CAMO (COMPARING ANIMAL MODELS TO ORGANOIDS) - TESTING MEDICAL COUNTERMEASURES WITH MICROPHYSIOLOGICAL SYSTEMS AND COMPARING TO TRADITIONAL ANIMAL MODELS AND CLINICAL TRAILS

Exploring The Effects Of In Utero Acute Organophosphorus Nerve Agent (opna) Exposure On Mouse Behavior

Olivia Bellek USAMRICD **C. Linn Cadieux** USAMRICD

Organophosphorus nerve agent (OPNA) poisoning leads to a cholinergic crisis resulting in difficulty breathing, seizures, and death due to the inhibition of acetylcholinesterase (AChE). Studying the effects of OPNA poisoning is difficult because common small animal research models produce serum carboxylesterase (CaE), an endogenous bioscavenger that offers protection against OPNA intoxication. Additionally, although AChE performs the same biochemical function in all animals, minor amino acid differences across species cause the enzyme to react quite differently to small molecules known as reactivators intended to restore the native activity of OPNA-inhibited enzyme. The KIKO (AChE Knock-In/CaE Knock-Out) mouse model incorporates two genetic modifications into a single animal that simultaneously addresses concerns for the chemical warfare agent research community and presents a unique opportunity for this animal to act as a model for the study of compounds which interact directly with AChE. This study aims to evaluate altered behaviors in offspring caused by an acute OPNA exposure in utero. The two main study objectives are: 1) explore the behavioral disturbances caused by in utero exposure to OPNA and/or countermeasures and 2) compare behavioral effects in C57BL/6J (WT) and KIKO mouse strains. In a previous study, pregnant mice were subjected to an acute OPNA exposure, and their offspring were analyzed for genetic abnormalities. While no changes in gross anatomy of the offspring were noted, several significant changes of gene expression profiles were found in exposed pups suggesting possible impacts on behavioral responses. The current study aims to quantify these potential changes via targeted behavioral testing in both WT and KIKO strains. All mice will undergo behavioral testing at multiple time points throughout their life. Ages at evaluation may include sexually mature (6-8 weeks old), adult (14-16 weeks old), mid-life (40-42 weeks old), and geriatrics (78-80 weeks old). Elevated Zero Maze (EZM) and Morris Water Maze (MWM) will be used to evaluate anxiety and learning respectively. Behavioral disturbances may be carried into later generations and could be evaluated to determine this potential inheritance. The results from this study may provide insight to how OPNA or countermeasure could impact the offspring of exposed civilians and/or warfighters.

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The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.