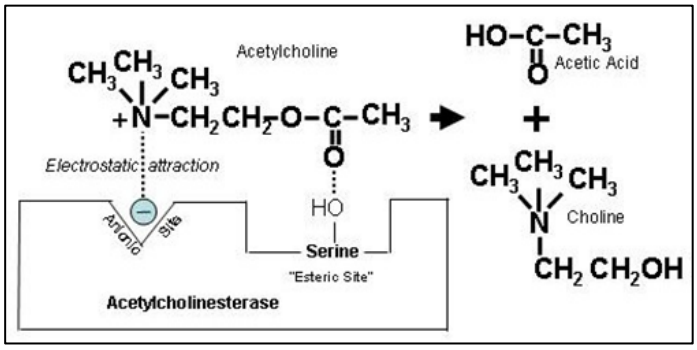
Acetylcholinesterase Physiology

Anesthetic Pearls: Anesthetic Implications and Physiology of Acetylcholinesterase

Acetylcholinesterase (**AChE**) (also called "specific cholinesterase" or "true cholinesterase) is one of the most efficient enzymes in the body that terminates the transmission of Acetylcholine (ACh) within milliseconds after its release from nerve endings.



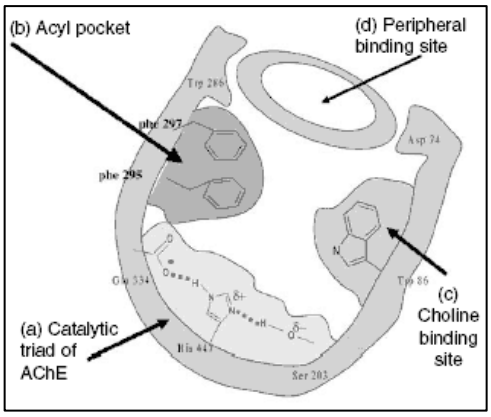
Location:

1. Synthesized and secreted in muscle tissue (however, it remains attached to muscle tissue via thin stalks of collagen fastened to the basement membrane)
2. Next to the ACh receptors at the motor end-plate membrane
3. ALL cholinergic synapses
4. Erythrocytes (function unknown)

Physiology:

A. **Hydrolysis** of 2,500 molecules of ACh per second to Acetate + Choline

B. Most of the molecules of acetylcholine released from the nerve initially pass between the enzymes to reach the post-junctional receptors. However, as the molecules are released from the receptors, they invariably encounter acetylcholinesterase and are enzymatically destroyed.



C. ACh is attracted to the acetylcholinesterase enzyme because the negative charge of the anionic enzyme site (approximately "14" aromatic amino acids line a deep groove in the enzyme structure) which attracts the positive charge in the quaternary nitrogen of ACh.

D. Initially there is an **electrophilic** attack on the ACh molecule which leads to an acetate linkage transferring a choline molecule to an amino acid in the enzyme. The choline molecule detaches and drifts away, leaving a **covalently** bound and acetylated enzyme. The acetate link is subsequently attacked and broken by a hydroxyl group from water. The acetate then drifts away and the regenerated enzyme is ready to interact with another molecule of ACh thereby repeating the process.

Acetylcholinesterase is the target of many Alzheimer's Dementia drugs, sage oil, nerve gases (organophosphate gas Sarin), and insecticides. These agents, known as cholinesterase inhibitors, block the function of acetylcholinesterase and thus cause excessive acetylcholine to accumulate in the synaptic cleft. The excess acetylcholine causes neuromuscular paralysis throughout the entire body, leading to death by asphyxiation. Cholinesterase inhibitors may also be used in treatment of Lewy Body Dementia. On the horizon is an a potential drug target is the endogenous inhibitor of acetylcholinesterase in neurons known as "Mir-133 microRNA." This endogenous AChE inhibitor may limit brain inflammation by silencing the expression of this protein and allowing acetylcholine to act an in anti-inflammatory capacity.