Towards a Pseudo-Catalytic Bioscavenger: in vitro Reactivation of Organophosphorus-Inhibited and Resurrection of Organophosphorus-Aged Butrylcholinesterase by Quinone Methide Precursors


*Department of Chemistry and Biochemistry, College of Arts and Sciences and **College of Pharmacy, Ohio State University, Columbus, Ohio 43210

INTRODUCTION

- Cholinesterases are covalently inhibited by organophosphorus (OP) compounds used as pesticides and chemical warfare agents.
- Inhibition of acetylcholinesterase (AChE) can lead to cholinergic crisis and death.
- Butyrylcholinesterase (BChE) is a non-essential cholinesterase naturally found in the body capable of stoichiometrically scavenging OP compounds.
- Upon AChE/BChE inhibition, a second spontaneous O-dealkylation event known as aging occurs that is recalcitrant to reactivation by pyridinium oximes.
- Quinone methide precursors (QMPs) have previously been shown to reactivate OP-inhibited and OP-aged AChE, and here are being tested against BChE.

METHODS

- OP compounds tested
- Authentic nerve agents
- Surrogate OP compounds
- BChE serine modification

RESULTS

- QMPs screened for reactivation
- Reactivation of OP-inhibited BChE
- Reactivation follows pseudo-first-order kinetics. EP represents phosphorylated BChE.
- Resurrection of methylphosphonate-aged human plasma-derived BChE after 24 hours with 1 mM QMP at pH 7.5
- Resurrection of methylphosphonate-aged BChE after 24 hours at varying concentrations of 14a
- Dashed line represents 2-PAM activity

CONCLUSIONS

Reactivation
- Multiple QMPs show more efficient reactivation of OP-inhibited BChE than current therapeutics (such as, 2-PAM).
- Notably, 2b shows broad activity against all three OP compounds and 4e is very effective against the VR surrogate.
- The extended and larger amine at the 4-position may improve reactivation compared to ADOG due to the larger active site of BChE.

Resurrection
- Best resurrection is observed with smaller NMe2 amines.
- Resurrection only observed with large 6-alkoxy substituent.

BIBLIOGRAPHY