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MEETING ABSTRACTS

ENHANCEMENT IN PYRIDINIUM OXIME-ASSISTED REACTIVATION OF TABUN-INHIBITED ACETYLCHOLINESTERASE ACHIEVED BY ACTIVE SITE MUTATIONS

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Tabun represents a phosphoramide class of organophosphates that are covalent inhibitors of acetylcholinesterase (AChE), an essential enzyme in neurotransmission. The currently used therapy in excessive cholinergic stimulation consists of the muscarinic antagonist of acetylcholine stimulation, an anti-seizure drug when indicated and an oxime as the reactivator of inhibited AChE. Since common oximes are particularly ineffective in tabun exposure, we probed the reactivation of phosphoramidate conjugates in more depth by using mutants of AChE and pyridinium oximes to reveal the structural subtleties and yield more information on the architecture of the active centre gorge needed for the reactivation of phosphoramidate agents used in terrorism and as pesticides. Our results indicated that the replacement of aromatic residues with aliphatic ones at the acyl pocket and choline binding site mostly interfered with the stabilization of the oxime's pyridinium ring(s) in the proper orientation of the oxime group toward the phosphorylated active site serine. The peripheral binding site mutation resulted in a 2-5 fold increase in the reactivation rates by bis-pyridinium oximes when compared to the AChE wild type. In the case of mono-pyridinium oximes, we reported a 150-fold enhancement of the maximal reactivation rate for the choline binding site mutation, while the molecular recognition seemed to remain preserved. Therefore, our results emphasized the positive effect of several mutations on oxime embedding and orientation into a position for productive interactions with the tabun-phosphorylated active site serine indicating a future potential for further development of pseudo-catalytic bioscavengers based on AChE mutants.

Keywords: nerve agents; antidotes; 2-PAM; HI-6

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