SL10 **Structure-based Drug Design**

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The synaptic enzyme acetylcholinesterase (AChE) terminates transmission at cholinergic synapses by rapidly hydrolysing acetylcholine (ACh). It is anchored within the synaptic cleft by a highly specialized anchoring device in which catalytic subunit tetramers assemble around a polyproline II helix. Examination of the 3D structure of AChE shows that the active site is located at the bottom of a deep and narrow gorge, lined largely by aromatic residues, with its peripheral anionic site located at the top, near the entrance to of the gorge. AChE is the target of nerve agents, insecticides and therapeutic drugs; in particular we have determined the 3D structures of the first generation of anti-Alzheimer drugs complexed with AChE [with the corresponding PDB IDcodes]: Aricept [**1eve**], Tacrine [**1acj**], Exelon [**1gqr**], Reminyl [**1dx6**], Huperzine [**1vot**]. Both target-guided synthesis and structure-based drug design have been used effectively to obtain potent anticholinesterase agents. In addition, AChE is believed to play 'non-classical' roles in addition to its 'classical' function in terminating synaptic transmission. Thus, it accelerates assembly of Aβ into amyloid fibrils, and also may serve as an adhesion protein. Both these 'non-classical' functions appear to involve the peripheral anionic site. Certain novel anticholinesterases are targeted against this site, rather than against the active site at the bottom of the gorge.