CNS, periperal nerves
ATP		sympathetic, sensory and enteric nerves
Nitric oxide, NO	Arginine	CNS, gastrointestinal tract

Many other neurotransmitters are derived from precursor proteins, the so-called peptide neurotransmitters. As many as 50 different peptides have been shown to exert their effects on neural cell function. Several of these peptide transmitters are derived from the larger protein pre-opiomelanocortin (POMC). Neuropeptides are responsible for mediating sensory and emotional responses including hunger, thirst, sex drive, pleasure and pain.

Synaptic Transmission

Synaptic transmission refers to the propagation of nerve impulses from one nerve cell to another. This occurs at a specialized cellular structure known as the synapse, a junction at which the axon of the presynaptic neuron terminates at some location upon the postsynaptic neuron. The end of a presynaptic axon, where it is juxtaposed to the postsynaptic neuron, is enlarged and forms a structure known as the terminal button. An axon can make contact anywhere along the second neuron: on the dendrites (an axodendritic synapse), the cell body (an axosomatic synapse) or the axons (an axo-axonal synapse). Nerve impulses are transmitted at synapses by the release of chemicals called

neurotransmitters. As a nerve impulse, or action potential, reaches the end of a presynaptic axon, molecules of neurotransmitter are released into the synaptic space. The neurotransmitters are a diverse group of chemical compounds ranging from simple amines such as dopamine and amino acids such as γ-aminobutyrate (GABA), to polypeptides such as the enkephalins. The mechanisms by which they elicit responses in both presynaptic and postsynaptic neurons are as diverse as the mechanisms employed by growth factor and cytokine receptors.

Neuromuscular Transmission

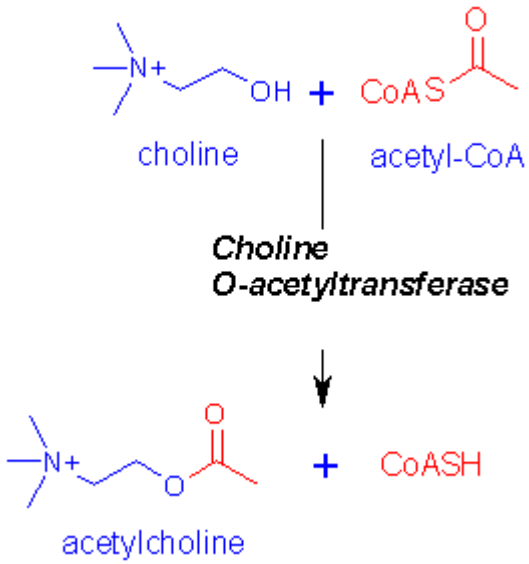
A different type of nerve transmission occurs when an axon terminates on a skeletal muscle fiber, at a specialized structure called the neuromuscular junction. An action potential occurring at this site is known as neuromuscular transmission. At a neuromuscular junction, the axon subdivides into numerous terminal buttons that reside within depressions formed in the motor end-plate. The particular transmitter in use at the neuromuscular junction is acetylcholine.

Neurotransmitter Receptors

Once the molecules of neurotransmitter are released from a cell as the result of the firing of an action potential, they bind to specific receptors on the surface of the postsynaptic cell. In all cases in which these receptors have been cloned and characterized in detail, it has been shown that there are numerous subtypes of receptor for any given neurotransmitter. As well as being present on the surfaces of postsynaptic neurons, neurotransmitter receptors are found on presynaptic neurons. In general, presynaptic neuron receptors act to inhibit further release of neurotransmitter. Once the molecules of neurotransmitter are released from a cell as the result of the firing of an action potential, they bind to specific receptors on the surface of the postsynaptic cell. In all cases in which these receptors have been cloned and characterized in detail, it has been shown that there are numerous subtypes of receptor for any given neurotransmitter. As well as being present on the surfaces of postsynaptic neurons, neurotransmitter receptors are found on presynaptic neurons. In general, presynaptic neuron receptors act to inhibit further release of neurotransmitter.

Acetylcholine

Acetylcholine (ACh) is a simple molecule synthesized from choline and acetyl-CoA through the action of ***choline acetyltransferase***.



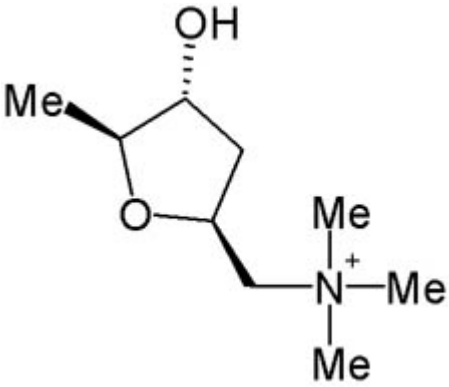
Neurons that synthesize and release ACh are termed cholinergic neurons. When an action potential reaches the terminal button of a presynaptic neuron a voltage-gated calcium channel is opened. The influx of calcium ions, Ca^{2+}, stimulates the exocytosis of presynaptic vesicles containing ACh, which is thereby released into the synaptic cleft. Once released, ACh must be removed rapidly in order to allow repolarization to take place; this step, hydrolysis, is carried out by the enzyme, *acetylcholinesterase*. The acetylcholinesterase found at nerve endings is anchored to the plasma membrane through a glycolipid. ACh receptors are ligand-gated cation channels composed of four different polypeptide subunits arranged in the form [(α2)(β)(γ)(δ)]. Two main classes of ACh receptors have been identified on the basis of their responsiveness to the toadstool alkaloid, muscarine, and to nicotine, respectively: the muscarinic receptors and the nicotinic receptors. Both receptor classes are abundant in the human brain. Nicotinic receptors are further divided into those found at neuromuscular junctions and those found at neuronal synapses. The activation of ACh receptors by the binding of ACh leads to an influx of Na^+ into the cell and an efflux of K^+, resulting in a depolarization of the postsynaptic neuron and the initiation of a new action potential.

Cholinergic Agonists and Antagonists

Numerous compounds have been identified that act as either agonists or antagonists of cholinergic neurons. The principal action of cholinergic agonists is the excitation or inhibition of autonomic effector cells that are innervated by postganglionic parasympathetic neurons and as such are referred to as parasympathomimetic agents. The cholinergic agonists include choline esters (such as ACh itself) as well as protein- or alkaloid-based compounds. Several naturally occurring compounds have been shown to affect cholinergic nerons, either positively or negatively.

The responses of cholinergic neurons can also be enhanced by administration of cholinesterase (ChE) inhibitors. ChE inhibitors have been used as components of

nerve gases but also have significant medical application in the treatment of disorders such as glaucoma and myasthenia gravis as well as in terminating the effects of neuromuscular blocking agents such as atropine.

Agonists	Source of Compound	Mode of Action
	Alkaloid prevalent in the tobacco plant	Activates nicotinic class of ACh receptors, locks the channel open
 Muscarine	Alkaloid produced by *Amanita muscaria* mushrooms	Activates muscarinic class of ACh receptors
α-Latrotoxin	Protein produced by the black widow spider	Induces massive ACh release, possibly by acting as a Ca^{2+} ionophore

Antagonists	Source of Compound	Mode of Action
and related compound	Alkaloid produced by the deadly nightshade, *Atropa belladonna*	Blocks ACh actions only at muscarinic receptors
Botulinus Toxin	Eight proteins produced by *Clostridium botulinum*	Inhibits the release of ACh
α-Bungarotoxin	Protein produced by *Bungarus* genus of snakes	Prevents ACh receptor channel opening
	Active ingredient of curare	Prevents ACh receptor channel opening at motor end-plate

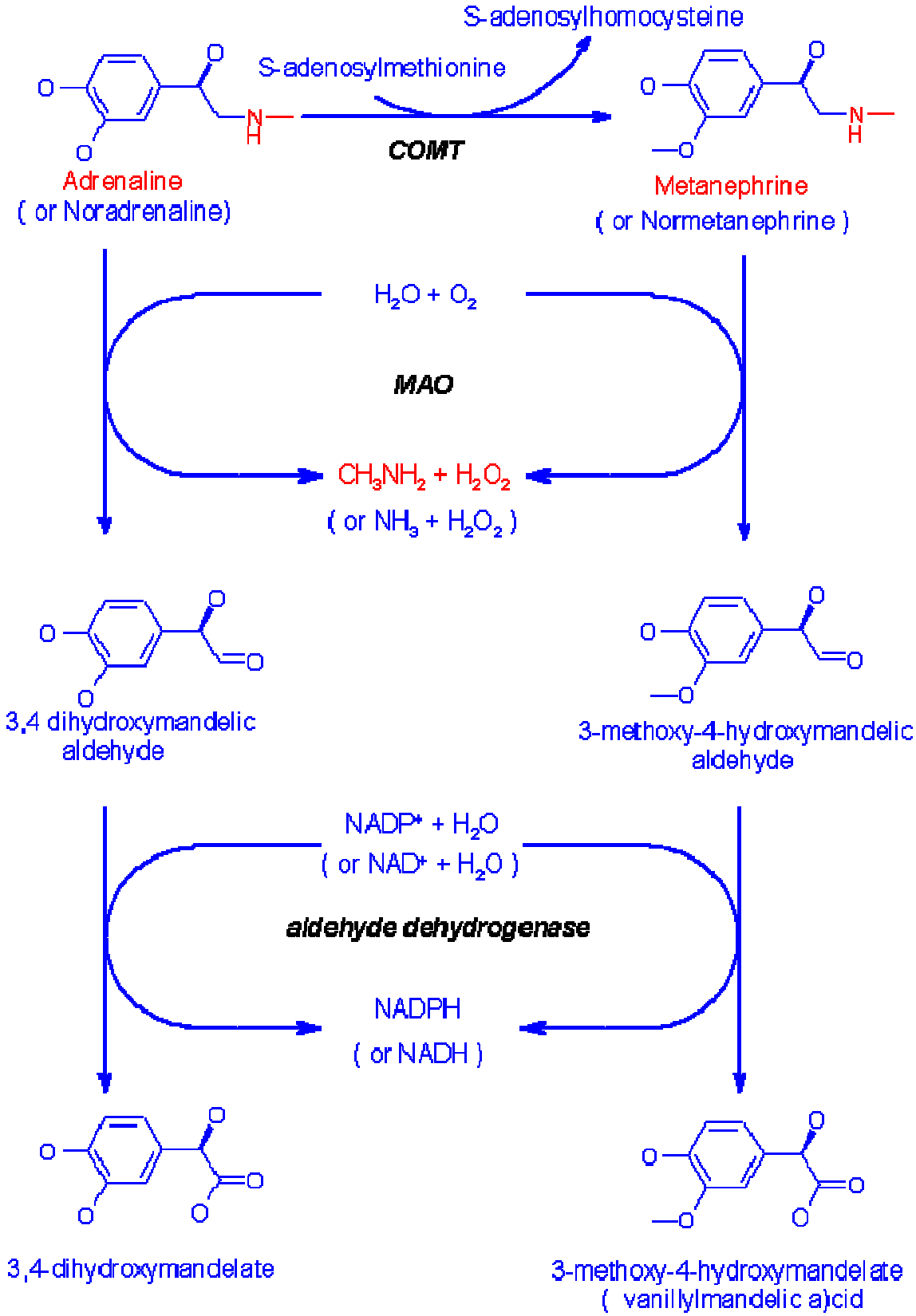
Catecholamines

The principal catecholamines are norepinephrine, epinephrine and dopamine. These compounds are formed from phenylalanine and tyrosine. Tyrosine is produced in the liver from phenylalanine through the action of ***phenylalanine***

hydroxylase. The tyrosine is then transported to catecholamine-secreting neurons where a series of reactions convert it to dopamine, to norepinephrine and finally to epinephrine. Catecholamines exhibit peripheral nervous system excitatory and inhibitory effects as well as actions in the CNS such as respiratory stimulation and an increase in psychomotor activity. The excitatory effects are exerted upon smooth muscle cells of the vessels that supply blood to the skin and mucous membranes. Cardiac function is also subject to excitatory effects, which lead to an increase in heart rate and in the force of contraction. Inhibitory effects, by contrast, are exerted upon smooth muscle cells in the wall of the gut, the bronchial tree of the lungs, and the vessels that supply blood to skeletal muscle. In addition to their effects as neurotransmitters, norepinephrine and epinephrine can influence the rate of metabolism. This influence works both by modulating endocrine function such as insulin secretion and by increasing the rate of glycogenolysis and fatty acid mobilization. The catecholamines bind to two different classes of receptors termed the α- and β-adrenergic receptors. The catecholamines therefore are also known as adrenergic neurotransmitters; neurons that secrete them are adrenergic neurons. Norepinephrine-secreting neurons are noradrenergic. The adrenergic receptors are classical serpentine receptors that couple to intracellular G-proteins. Some of the norepinephrine released from presynaptic noradrenergic neurons recycled in the presynaptic neuron by a reuptake mechanism.

Catecholamine Catabolism

Epinephrine and norepinephrine are catabolized to inactive compounds through the sequential actions of ***catecholamine-O-methyltransferase*** **(COMT)** and ***monoamine oxidase*** **(MAO)**.



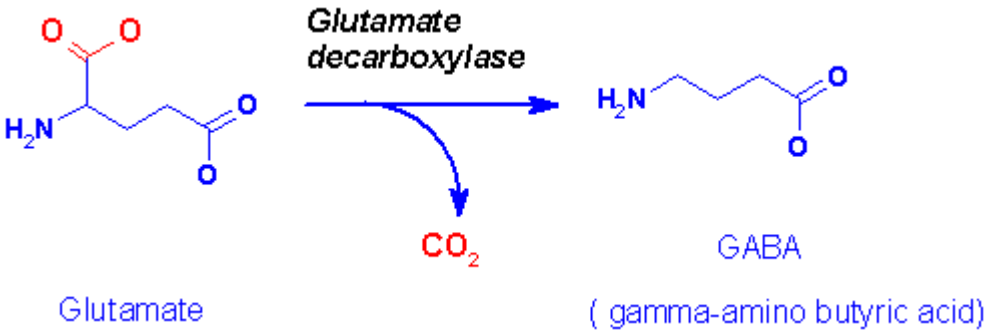
Compounds that inhibit the action of MAO have been shown to have beneficial effects in the treatment of clinical depression, even when tricyclic antidepressants are ineffective. The utility of MAO inhibitors was discovered serendipitously when patients treated for tuberculosis with isoniazid showed signs of an improvement in mood; isoniazid was subsequently found to work by inhibiting MAO.

Serotonin

Serotonin (5-hydroxytryptamine, 5HT) is formed by the hydroxylation and decarboxylation of tryptophan (see Specialized Products of Amino Acids). The greatest concentration of 5HT (90%) is found in the enterochromaffin cells of the gastrointestinal tract. Most of the remainder of the body's 5HT is found in platelets and the CNS. The effects of 5HT are felt most prominently in the cardiovascular system, with additional effects in the respiratory system and the intestines. Vasoconstriction is a classic response to the administration of 5HT. Neurons that secrete 5HT are termed serotonergic. Following the release of 5HT, a portion is taken back up by the presynaptic serotonergic neuron in a manner similar to that of the reuptake of norepinephrine. The function of serotonin is exerted upon its interaction with specific receptors. Several serotonin receptors have been cloned and are identified as $5HT_1$, $5HT_2$, $5HT_3$, $5HT_4$, $5HT_5$, $5HT_6$, and $5HT_7$. Within the $5HT_1$ group there are subtypes $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$, and $5HT_{1F}$. There are three $5HT_2$ subtypes, $5HT_{2A}$, $5HT_{2B}$, and $5HT_{2C}$ as well as two $5HT_5$ subtypes, $5HT_{5a}$ and $5HT_{5B}$. Most of these receptors are coupled to G-proteins that affect the activities of either ***adenylate cyclase*** or ***phospholipase Cγ***. The $5HT_3$ class of receptors are ion channels. Some serotonin receptors are presynaptic and others postsynaptic. The $5HT_{2A}$ receptors mediate platelet aggregation and smooth muscle contraction. The $5HT_{2C}$ receptors are suspected in control of food intake as mice lacking this gene become obese fromincreased food intake and are also subject to fatal seizures. The $5HT_3$ receptors are present in the gastrointestinal tract and are related to vomiting. Also present in the gastrointestinal tract are $5HT_4$ receptors where they function in secretion and peristalsis. The $5HT_6$ and $5HT_7$ receptors are distributed throughout the limbic system of the brain and the $5HT_6$ receptors have high affinity for antidepressant drugs.

GABA

Several amino acids have distinct excitatory or inhibitory effects upon the nervous system. The amino acid derivative, γ-aminobutyrate, also called 4-aminobutyrate, (GABA) is a well-known inhibitor of presynaptic transmission in the CNS, and also in the retina.



The formation of GABA occurs by the decarboxylation of glutamate catalyzed by ***glutamate decarboxylase*** (GAD). GAD is present in many nerve endings of the brain as well as in the β-cells of the pancreas. Neurons that secrete GABA are termed GABAergic.GABA exerts its effects by binding to two distinct receptors, GABA-A and GABA-B. The GABA-A receptors form a Cl^- channel. The binding of GABA to GABA-A receptors increases the Cl^- conductance of presynaptic neurons. The anxiolytic drugs of the benzodiazepine family exert their soothing effects by potentiating the responses of GABA-A receptors to GABA binding. The GABA-B receptors are coupled to an intracellular G-protein and act by increasing conductance of an associated K^+ channel.