THREAT AGENT DEFEAT MODELING AND TESTING USING WMD SIMULANTS

Developing An Assay To Further Elucidate The Interactions Of Chemical Warfare Agents And Reactivators With Acetylcholinesterase

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Organophosphorus nerve agents (OPNAs) inhibit acetylcholinesterase (AChE) via a covalent interaction at the active site, leading to a buildup of acetylcholine (ACh) in the neuronal synapse. This buildup of ACh leads to a systemic cholinergic crisis with clinically adverse effects that can eventually lead to death if left untreated. Present countermeasures include atropine (an antimuscarinic), diazepam (an anticonvulsant), and pralidoxime (a reactivator of OPNA-inhibited AChE). Pralidoxime and similar compounds are the only countermeasures that treat the cause of OPNA intoxication and designing molecules with improved reactivation activity is an active field of research. A modified Ellman's assay measuring the innate enzyme activity of AChE is the research field's cornerstone reporter system used to elucidate the Michaelis-Menten-like kinetics of the productive interactions of reactivator molecules with OPNA-inhibited AChE. Empirical observations of naïve and OPNA-inhibited AChE behavior during standard reactivation kinetics assays suggest that the inherent stability of the enzyme may be affected by the interactions of OPNAs and/or reactivator compounds. Previously, in research conducted in other enzyme systems, fluorescent dyes combined with thermal denaturation have been utilized to study protein stability as it relates to ligand interactions. Use of a similar assay technique would provide further insight into the behavior of AChE upon interaction with OPNAs and/or reactivators. The resulting data regarding the structure-activity relationships of AChE and a variety of small molecules could lead to the development of improved treatments for OPNA exposures in both the warfighter and civilian populations.

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