MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Protection Against Organophosphorus Threats: Quinone Methide Precursors For The Broad-scope Treatment Of OP-inhibited Ache And Bche, And OP-aged Ache

Kevin Miller Ohio State University **Poojya Anantharam** MRIGlobal **Phillip Beske** MRIGlobal **William Sosna** MRIGlobal **Christopher Hadad** Ohio State University

Organophosphorus (OP) compounds inhibit the cholinesterase enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Inhibition of AChE leads to a cholinergic crisis and potential death while BChE is a stoichiometric bio-scavenger of OP compounds found predominantly in the blood. If OP-inhibited AChE and BChE are not treated timely, the enzymes undergo spontaneous O-dealkylation, generating the OP-aged form. The aging process can occur anywhere between minutes to days, highlighting the need for therapeutics that can recover both the inhibited and aged form of the enzymes. There are no FDA-approved therapeutics for the OP-aged forms of AChE and BChE; however, we have previously reported that in vitro 4-amidophenol based quinone methide precursors (QMPs) are capable of reactivating OP-inhibited AChE and BChE as well as “resurrecting” OP-aged AChE. We will present high survivability for in vivo studies with humanized mice when exposed to a lethal dose of an authentic OP compound. To improve upon the framework of initial QMPs, an additional 75 compounds were synthesized to explore structure-activity relationship. Of these, multiple novel QMP compounds were identified that show even higher activity across multitude classes of OP compounds including methylphosphonates, pesticides, and phosphoramidates. This QMP framework shows robust recovery of inhibited/aged AChE and moderate recovery of inhibited BChE. Targeting BChE is relevant because returning BChE to its native state would transform the enzyme from stoichiometric scavenger to a pseudocatalytic scavenger of OP compounds. We also report a separate framework of QMPs consisting of a 6-methylpyridin-3-ol core that are extremely efficient BChE reactivators and for multiple OP compounds. Unfortunately, these QMPs show no efficacy against inhibited or aged AChE. However, it was hypothesized that when combined with the 4-amidophenol QMPs, the mixture could efficiently recover AChE activity even in a stoichiometric excess of a given OP compound. We developed an in vitro assay to independently measure AChE and BChE activity in the same solution over time and show improved recovery of AChE with a QMP cocktail compared to an oxime control. Improving upon the current therapeutics for OP exposure is critical for the warfighter who is likely to be unaware of which OP they have been exposed to, emphasizing the need for an efficient and broad-scope solution. The QMPs reported here are effective against multiple classes of OP compounds, are predicted to cross the blood-brain barrier, and with the additional benefit of targeting both cholinesterases increase the potential for higher lethal doses of OP compounds to be tolerated.

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