APOE genotype and sex dependent effects of 17-alpha-estradiol on AD pathology

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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is characterized at post-mortem examination by high densities of ß-amyloid (Aß)-containing plaques and extensive neurogliosis in cortical brain regions, with severe loss of neurons, including the pyramidal

neurons in the CA sub-regions of the hippocampus and noradrenergic neurons in the locus coeruleus (LC). AD is the most common cause of elderly dementia and women have a higher incidence of AD than men. The gradual loss of sex steroid hormones may contribute to age associated cognitive decline. A neuroprotective role of estrogens in murine models has been established. Specifically, 17-?-estradiol has been shown to stimulate enhanced synaptic plasticity, neurite growth, hippocampal neurogenesis and long-term potentiation. However, its effects on peripheral targets in humans limit the usefulness of ?-E2 as a potential therapy. Negative outcomes from the large Women's Health Initiative Memory Study (WHIMS), a clinical study using ?-E2 highlight the dire need to analyze non-feminizing estrogens. Recently, we discovered that 17-?-estradiol (?-E2), an isomer of 17?-estradiol, appear to mitigate the severiy of neuron loss, amyloid burden, and neuroglial proliferation in adult dtg APP/PS1 mice. To begin to address this hypothesis in-vivo, we propose to identify mechanisms for the neuroprotective effects of ?-E2 in APOE knock in (APOE3 and APOE4) and 5x FAD mice. Using equal numbers of both male and female mice, we will deliver ?E2 over sixty days via subcutaneous pellets. Sacrifice and brain removal will follow to identify if neuroprotective effects of ?E2 are mediated in a sex and/or apoE genotype dependent manner. Endpoints for these studies will be computerized stereology to quantify neuron loss in CA1 and LC, amyloid burden and neuroglial proliferation in the hippocampal formation; and enzyme-linked immunoassays to quantify levels of Aß peptides and pro-inflammatory cytokines in hippocampal molecular layers. Taken together, these experiments will provide perhaps the most direct in-vivo assessment of cellular sites for ?E2's neuroprotective effects in APOE knock-in (APOE3 and APOE4) and 5x FAD mice. Results will assess whether ?E2 deserves further study as a potential strategy for the therapeutic management of AD in middle-aged and elderly men and women.

Further information available at:

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