A Toxidromic Approach for Chemical Medical Countermeasure Development

A Novel Genetically Modified Mouse Model for Evaluating Nerve Agent Countermeasures

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Although acetylcholinesterase (AChE) performs the same function in all animals, minor amino acid differences exist across species. These differences cause AChE to react differently to small molecules intended to restore its native activity after inhibition by organophosphorus (OP) nerve agent. To generate a novel humanized mouse strain, serum carboxylesterase knock out mice (Es1 KO) in which the gene expressing serum carboxylesterase (CaE) has been interrupted such that mature protein is not expressed were cross-bred with a mouse strain (AChE KI) in which the gene expressing AChE has been altered to express the amino acid sequence of the human form of the same protein. The resulting AChE KI/Es1 KO (KIKO) mouse strain incorporates these modifications into a single model that addresses some major concerns for the chemical warfare agent research community. The lack of functional CaE in these mice mirrors that in humans and nonhuman primates, neither of which expresses CaE. Most other commonly used small animal models (other strains of mice, rats, guinea pigs) express CaE, which directly contributes to those animals' resistance to OP nerve agent toxicity. The production of human AChE in place of mouse AChE combined with the lack of CaE in KIKO mice establishes a unique animal model that should not only exhibit OP intoxication in a manner more similar to humans, but also display AChE-specific treatment responses more closely mimicking those of humans. In this study, KIKO mice are characterized using genotype confirmation, differential tissue staining and median lethal dose determination experiments. Finally, the KIKO strain is evaluated as a model for OP countermeasure development using in vitro evaluation of recombinant forms of human and mouse AChE, ex vivo phrenic nerve diaphragm preparations to evaluate restoration of physiological function during reactivation, and in vivo testing of reactivation in live animals after OP exposure. (The experimental protocol was approved by the Animal Care and Use Committee at the USAMRICD, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011), and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.)