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In silico analysis of binding of neurotoxic venom ligands with acetylcholinesterase for therapeutic use in treatment of Alzheimer's disease

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HIGHLIGHTS

- Acetylcholinesterase have surfaced as therapeutic targets for the treatment of cognitive impairments associated with Alzheimer's.
- In this study we have analyzed the protein–protein interactions between acetylcholinesterase receptor and venom toxins.
- Binding site residue information was collected and in detail analysis of their binding interactions with venom ligands was done using computational approaches and tools.

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ABSTRACT

Acetylcholinesterases (AChE) are enzymes that function in hydrolyzing the neurotransmitter acetylcholine. Diminished levels of acetylcholine have been reported for various neurodegenerative diseases, especially Alzheimer's. Therefore, acetylcholinesterase inhibitors are being considered quite effective in treating these diseases. Fasciculin 2 is a toxin isolated from Eastern green mamba that had been reported as a reversible acetylcholinesterase inhibitor. In this study, we have reported the *in silico* analysis of venom toxins via various computational tools used for drug designing, to find out the protein–protein interaction of these toxins in complex with acetylcholinesterase enzyme. In total 15 toxins have been selected from the venoms of various species as ligand dataset, to study their binding interactions with the acetylcholinesterase enzyme.

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1. Introduction

Acetylcholinesterases, also known as acetyl-hydrolases and commonly abbreviated as AChE are hydrolase enzymes that function in hydrolyzing the neurotransmitter acetylcholine. Due to their function they are predominantly found in cholinergic synapsis of the brain and in the synapsis that serve as junction between the muscular system and nervous system (Tripathi and Srivastava, 2008). Once a signal is passed via the acetylcholine neurotransmitter, the acetylcholinesterase breaks down the acetylcholine into its two component parts, acetic acid and choline. As a result, this mode of action halts the signaling process (Dvir et al., 2010). This allows the components to be recycled back into new neurotransmitters which will function in the next signal processing (Jolkkonen, 1996).

The activity of acetylcholine has been linked to various neurodegenerative diseases; primarily Alzheimer's but also others like Parkinson's, Huntington's and schizophrenia (Rolinski et al., 2012). The activity of diminished acetylcholine neurotransmitter levels may result in cognitive impairment such as the memory deficits associated with Alzheimer's disease (McGleenon et al., 1999). By administering a drug that inhibits the activity of acetylcholinesterase, the levels of the neurotransmitter can be heightened to normal. Thus acetylcholinesterase inhibitors have become popular for the treatment of the cognitive problems associated with Alzheimer's, by inhibiting the action of this enzyme. This will in turn prevent acetylcholine breakdown, to alleviate its loss which was caused by the death of

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cholinergic neurons. The efficacy of this mechanism has been evident in patients with mild to moderate Alzheimer's disease and somewhat for their use in patients with advanced stages of Alzheimer's also (Winblad and Jelic, 2004).

Recently, the therapeutic abilities of venoms and toxins from various reptiles and insects have surfaced. Various neurotoxic venom peptides have become a subject of particular interest due to their potential use in neurological disorders. Such a venom toxin is the Fasciculin (FAS), which is a 61-residue polypeptide that has been successfully extracted and purified from the venom of eastern green mamba, *Dendroaspis angusticeps*. It is a three-fingered toxin and is a powerful reversible inhibitor of acetylcholinesterase enzyme (Harel et al., 1995). This activity from this highly potent snake toxin has rendered it pharmacologically important as it can be used to treat the cognitive problems associated with Alzheimer's (Taylor, 1996).

A number of *in silico* studies have been reported that have investigated various computational approaches to treat Alzheimer's. These studies include construction of structural models to understand many of the critical protein receptors involved in Alzheimer's (Carter, 1998; Howe, 2002; Chou, 2005; Jones and Heinrikson, 1997) and to investigate and find potential drug candidates for treating Alzheimer's (Wei et al., 2005; Chu et al., 2014; Gu et al., 2009; Zheng et al., 2007).

After doing extensive literary research on Fasciculin and its pharmacological importance, we studied similar venom toxins *in silico* to identify their binding residues with the enzyme acetylcholinesterase. This study covered various core bioinformatics analysis procedures to identify the binding residues of the acetylcholinesterase with the venom ligands. The results helped us demonstrate and report the pharmacological ability of these venom ligands similar to those of Fasciculin and their prospective use in the drug development for Alzheimer's and other neurodegenerative diseases.

2. Materials and methods

2.1. Receptor data set collection

Relevant protein data bank (pdb) entries for acetylcholinesterases were searched on the RSCB (Berman et al., 2000) protein data bank. Relevant pdb entries were identified for human, mouse *Mus musculus* (Bourne et al., 2003) and pacific electric ray *Torpedo californica* (Harel et al., 1995) as well. All three of the structures were superimposed and aligned on Chimera (Pettersen et al., 2004) and their residues were checked for conservation among the three species, as shown in Fig. 1. A sequence alignment for acetylcholinesterase of all three species was also performed using PRALINE multiple sequence alignment toolbox (Simossis and Heringa, 2005) as shown in Fig. 2. The identification of the binding pocket is crucial in understanding the binding interaction between the receptor and a ligand. Successful identification of the receptor's binding pocket makes it an important target for drug designing (Chou, 2004). The binding pocket residues observed for human acetylcholinesterase are shown in Table 1. The structures for mouse and human showed more conservation than those with the electric ray.

The structure of acetylcholinesterase in human in complex with Fasciculin 2, with pdb id: 4BDT (Nachon et al., 2013) was selected as the receptor for ligand bindings and dockings as shown in Fig. 3.

2.2. Ligand data set collection

A dataset of 15 venom toxins from multiple snake and scorpion species, including the toxin Fasciculin 2 were taken to study binding interactions with the selected receptor. The selected toxins shown in Table 2 are all neurotoxins that have been reported to have potential therapeutic abilities towards neurodegenerative diseases (Essack et al., 2012; Petricevich et al., 2013; Anderson and Harvey, 1988).

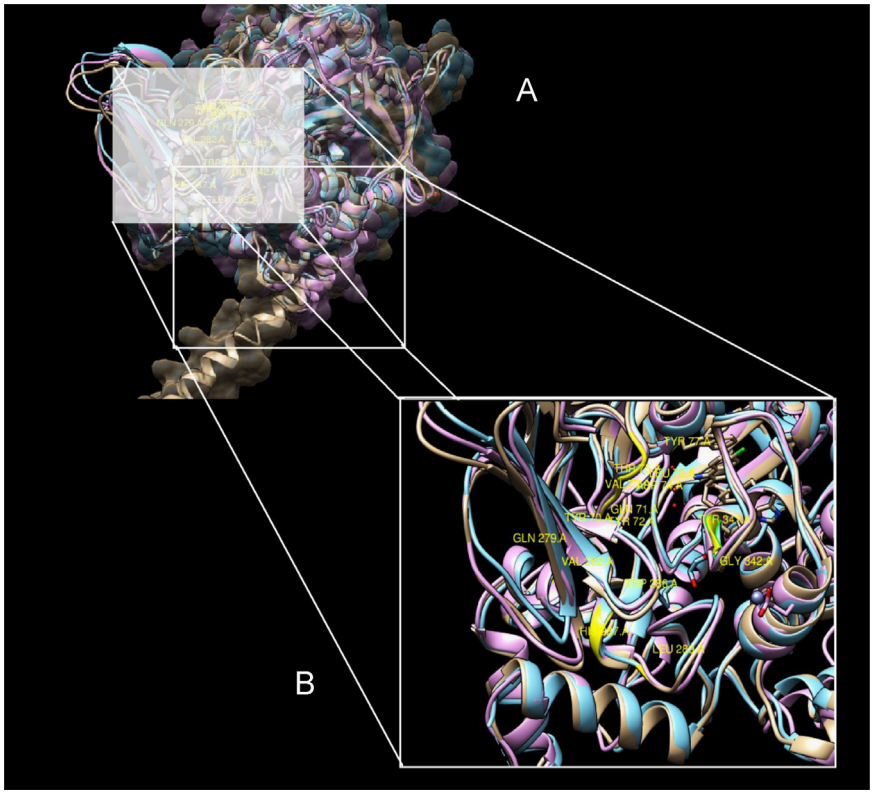

Fig. 1. (A) Cross-species superimposition of acetylcholinesterase structures of human (pale brown), mouse (blue) and Pacific electric ray (pink). (B) Conserved residues are shown in yellow in the zoom in view. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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