

The fluctuation analysis of conformational mobility for pyridoxine derivatives in the active site of acetylcholinesterase

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Abstract

© 2016, International Journal of Pharmacy and Technology. All rights reserved. Acetylcholinesterase (AChE) is the main enzyme of the nervous system that is responsible for the regulation of a nerve impulse transfer by a rapid hydrolysis of the neurotransmitter - acetylcholine. The most important aspect in the studies related to AChE is the issue of specific interaction with ligands for its activity regulation. In most cases it is necessary for AChE site-specific inhibitors design for development of potential new drugs for the treatment of neurodegenerative diseases with more efficiency and less side effects. Currently the methods of molecular modeling are widely used for new drugs design. In this study AChE structure of 2JEY mouse served as biological target. The derivatives of pyridoxine were used as ligands, with anticholinesterase effect shown in vivo. Moreover the position of these ligands in AChE active center during docking was similar to AChE inhibitors used in medicine (proserin, physostigmine). A combination of molecular docking and Molecular Dynamics methods allowed us to estimate the drug potential of inhibitors more efficiently. The study was carried out using the following software packages: AutoDock.1.5.6 (Vina application) and NAMD 2.8 with AMBER 99 force field. The result showed that the ligand position in the active cavity of an enzyme may vary significantly even for related compounds and these positions depend on ligand modification. The analysis of molecular dynamics revealed that the ligand mobility and respective inhibitory activity depend on an inhibitor size and on ligand affinity to AChE. The number of interatomic interactions between molecules and probabilities of their interactions in an active site of the enzyme were used for analysis. It was shown that the molecules with a high affinity for the enzyme active cavity not always will be able to get into active cavity by reason of their size. The hydrophobic interactions of ligands with uncharged amino acid residues allows them to bind more efficiently to the active center of AChE. Thus the structural features of the ligand exactly define long-term anticholinesterase effect.

Keywords

A specific interaction of enzyme with ligand, Acetylcholinesterase (AChE), Molecular docking, Molecular dynamics, Pyridoxine derivatives, Screening