Resurrecting the Dead: Recovery of Organophosphorus Poisoned Acetylcholinesterase using Quinone Methide Precursors


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Acetylcholinesterase (AChE):
- A vital enzyme located in the blood, as well as the central and peripheral nervous system
- Activity due to a Ser-His-Glu catalytic triad with multiple amino acid residues working together

Organophosphorus Nerve Agents and Pesticides:
- Responsible for inhibition of AChE by phosphorylation of the active site serine residue
- Pesticides estimated to cause 3 million hospitalizations & 220,000 deaths annually

OP Inhibition and Aging of AChE:
Inhibition of AChE can result in death by respiratory failure.
- OP-inhibited form can be reactivated to its native state with pyridinium oximes, like PAM
- OP-inhibited enzyme can dealkylate to the "aged" form of AChE (shown in red below), that forms an oxanion at the phosphorylated serine residue.
- The aged form of AChE is resistant to pyridinium oxime therapeutics.
- Currently there are no approved therapeutics for the OP-aged form.

Hypothesis: "Resurrect" the OP-aged form to the native state with a quinone methide to re-alkylate the aged form of AChE, along with subsequent reactivation:

A Quinone Methide (QM) must be disguised as a Quinone Methide Precursor (QMP) for drug-like utility:

References:
1. Nosser, O.; Hadad, C. Chemical Warfare Agents & Treatments; ACS In Focus, American Chemical Society: Washington, DC, USA, 2021.

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