

Acetylcholine Synthesis and Metabolism

Key References

- Collier, B. et al. "Storage and release of acetylcholine in a sympathetic ganglion." *Prog. Brain Res.* **98**, 183-189 (1993).
- Cummings, J.L. "Cholinesterase inhibitors: A new class of psychotropic compounds." *Am. J. Psychiatry* **157**, 4-15 (2000).
- Giacobini, E. "Cholinesterase inhibitors for Alzheimer's disease therapy: From tacrine to future applications." *Neurochem. Intl.* **32**, 413-419 (1998).
- Israel, M., Dunant, Y. "Acetylcholine release and the cholinergic genomic locus." *Mol. Neurobiol.* **16**, 1-20 (1998).
- Karczmar, A. "Anticholinesterases: Dramatic aspects of their use and misuse." *Neurochem. Intl.* **32**, 401-411 (1998).
- Krall, W.J. et al. "Cholinesterase inhibitors: A therapeutic strategy for Alzheimer disease." *Ann. Pharmacother.* **33**, 441-450 (1999).
- Massoulie, J. et al. "Structure and functions of acetylcholinesterase and butyrylcholinesterase." *Prog. Brain Res.* **98**, 139-146 (1993).
- Oda, Y. "Choline acetyltransferase: The structure, distribution and pathologic changes in the central nervous system." *Pathology Intl.* **49**, 921-937 (1999).
- Parsons, S.M. et al. "Acetylcholine transport, storage, and release." *Int. Rev. Neurobiol.* **35**, 279-390 (1993).
- Scremin, O.U., Jenden D.J. "Acetylcholine turnover and release: The influence of energy metabolism and systemic choline availability." *Prog. Brain Res.* **98**, 191-195 (1993).
- Tucek, S. "Short-term control of the synthesis of acetylcholine." *Prog. Biophys. Mol. Biol.* **60**, 59-69 (1993).
- Wu, D., Hersh L.B. "Choline acetyltransferase: Celebrating its fiftieth year." *J. Neurochem.* **62**, 1653-1663 (1994).

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. 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

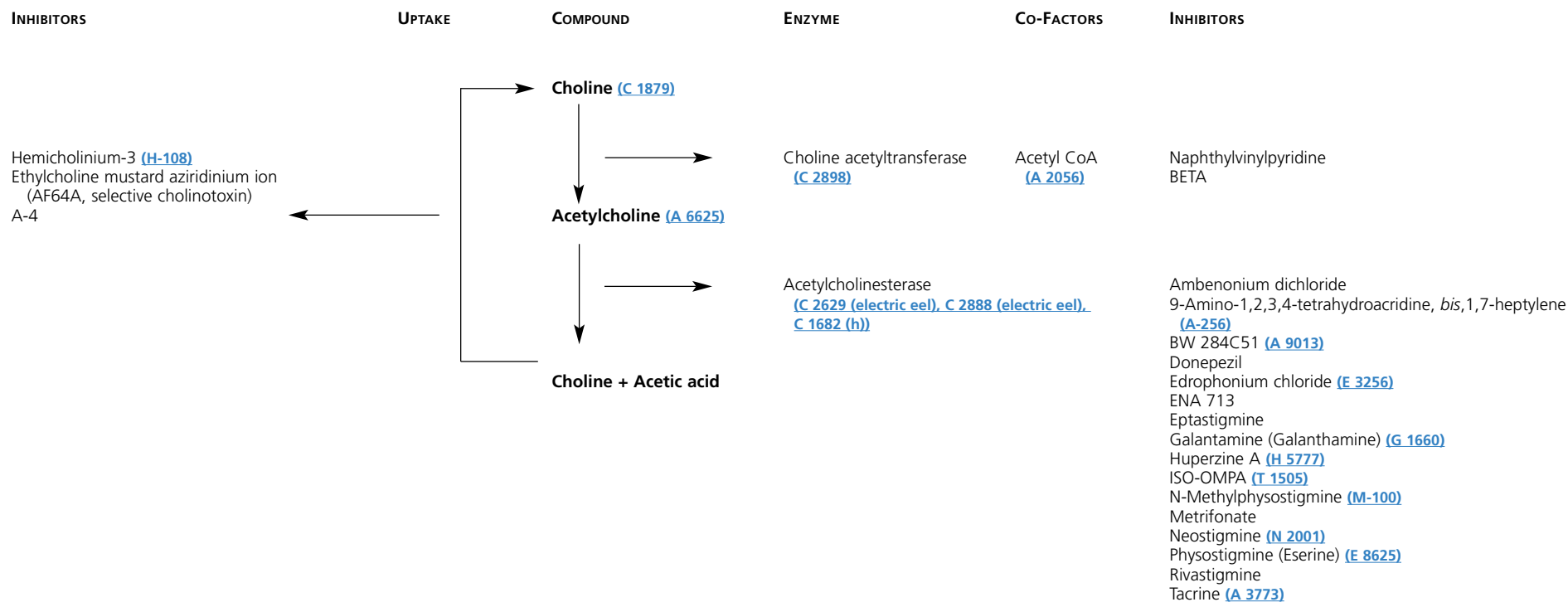
vesicles. (\pm)-Vesamicol is a selective inhibitor of this transporter, with L-($-$)-vesamicol being more potent than D-($+$)-vesamicol. Once packaged in vesicles, acetylcholine is subject to stimulus-induced release by exocytosis. Several powerful toxins impact on acetylcholine release, notably botulinum 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 effects of acetylcholine. Second generation anticholinesterases such as donepezil, rivastigmine, huperzine A, eptastigmine, metrifonate, ENA 713 and galantamine (galanthamine) are being investigated as treatments for Alzheimer's disease. 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.

Acetylcholine Synthesis and Metabolism



Abbreviations

A-4: α bis4-Methyl-piperidine analog of HC-3

BETA: (2-Benzoyl-ethyl)-trimethylammonium iodide

BW 284C51: 1,5-bis(4-Allyldimethylammoniumphenyl)-pentan-3-one

ENA 713: (S)-N-Ethyl-3-[(1-dimethyl-amino)ethyl]-N-methylphenylcarbamate hydrogentartrate

ISO-OMPA: Tetraisopropyl pyrophosphoramidate

h: human