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

Identifying Epimutation Inheritance Following Acute Maternal Organophosphorus Nerve Agent (OPNA) Exposure

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The field of epigenetics has allowed for the exploration of environmental influences on non-genotoxic gene expression, influences including exposure to both organophosphorus nerve agents (OPNAs) and acetylcholinesterase (AChE) reactivators. Previous studies have identified brain-specific epimutations in offspring, via DNA methylation, following maternal OPNA and reactivator exposure in a humanized mouse model. While OPNA- and reactivator-induced multigenerational epimutations have been observed previously in mice, the possibility and subsequent genotypic comparability of transgenerational epimutations has not yet been explored. As an improved model of human organophosphorus nerve agent (OPNA) exposure and treatment, C57BL/6J mice were genetically modified to knockout (C57BL/6-Ces1tm1.1Loc/J; Es1 KO) serum carboxylesterase (CaE) and knock in (C57BL/6-AChEtm1.1Loc/J; AChE KI) the AChE human enzyme homolog. The resulting KIKO mouse strain eliminated the respective limitations of species-specific OPNA resistance and AChE interactions. While researchers are aware of the adverse effects of OPNA exposure, it is vital to identify if these effects can influence the health of future generations. By utilizing both WT and KIKO mice, knowledge of comprehensive epigenetic effects and molecular mechanisms could be applied to both broad scale mouse models as well as human health research. In this study, pregnant WT and KIKO mice (P0) will be assigned to one of three exposure/treatment combinations (vehicle/vehicle, vehicle/reactivator, or OPNA/reactivator) on embryonic day 14 (E14). These dams will then progress through pregnancy and weaning, at which point tissue will be collected for further analysis. The offspring of exposed animals (F1) will be randomly assigned as breeders (females only) or for tissue collection at key stages in their lifecycle. DNA methylation, quantitative polymerase chain reaction (qPCR), and matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI MSI) may be used to analyze a variety of key tissues. F1 breeders from each condition will be utilized to produce two subsequent generations from which tissue will be collected for analysis. We anticipate observable epimutations will be stable across multiple generations from both genotypes, thus confirming the transgenerational effects of OPNA and reactivator exposure.

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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.