Assessing DDT/DDE in Alzheimer's Disease Pathways in Human Stem Cell-Derived Neurons Carrying APOE Gene Variants

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The E4 allele of the Apolipoprotein E (*APOE*) gene contributes the greatest single genetic risk for late-onset Alzheimer's disease (LOAD), but it is also affected by factors including age and environmental exposure. The pesticide dichlorodiphenyltrichloroethane (DDT) has been identified as a risk factor for LOAD due to its persistent bioaccumulation and elevated serum levels of the DDT metabolite, dichlorodiphenyldichloroethylene (DDE) of AD patients even after it was banned in the US over forty years ago. Previous results found that there were significant interactions between serum DDE levels, *APOE* genotype and cognitive dysfunction, with *APOE* E4 genotype and higher DDE levels being associated with worsened cognitive function. Mechanistically, our previous experiments found significant increases in amyloid precursor protein (APP) levels in differentiated SH-SY5H cells and primary mouse hippocampal neurons after DDT/DDE exposure. To quantify this relationship in human neurons, an appropriate model system needs to be generated. We prepared induced excitatory neurons (iNs) by reprogramming two isogenic induced pluripotent stem cell (iPSC) lines, a heterozygous APOE E3/E4 and an engineered line carrying frameshift mutations in both alleles (APOE-null). A 24 hour treatment of APOE-null neurons with 1 µM DDT increases APP levels on Western blots by approximately 50% compared with vehicle control. To test interaction with APOE, neurons will be cultured in the presence of conditioned medium containing APOE-e2, e3, or e4 and/or oligomeric amyloid beta collected from lentiviral-transduced HEK293 cell lines to mimic conditions of Alzheimer's disease. Utilizing this novel human neuron model, we examine direct effects of DDT and DDE on neuronal function and indirect effects on AD markers. The combination of electrophysiologically-mature human neurons, addition of APOE and/or amyloid toxic signals, and environmental toxicants such as DDT/DDE represents a novel approach to modeling AD.