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ANATOMY

BCH 308

QUESTION

Describe in details the synthesis of two named neurotransmitters.

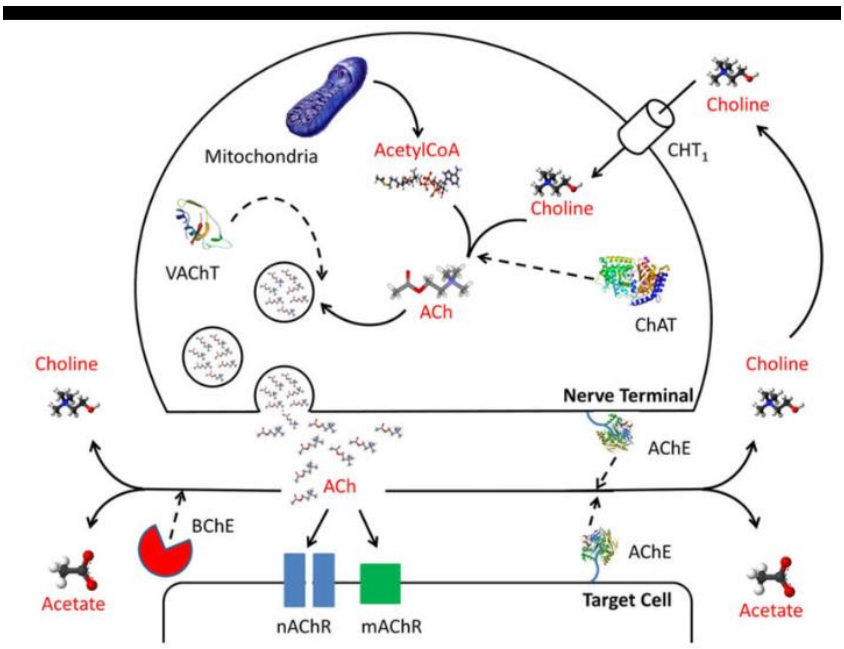
Neurotransmitter, also called chemical transmitters or chemical transmitter, any of a group of chemicals agents released by neurons to stimulate neighboring neurons or muscle or gland cells, thus allowing impulses to be passed from one cell to the next throughout the nervous system.

Neurotransmitters are synthesized by neurons and are stored in vesicles, which typically are located in the axon's terminal end, also known as the presynaptic terminal. The pre synaptic terminal is separated from the neuron or muscle or gland cell onto which it impinges by a gap called the synaptic cleft. The synaptic cleft, presynaptic terminal and receiving dendrites of the next cell together form a junction known as synapse.

They are two broad categories of neurotransmitters:

- Small molecule neurotransmitters
- Neuropeptide neurotransmitters

Small molecule neurotransmitters



Acetylcholine is synthesized from acetyl coenzyme A and choline by the enzyme choline acetyltransferase. In the nervous system, this enzyme is thought to exist primarily in the nerve terminal cytoplasm. Coenzyme A is synthesized in mitochondria and accesses choline acetyltransferase following transport across the mitochondrial membrane into the cytoplasm. In addition to its synthesis in the liver, choline employed in acetylcholine production is derived from dietary sources. There is a carrier system in capillary endothelial cells that is responsible for transport of choline, in its free and phospholipid forms, into the brain.

Hydrolysis of choline-containing phospholipids may also liberate choline that is used in acetylcholine synthesis. As choline acetyltransferase is not saturated by concentrations of acetyl coenzyme A and choline that are estimated to be present in the nerve terminal, it appears that the rate of acetylcholine synthesis is dependent on precursor availability. Enzyme activity is also regulated by product inhibition; by binding at an allosteric site on choline acetyltransferase, acetylcholine inhibits its activity. In addition, mass action and neuronal activity influence the rate of acetylcholine formation. Short-term regulation of enzyme activity is partly achieved by phosphorylation induced by protein kinases. There are no very specific and potent inhibitors of the enzyme and it should be noted that pharmacological blockade of this step (e.g. with naphthylvinylpyridine) in the life-cycle of acetylcholine produces a less profound effect on the transmitter than does inhibition of choline transport.

A specific low-affinity acetylcholine transporter is responsible for uptake of the transmitter from the cytoplasm into vesicles. The genes for choline acetyltransferase and the vesicular acetylcholine transporter are organized in a single gene locus, and transcription of the two genes is typically co-regulated. (±)-Vesamicol is a selective inhibitor of this transporter, with L-(–)-vesamicol being more potent than D-(+)-vesamicol. Once packaged in vesicles, acetylcholine is subject to stimulus-induced release by exocytosis. Several powerful toxins impact on acetylcholine release, notably botulinum toxin which inhibits its release.

Neuronal acetylcholinesterase very rapidly inactivates the majority of acetylcholine released in brain, although butyrylcholinesterase contained in glial cells may hydrolyze a small proportion of acetylcholine in the synapse. In the periphery, acetylcholinesterase is present in muscle that receives cholinergic innervation, while butyryl-cholinesterase is more widely distributed. A number of reversible (e.g. physostigmine, BW284C51) and irreversible (e.g. iso-OMPA) inhibitors of acetylcholinesterase are known, and these drugs have the effect of prolonging the synaptic effects of acetylcholine. Second generation reversible anticholinesterases such as donepezil, rivastigmine (ENA 713), eptastigmine, and galantamine (galanthamine) are being employed as treatments for Alzheimer's disease. Some second generation cholinesterases have been withdrawn from clinical use because of unacceptable side effects (e.g, tacrine, metrifonate). Irreversible acetylcholinesterase inhibitors are used as insecticides and chemical warfare agents. Choline, which is liberated from acetylcholine by acetylcholinesterase, is taken back up into cholinergic terminals by a high-affinity transporter, and reused in transmitter synthesis. Hemicholinium-3 potently and reversibly inhibits choline transport, and these results in a profound decrease in acetylcholine formation. Unlike hemicholinium-3, A-4 (a bis 4-methylpiperidine analog of HC-3), is active following peripheral administration. Nitrogen mustard analogs of choline are potent irreversible inhibitors of high-affinity choline uptake.

Neuropeptide neurotransmitters

Beta endorphins are neuropeptides involved in pain management, possessing morphine like effect, and are involved in natural reward such as feeding, drinking, sex and maternal behavior.

Beta endorphins are primarily synthesized and stored in the anterior pituary gland from their precursor protein proopiomelanocortin(POMC). However, recent studies suggest cells of the immune system are also capable of beta endorphin synthesis because immune cells possess mRNA transcript for POMC and T-lympocytes, B-lympocytes, monocytes and macrophages have been shown to contain endorphins during inflammation.

In the peripheral nervous system (PNS), beta endorphins produce analgesia by binding to opioid receptors at both pre and post synaptic nerve terminals primarily exerting their effect through presynaptic binding. When bound, a cascade of interactions results in inhibition of the release of tachykinins, particularly substance P, a key protein involved in the transmission of pain. In the PNS, mu-opioid receptors are present throughout peripheral nerves and have been identified in the central terminals of primary afferent neurons, peripheral sensory nerve fibers and dorsal root ganglia.

In the central nervous system, beta-endorphins similarly bind mu-opioid receptors and exert their primary action at presynaptic nerve terminals. However, instead of inhibiting substance P, they exert their analgesic effect by inhibiting the release of GABA, an inhibitory neurotransmitter, resulting in excess production of dopamine.8,9 Dopamine is associated with pleasure. In the CNS, mu-opioid receptors are most abundant in descending pain control circuits including the amygdala, mesencephalic reticular formation, periaqueductal gray matter (PAG) and rostral ventral medulla.