RNA-seq Evaluation of DDT Exposure in the Hippocampus of Humanized APOE Mice

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The Apolipoprotein 4 (APOE) gene variant is the strongest genetic risk factor for late-onset Alzheimer's disease (LOAD). However, it is not entirely predictive of LOAD, and emerging evidence points to environmental factors in the etiology of disease. We have previously reported that individuals with increased levels of the primary metabolite of the pesticide dichlorodiphenyltrichloroethane (DDT) and harboring an APOE4 allele performed worse on a task of cognitive function. In the present study, we utilized male and female targeted replacement humanized APOE3 (E3) and APOE4 (E4) mice to identify the effects of DDT exposure on gene expression changes in the hippocampus. Three-month-old E3 and E4 mice were exposed to 3 mg/kg DDT by oral gavage every 3 days for 5 months. Animals were euthanized at 8 months and RNA-sequencing was performed on hippocampal samples using the NovaSeq 6000. Data were analyzed using DESeq2 in R. Contrasts were made within each genotype across sex, between the genotypes, and across exposure groups. Each contrast underwent a Wald test, and a likelihood-ratio test for significance and only significant transcripts were used for g:profiler analysis. Between males and females, within each genotype, there were 13 (E3) and 36 (E4) differentially regulated biological process pathways. Between each genotype, within each sex, there was 1 (males) and 49 (females) differentially regulated biological process pathways. There were no significantly altered biological processes in any of the DDT exposed animals compared to their respective control within each sex and genotype. However, when analysis was restricted to DDT-treated E4 and E3 males, there were a total of 51 downregulated biological process pathways in the E4 males compared to the E3 males. These pathways included cell-cell signaling ($P_{adj}=1.1\times10^{-3}$), chemical synaptic transmission ($P_{adj}=7.3\times10^{-3}$), regulation of cation channel activity ($P_{adj}=1.5\times10^{-2}$) and regulation of the action potential ($P_{adj}=1.8\times10^{-2}$). These data suggest a gene x environment interaction with exposure to DDT and the APOE4 genotype, that occurs exclusively in males and affects pathways consistent to the known effects of DDT on the neuron. *Supported in part by NIH R01ES026057.*