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How Nerve Agents Function Through Anti Alzheimer Drugs: 3D Structure of Acetylcholinesterase



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Abstract

The synaptic enzyme acetylcholinesterase (AChE) terminates transmission at cholinergic synapses by very rapidly hydrolysing acetylcholine. Examination of the 3D structure of AChE shows that the active site is located at the bottom of deep and narrow gorge, lined largely by aromatic residues, with its peripheral anionic site located at the top, near the entrance of the gorge. AChE is the target of nerve agents, insecticides and therapeutic drugs, in particular the first generation of anti-Alzheimer drugs. 3D structures of AChE have been determined for the Torpedo, Electrophorus, Mouse, Drosophila and human enzymes. Overall, more than a hundred crystal structures of AChEs, and of covalent conjugates and reversible complexes with various inhibitors and substrate analogues have been determined. Although the 3D structure of the enzyme itself, and of its molecular dimer, are highly conserved, subtle structural differences are seen to occur upon the binding of certain inhibitors. These changes are well correlated with molecular dynamics data, and appear to be of functional significance.