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Research Article

Discovery of potential inhibitor against human acetylcholinesterase: a molecular docking and molecular dynamics investigation

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease of central nervous system among elderly people. Human acetylcholinesterase (hAChE), an important enzyme in neuronal signaling, is responsible for the degradation of acetylcholine which in turn prevents the post synaptic signal transmissions. hAChE has been an attractive target of drug discovery for the search of therapeutics against AD. In the recent past hAChE has become hot target for the investigation of new potential therapeutics. We performed virtual screening of entire database against hAChE. Further, the extra precision molecular docking was carried out to refine the docking results and the best complex was passed for molecular dynamics simulations in order of understanding the hAChE dynamics and its behavior in complex with the ligand which corroborate the outcomes of virtual screening. This also provides binding free energy data that establishes the ligands efficiency for inhibiting hAChE. The computational findings discussed in this paper provide initial information of inhibitory effects of ligand, (drugbank entry DB00983), over hAChE.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and is characterized by loss of memory and cognition. It is a progressive, neurodegenerative disorder, which affects the central nervous system of old age people. The key pathological symptoms include extensive synaptic and neuronal loss as well as proteinaceous plaque formation (Blennow et al., 2006). The proteinaceous plaque is an extracellular deposit of small peptide β-amyloid protein (Aβ), which is produced from a large β-amyloid precursor protein (APP; Masters et al., 1985; Kang et al., 1987) by the proteolytic action of secretases (recently reviewed by Zhang et al., 2011). Moreover, the AD brain is also characterized by neurofibrillary tangles composed of microtubule associated protein tau which are remarkably hyperphophorylated (Grundke-Iqbal et al., 1986). Thus, it has become vital, and much research is focused, to understand the toxicity of Aβ and P-tau linked with AD. To achieve effective therapy against AD it is vital to understand that how these peptides affect the expression of other important brain proteins and ultimately causing neurodegeneration, moreover, it will be a big plus to decode the pattern of interaction of Aβ and P-tau in order to understand the mechanism of neurotoxicity caused by them.

Human acetylcholinesterase (hAChE), one of the fastest enzymes belonging to serine esterases, is key regulator of cholinergic signaling (Cheung et al., 2012; Silman and Sussman, 2008). hAChE present in the post-synaptic membrane is responsible for the termination of neuronal signal transmission by hydrolyzing acetylcholine. The progression of AD results in loss of many neurons including the forebrain cholinergic neurons it has also been associated with the abnormal metabolism of acetylcholine which is correlated with the intelligence impairments (Perry et al., 1980). Both the acetylcholine synthesizing as well as hydrolyzing enzymes (choline acetyltransferase and hAChE respectively) are affected. hAChE has been an attractive target for the drug design against AD (Racchi et al., 2004), in hope to delay the degradation of acetylcholine among affected people thus increasing the half life of cholinergic signal, and many studies have been reported in previous years for the therapy of AD (García-Ayllón et al., 2011; Carvajal and Inestrosa, 2011) but with moderate and reversible effects (McGleenon et al., 1999; Kaduszkiewicz et al., 2005). Further, the limited efficacies of different hAChE inhibitors, currently under clinical trials, have been recently reviewed by

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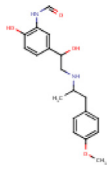
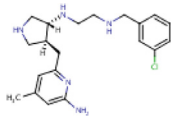
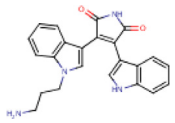
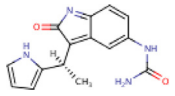
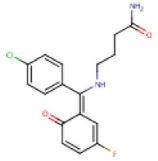
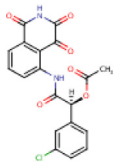
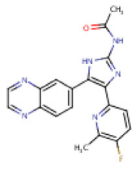
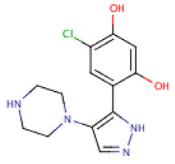
Zemek et al. (2014) and Galimberti and Scarpini (2016). A common feature of AD pathology includes increased level of hAChE around amyloid plaques with unknown reasons. Moreover, prolonged use of hAChE inhibitors has shown up-regulation of hAChE activity. These abnormality in expression as well regulation of hAChE can be attributed to the limited efficiency and transient effects of hAChE inhibitors leading to the genesis of the amyloid plaques (Khan, 2009). Therefore, it has become a necessity of time to identify new potential therapeutics for hAChE (Chadha et al., 2015 and Khan, 2009).

Although experimental techniques such as x-ray crystallography have proved its role in the study of biomolecules, yet it is

Table 1
Details of flexible docking output.

S. No.	Database Entry	Ligand	Docking Score	Hydrogen Bonding
1	DB00983		−15.179	(Asp 74) NH···O (Thr 86) OH···O OH···O (Asn 87) NH···O (Tyr 124)
2	DB08019		−14.335	NH···O (Trp 86) NH···O (Asn 87) NH···O (Gly 120) NH···O (Glu 202) NH···O (Tyr 341)
3	DB07456		−14.225	NH···O (Asp 74) NH···O (Thr 83) NH···O (Asn 87) NH···O (His 447)
4	DB07132		−12.765	NH···O (Trp 86) (Tyr 124) OH···O NH···O (Ser 125) NH···O (Tyr 341) NH···O (His 447)
5	DB00837		−12.658	(Asp 74) NH···O NH···O (Trp 86) NH···O (Asn 87) OH···O (His 447)
6	DB08498		−11.862	(Thr 83) OH···O NH···O (Thr 83) (Gly 121) NH···O (Gly 122) NH···O O···OH (Ser 203) (Lys 348) NH···O
7	DB07152		−10.880	(Asp 74) NH···O NH···O (Tpr 86) NH···O (Ser 125) F···OH (Ser 203)
8	DB07100		−10.869	NH···O (Asp 74) (Gly 120) NH ···O OH···O (Glu 202) NH···O (His 447) OH···O (His 447)