Development of Uncharged Reactivators as New Treatment Against Organophosphorus Nerve Agent Poisoning

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Acetylcholinesterase (AChE) is a critical enzyme in the central nervous system (CNS) that hydrolyzes the neurotransmitter acetylcholine. Organophosphorus nerve agents (OPNAs) and akin pesticides irreversibly inhibit AChE through catalytic serine residue phosphylation, thereby disrupting neuronal communication and potentially causing death if untreated. In contrast, butyrylcholinesterase (BChE) — a related enzyme predominantly found in blood plasma — exhibits broader physiological functions and is similarly inhibited by OPNAs. The current French military treatment for OPNA exposure employs an auto-injector containing a methanesulfonate salt of 2-PAM (a reactivator of AChE, able to dephosphylate the serine residue), alongside atropine, an anticholinergic agent, and avizafone, a prodrug of diazepam intended to mitigate convulsions. However, this treatment is limited by its suboptimal CNS penetration, a narrow spectrum of activity against diverse nerve agents, and variable efficacy. Our research group has been developing uncharged reactivators to dephosphylate inhibited cholinesterases for over a decade. These novel compounds are designed to improve CNS accessibility, exhibit a broader range of activity against various nerve agents, reactivate both AChE and BChE, and potentially modulate nicotinic receptor activity. In our upcoming presentation, we will discuss the latest advances in these uncharged reactivators and explore their potential as new treatment against OPNA poisoning.