Veena Beri et al., Clinic Pharmacol Biopharm 2014, 3:2
http://dx.doi.org/10.4172/2167-065X.S1.006

OMICS Group Conferences
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2nd International Summit on
Clinical Pharmacy
December 02-03, 2014 DoubleTree by Hilton Hotel San Francisco Airport, USA

Naturally occurring inhibitors of acetylcholinesterase that block organophosphate poisoning

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Acetylcholinesterase (AChE) is the most important enzyme in vertebrate nervous system. It hydrolyses the neurotransmitter acetylcholine (ACh) into choline and acetate. It is involved in transmission of signals between nerves and between nerves and muscles. In recent years, there is increasing evidence to support the involvement of ACh and AChE in non-neuronal function in animals as well as in plants. Chemicals that inhibit AChE or a related enzyme butyrylcholinesterase (BChE) are known as anticholinesterases (AntiChE). AntiChE like organophosphates (OPs), which are commonly used in chemical warfare (nerve agents), can inactivate AChE. The resulting accumulation of acetylcholine (ACh) in cholinergic synapses can lead to the failure of cholinergic synaptic transmission, deterioration of muscular junctions, flaccid muscle paralysis, seizures in the central nervous system and can lead to death. A potential long term strategy for preventing AChE inactivation by OPs is based on evidence that OPs must pass through a peripheral site or P-site near the mouth of the AChE active site gorge before reacting with a catalytic serine in an acylation site or A-site at the base of the gorge. An ultimate goal of this strategy is to design compounds that bind tightly at or near the P-site and exclude OPs from the active site while interfering minimally with the passage of acetylcholine. However, to target the AChE P-site with ligands and potential drugs that selectively restrict access, much more information must be gathered about the structure–activity relationships of ligands that bind specifically to the P-site. An inhibitor competition assay that can correctly determine whether an AChE inhibitor binds to the P-site, the A-site, or both sites is used. We have used this assay to examine three uncharged, natural product inhibitors of AChE, including aflatoxin B1, dihydrotanshinone I, and territrem B. The first two of these inhibitors are predicted by the competition assay to bind selectively to the P-site, while territrem B is predicted to span both the P- and A-sites. These predictions have recently been confirmed by X-ray crystallography (Cheung, J. et al., 2013). Dihydrotanshinone I, with an observed binding constant (KI) of 750 nM, provides a good lead compound for the development of high-affinity, uncharged inhibitors with specificity for the P-site.

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