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Modeling of substrates sorption into acetylcholinesterase and butyrylcholinesterase active sites using molecular docking method

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Cholinesterases (ChE) acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are capable for hydrolyzing esters. Our previous structure-activity analysis of ChE substrates showed that extended conformation of substrate choline moiety is productive for hydrolysis by AChE and its semi-folded conformation is productive for hydrolysis by BChE. The formation of activated complex between ChE and substrate molecules is possible only when the substrate molecule is in the productive conformation [1]. The purpose of the present work was to model sorption stage of ChE hydrolysis and to determine the substrate orientation of a substrate in the binding site of AChE and BChE using molecular docking and computer simulation methods.

17 ACh analogs of general formula R-C(O)-O-$(CH_2)_2$-$N^+(CH_3)_3$ have been docked into AChE and BChE active sites using ICM [2]. The X-ray structures of Torpedo Californica AChE and Human BChE were retrieved from Protein Data Bank [3]. Ligands models were built with ICM. Force field and grid parameters for rigid protein docking and further refinement with flexible protein side-chain were taken as in [4].

The calculations and graphical analysis of obtained complexes have shown that the quaternary nitrogen atom of substrate is sorbed near the benzol moiety of Trp84(82) at a distance between 4.0 and 4.5Å. The acyl moiety of the substrates is oriented towards the entrance of ChE active site gorge. The distance between ligand carboxyl carbon and hydroxyl oxygen of catalytic serine varies between 6 and 13 Å, so activated complexes can not be formed in such positions. The conformations of choline moiety are various for sorbed substrate molecules.

It has been concluded that sorption of a substrate molecule in the AChE and BChE active site is conditioned by the mooring of the substrate nitrogen near Trp84(82). It has been proposed that such interaction could be the launching for conformational changes in polypeptide chain, in particular in the region around the so-called omega-loop which is located near the entrance to the binding site. The molecular docking results are employed to investigate with molecular mechanics simulations the conformation changes of protein-ligand complex during the sorption process.

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