MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Quinone Methide Precursors For Remediating Organophosphorus Intoxication: Novel Reactivators Of OP-inhibited And Resurrectors Of OP-aged Cholinesterases

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Organophosphorus (OP) compounds include multiple classes of toxic species, from organophosphate pesticides to more dangerous methylphosphonates and phosphoramidates. Such OP compounds generate their toxicity to humans through rapid distribution throughout the peripheral and central nervous systems and then covalent inhibition of the hydrolytic enzyme acetylcholinesterase (AChE), leading to a cholinergic crisis, and if left untreated, death. The phosphylated serine can undergo a spontaneous O-dealkylation, leading to a dead, inactive enzyme, a process termed aging. In addition, endogenous butyrylcholinesterase (BChE), a stoichiometric scavenger of OP compounds, is also phosphylated and undergoes inhibition and subsequent aging. Current FDA-approved therapeutics have many weaknesses, including no activity against the OP-aged forms of cholinesterases and poor or non-existent blood-brain barrier penetrability, thus limiting their effectiveness in the central nervous system. We hypothesized that by using quinone methide precursors (QMPs), it is possible to realkylate the aged adduct, and through subsequent nucleophilic attack, to reactivate the once dead enzyme back to its native functional form, an overall process termed resurrection. Resurrection is critical for some OP compounds which have very short aging half-times, including some OP analogues that age in a few minutes. Therefore, resurrection of OP-aged cholinesterases is a vital complement in many cases to reactivation of the OP-inhibited cholinesterases. Indeed, our QMP compounds are the only known in vitro resurrectors of OP-aged AChE. We have recently demonstrated that QMP compounds can resurrect OP-aged BChE as derived from the most toxic methylphosphonate OP compounds. Moreover, through our efforts, we have prepared diverse libraries of QMP compounds which demonstrate both reactivation and resurrection capabilities, often with high efficacies against multiple OP compounds, and for both cholinesterases, AChE and BChE. Our QMP compounds provide blood-brain barrier penetrability, reasonable pharmacokinetics, satisfactory safety profiles in animal studies via maximum tolerated doses, and most importantly, efficacious results in animal studies with a humanized mouse model after toxic exposures to both pesticides and more deleterious OP compounds. In this presentation, we will describe the diverse QMP frameworks which we have been able to synthesize and to test in high-throughput biochemical assays. In addition, we will describe the deduced structure-activity relationships for both in vitro and in some cases, in vivo efficacy, against different OP compounds, from pesticides to more toxic OP compounds.

MCDC 1905-006; and JSTO - CB10791