A Toxidromic Approach for Chemical Medical Countermeasure Development

Development of Novel Substituted Phenoxyalkyl Pyridinium Oximes Demonstrating Central Neuroprotection Following Lethal Level Administration of Organophosphates

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Few oxime reactivators of acetylcholinesterase (AChE) inhibited by organophosphates have shown efficacy within the brain in reactivating inhibited AChE and providing neuroprotection from the signs of poisoning or the neuropathology. Our laboratories have invented and patented (US patent 9,227,937) a platform of novel substituted phenoxyalkyl pyridinium oximes with the goal of achieving an oxime that can improve survival of high dosages of highly toxic organophosphates (OPs) that also have the ability to penetrate the blood-brain barrier and provide central neuroprotection; the currently FDA-approved oxime, pralidoxime (2-PAM) cannot appreciably enter the brain. In a laboratory rat model some of these oximes have shown evidence of central therapy from the toxic effects of OPs: two highly relevant nerve agent surrogates (nitrophenyl isopropyl methylphosphonate, NIMP, a sarin surrogate, and nitrophenyl isopropyl methylphosphonate, NEMP, a VX surrogate) as well as paraoxon, the active metabolite of the highly toxic insecticide parathion. Rats were challenged with a high sublethal dosage of OP and subsequently treated with oxime at the time of peak AChE inhibition to ensure that little or no OP was still available for reinhibition of any reactivated AChE. In this paradigm, some of our novel oximes resulted in up to about 35% brain AChE reactivation, while 2-PAM yielded no reactivation at 2 hours after OP challenge. In addition, histological evaluation with glial fibrillary acidic protein showed protection not shown by 2-PAM. Subsequently rats were challenged with a lethal dosage of NIMP or paraoxon and provided atropine and oxime at the time of development of signs of toxicity, about 30 minutes after OP challenge. The 24 hour survival of these lethal dosages was improved by the novel oximes over the survival by 2-PAM for most of the oximes tested in both male and female rats and the time of cessation of seizure-like behavior was shortened by several of the novel oxime during the first 8 hours after challenge in both male and female rats. Additionally following this lethal dose challenge of NIMP or paraoxon, some of the novel oximes provided protection from the neuropathology seen in the hippocampus with the marker neuN in animals receiving 2-PAM therapy. Therefore some of the members of our novel oxime platform have shown functional evidence of protection of the brain from high sublethal or lethal level poisoning by OPs of both nerve agent and insecticidal chemistries as evidenced by attenuation of seizure-like behavior and protection from neuropathology that support the conclusion that our oximes can penetrate the blood-brain barrier while 2-PAM cannot. Therefore our novel oximes have the potential to provide neuroprotection to the warfighter exposed to nerve agents. (Supported by DTRA 1.E005608_AHB_C and NIH CounterACT NS NS083430 and NS107127).