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Acetylcholinesterase: Substrate Traffic and Inhibition

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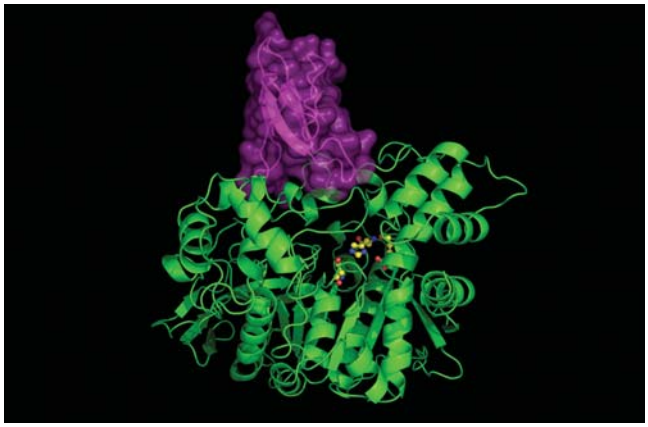
In 1991, the laboratory of Joel L. Sussman and Israel Silman determined the 3D structure of the enzyme acetylcholinesterase (AChE) isolated from the Pacific electric ray (*Torpedo californica*). Later, in 1995, the structure of AChE in complex with the snake toxin fasciculin-II (FAS-II) was solved by Sussman, Silman, Bourne, Taylor, and Marchot. This *Proteopedia* page, (http://www.proteopedia.org/w/Acetylcholinesterase:_Substrate_Traffic_and_Inhibition) with the use of two physical models, compares the structure of the AChE/acetylcholine (ACh) complex to illustrate the process of ACh hydrolysis; which we term the substrate traffic story, and the structure of the AChE/FAS-II complex to illustrate the process of AChE inhibition by FAS-II; which we refer to as the inhibition story. Visitors to this page may view video clips of these physical models, demonstrating the substrate traffic story and the inhibition story, as well as comparative computer models.

AChE, embedded in the postsynaptic membrane, is essential for termination of the nerve impulse at the cholinergic synapse. Unlike other enzymes that have active sites located near the surface, AChE was found to have an active site located at the base of a deep (~20 Å) and narrow (~5 Å) gorge lined by 14 highly-conserved aromatic residues. ACh is a neurotransmitter and the optimal substrate for AChE. It consists of an acyloxy group, an ethylene group, and a quaternary ammonium ion. The quaternary ammonium ion of ACh is initially attracted to three aromatic residues located at the top of the gorge, i.e., the *peripheral anionic site*. The remaining aromatic residues that line the gorge filter ACh down to the active site. The active site is a catalytic triad composed of the amino acids histidine, serine, and glutamic acid. Inhibition of AChE can be caused by FAS-II, a 61-residue polypeptide that is a component of the venom of the East African green mamba snake (*Dendroaspis angusticeps*). FAS-II is first attracted to AChE by long-range electrostatic complementarity, specifically the side of FAS-II that binds to AChE is highly positive while the surface of the AChE gorge is highly negative. FAS-II consists of three loops; two of the loops fit into the AChE gorge blocking the neurotransmitter ACh from entering (see Fig. 1). Once AChE is inhibited by FAS-II, fasciculation occurs, leading to death by suffocation.



COLOR

FIG. 1. **Structure of the AChE/FAS-II complex**. AChE is colored green and is shown as a ribbon diagram, whereas FAS-II is colored magenta and is shown as a ribbon diagram with the molecular surface highlighted. Residues that form the AChE active site: serine at position 200, glutamic acid at position 327 and histidine at position 440, are shown in ball and stick format (carbon atoms, yellow; nitrogen atoms, blue; oxygen atoms, red).

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