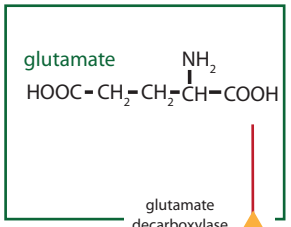
NEUROTRANSMITTERS

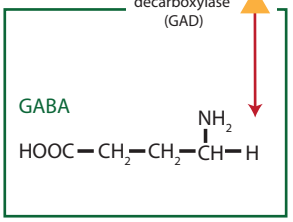
To be accepted as a neurotransmitter, a candidate chemical must (1) be present in higher concentration in the synaptic area than in other areas (ie, must be localized in appropriate areas), (2) be released by electrical or chemical stimulation via a calcium-dependent mechanism, and (3) must exhibit synaptic mimicry ie produce the same sort of postsynaptic response that is seen with physiologic activation of the synapse. Below are the major neurotransmitters.

AMINO ACIDS

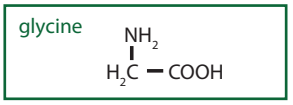
Glutamate is the main excitatory transmitter in the brain and spinal cord, and it has been calculated that it is the transmitter responsible for 75% of the excitatory transmission in the brain. Synthesis: Glutamate is formed by reductive amination of the Krebs cycle intermediate -ketoglutarate in the cytoplasm. Receptors: Glutamate receptors are of two types: metabotropic receptors and ionotropic receptors. The metabotropic receptors are G protein-coupled receptors that increase intracellular IP3 and DAG levels or decrease intracellular cAMP levels. The ionotropic receptors are ligand-gated ion channels that resemble nicotinic cholinergic receptors and GABA and glycine receptors. There are three general subtypes, the kainate receptors, AMPA receptors, and NMDA receptors. The all three allow Na and K flux, and NMDA also allows significant Ca flux. Fate: Glutamate is removed from the synaptic cleft by active transport into neurons and astrocytes. This uptake is important because persistant excitation by glutamate is an excitotoxin which may kill cells by overstimulating them.



GABA is the major inhibitory mediator in the brain, including being responsible for presynaptic inhibition. Synthesis GABA, which exists as gamma-aminobutyrate in the body fluids, is formed by decarboxylation of glutamate. The enzyme that catalyzes this reaction is glutamate decarboxylase (GAD), which is present in nerve endings in many parts of the brain. Receptors: The $GABA_A$ and $GABA_C$ receptors are ion channels made up of five subunits surrounding a pore, and allow the influx of Cl^-. The $GABA_B$ receptors are metabotropic and are coupled to heterotrimeric G proteins that increase conductance in K+ channels, inhibit adenylyl cyclase, and inhibit Ca2+ influx. Fate: GABA is metabolized primarily by transamination to succinic semialdehyde and thence to succinate in the citric acid cycle. GABA transaminase (GABA-T) is the enzyme that catalyzes the transamination.

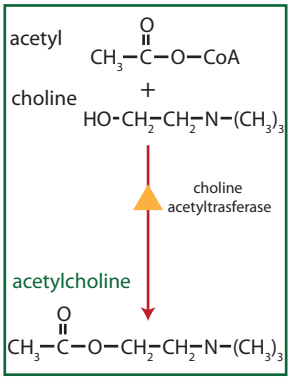


Glycine has both excitatory and inhibitory effects in the CNS. When it binds to NMDA receptors, it makes them more sensitive. However, glycine is also responsible in part for direct inhibition, primarily in the brain stem and spinal cord. Like GABA, it acts by increasing Cl^- conductance.

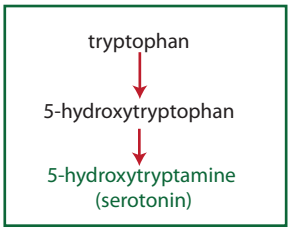


MONOAMINES

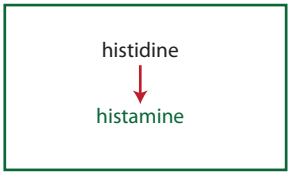
Acetylcholine is a major neurotransmitter in the peripheral nervous system, and it is also present in the brain. Fibers that release ACh are called cholinergic fibers. Acetylcholine is the transmitter at the neuromuscular junction, in autonomic ganglia, and in postganglionic parasympathetic nerve-target organ junctions and some postganglionic sympathetic nerve-target junctions. It is also found within the brain, including the basal forebrain complex and pontomesencephalic cholinergic complex. These systems may be involved in regulation of sleep-wake states, learning, and memory (hence anticholinesterases in dementia). Synthesis: from choline and acetyl coenzyme A in the cytoplasm of synaptic terminals and stored in synaptic vesicles. Receptors are separated into two main groups, the muscarinic and the nicotinic. Nicotinic receptors are ligand gated ion channels which are located in skeletal muscle, on postganglionic neurons in both the SNS and PNS, on adrenal chromaffin cells and within the CNS where they are important in memory and learning. Muscarinic receptors are GPCR that inhibit adenylyl cyclase activity. They are located on the heart where they are inhibitory, and in the smooth muscle and the glands where there are excitatory and are blocked by atropine. Fate: After it is released and activates receptors on the postsynaptic membrane, the concentration of ACh at the postsynaptic membrane is reduced (thereby stopping receptor activation) by the enzyme acetylcholinesterase. This enzyme is located on the pre- and postsynaptic membranes and rapidly destroys ACh, releasing choline. The choline is then transported back into the axon terminals where it is reused in the synthesis of new ACh. The ACh concentration at the receptors is also reduced by simple diffusion away from the site and eventual breakdown of the molecule by an enzyme in the blood.



Serotonin (5-hydroxytryptamine; 5-HT) In general, serotonin has an excitatory effect on pathways that are involved in the control of muscles, and an inhibitory effect on pathways that mediate sensations. The activity of serotonergic neurons is lowest or absent during sleep and highest during states of alert wakefulness. In addition to their contributions to motor activity and sleep, serotonergic pathways also function in the regulation of food intake, reproductive behavior, and emotional states such as mood and anxiety. Synthesis: formed in the body by hydroxylation and decarboxylation of the essential amino acid tryptophan. Receptors: serotonin receptors are diverse in both distribution and function. They are found throughout the brain and peripherally on platelets and smooth muscle and the gut. They are both pre and post synaptic. They may be GPCR with a range of second messengers including andenylyl cyclase and phospholipase C or ligand gated channels. Fate: After release from serotonergic neurons, much of the released serotonin is recaptured by an active reuptake mechanism and inactivated by monoamine oxidase (MAO).

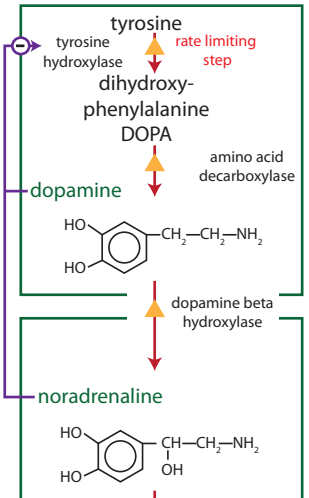


Histamine Histaminergic neurons have their cell bodies in the tuberomammillary nucleus of the posterior hypothalamus, and their axons project to all parts of the brain, including the cerebral cortex and the spinal cord. Histamine is also found in cells in the gastric mucosa and in heparin-containing cells called mast cells that are plentiful in the anterior and posterior lobes of the pituitary gland as well as at body surfaces. Histamine is formed by decarboxylation of the amino acid histidine. The function of this diffuse histaminergic system is unknown, but evidence links brain histamine to arousal, sexual behavior, blood pressure, drinking, pain thresholds, and regulation of the secretion of several anterior pituitary hormones.



CATECHOLAMINES

Dopamine Dopaminergic neurons are located in several brain regions including the nigrostriatal system, which projects from the substantia nigra to the striatum and is involved in motor control, and the mesocortical system, which arises primarily in the ventral tegmental area. The mesocortical system projects to the nucleus accumbens and limbic subcortical areas, and it is involved in reward behavior and addiction. Synthesis: Dopamine is formed by hydroxylation and decarboxylation of the amino acid tyrosine. Some of the tyrosine is formed from phenylalanine, but most is of dietary origin. Tyrosine is transported into catecholamine-secreting neurons and adrenal medullary cells by a concentrating mechanism. It is converted to dopa and then to dopamine in the cytoplasm of the cells by tyrosine hydroxylase and dopa decarboxylase. The dopamine then enters the granulated vesicles (where it is converted to norad). The rate-limiting step in synthesis is the conversion of tyrosine to dopa. Tyrosine hydroxylase, which catalyzes this step, is subject to feedback inhibition by dopamine and noradrenaline, thus providing internal control of the synthetic process. Storage: is granulated vesicles Receptors: There are five known dopamine receptors which are GPCR which either upregulate or down regulate cAMP. Fate: Dopamine is metabolized to inactive compounds by MAO (oxidisation) and COMT (methylation) in a manner analogous to the inactivation of norepinephrine.



Noradrenaline The chemical transmitter present at most sympathetic postganglionic endings is noradrenaline. In the CNS, noradrenergic neurons are located in the locus ceruleus and other medullary and pontine nuclei. From the locus ceruleus, the axons of the noradrenergic neurons form the locus ceruleus system. They descend into the spinal cord, enter the cerebellum, and ascend to innervate the paraventricular, supraoptic, and periventricular nuclei of the hypothalamus, the thalamus, the basal telencephalon, and the entire neocortex Synthesis is from dopamine (as described above) which it is converted to noradrenaline by dopamine -hydroxy-lase (DBH). which occurs in neurons and the adrenal medulla. Storage: is granulated vesicles Receptors: are the alpha receptors 1 (increases IP3 and DAG) and 2 (decreases cAMP) and the beta receptors 1 to 3 which all increase cAMP. Fate: metabolized to inactive compounds by MAO (oxidisation) and COMT (methylation).

Adrenaline Is very similar to noradrenaline in most of its actions, as it uses the same receptors, although it is mostly released from the adrenal medulla not at symptathetic nerve endings. It is released from neurons throughout the brain and like norad is plays essential roles in states of consciousness, mood, motivation, directed attention, movement, blood-pressure regulation, and hormone release. Synthesis: is from norad phenylethanolamine -N- methyltransferase (PNMT) which occurs in neurons and the adrenal medulla. Storage: is granulated vesicles Receptors: are the alpha receptors 1 (increases IP3 and DAG) and 2 (decreases cAMP) and the beta receptors 1 to 3 which all increase cAMP. Fate: metabolized to inactive compounds by MAO (oxidisation) and COMT (methylation).

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