



A Toxidromic Approach for Chemical Medical Countermeasure Development

A Novel, Porcinated Human Butyrylcholinesterase Catalytically Degrades the Chemical Warfare Nerve Agent, Sarin

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Chemical warfare nerve agents (CWNAs) present a global threat to both military and civilian populations. The acute toxicity of CWNAs stems from their ability to effectively inhibit acetylcholinesterase (AChE). This inhibition can lead to uncontrolled cholinergic cellular signaling, resulting in cholinergic crisis and, ultimately, death. While the current FDA-approved standard of care is moderately effective when administered early, development of novel treatment strategies is necessary. Butyrylcholinesterase (BChE) is an enzyme which displays a high degree of structural homology to AChE. Unlike AChE, the roles of BChE are uncertain and possibilities are still being explored. However, BChE appears to primarily serve as a bioscavenger of toxic esters due to its ability to accommodate a wide variety of substrates within its active site. Like AChE, BChE is also readily inhibited by CWNAs. Due to its high affinity for binding CWNAs, and that null-BChE yields no apparent health effects, exogenous BChE has been explored as a candidate therapeutic for CWNA intoxication. Despite years of research, minimal strides have been made to develop a catalytic bioscavenger. Further, BChE is only in early clinical trials as a stoichiometric bioscavenger of CWNAs, and large quantities must be administered to treat CWNA toxicity. Here we describe previously unidentified mutations to residues within and adjacent to the acyl binding pocket (positions 282-285 were mutagenized from YGTP to NHML) of BChE that confer catalytic degradation of the CWNA, sarin. These mutations, along with corresponding future efforts, may finally lead to a novel therapeutic to combat CWNA intoxication.