

Acetylcholine Synthesis and Metabolism

Key References

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Overview

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. (\pm)-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 butyrylcholinesterase 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 this 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.

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INHIBITORS	UPTAKE	COMPOUND	ENZYME	Co-FACTORS	INHIBITORS
Hemicholinium-3 (H108) Choline mustard aziridinium A-4	<pre> graph TD Choline --> ACh[Acetylcholine] ACh --> Choline_Ac[Choline + Acetic acid] Choline_Ac --> Choline </pre>	Choline Acetylcholine Choline + Acetic acid	Choline acetyltransferase Acetylcholinesterase	Acetyl CoA	Naphthylvinylpyridine Physostigmine (E8375) N-Methylphysostigmine (M100) Neostigmine (N2001) Ambenonium dichloride Tacrine (A3773) Edrophonium chloride (E3256) BW 284C51 (A9013) ISO-OMPA (T1505) SDZ ENA 173 9-Amino-1,2,3,4-tetrahydroacridine, bis, 1,7-heptylene (A256) Galanthamine (G1660)

Abbreviations
ISO-OMPA: Tetraisopropyl pyrophosphoramidate

FOOTNOTES