

Possible APOE Genotype and Sex Dependent Effects of 17- α -estradiol on Alzheimers Disease Pathology

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Alzheimer's disease (AD) remains the most prevalent cause of elderly dementia, posing an increasingly important health problem as the population ages [1]. AD is a neurodegenerative disorder defined by the presence of extracellular deposits of β -amyloid ($A\beta$), intraneuronal accumulations of neurofibrillary tangles containing hyperphosphorylated tau protein, and the progressive loss of synapses and neurons that correlate with atrophy of brain regions [2]. Specific areas of the brain that show particularly severe neuronal loss include the entorhinal cortex, pyramidal neurons in the CA1 subregion of the hippocampus, and the noradrenergic neurons of the locus coeruleus [3-5]. The neuronal populations within these areas mediate attention, learning, memory and other neural processes associated with higher cognitive function. The specific mechanism(s) that underlie neuronal loss are not clearly understood, and there are no approved methods to slow this neurodegeneration.

Of the risk factors identified that facilitate AD progression, the strongest are aging, the inheritance of the $\epsilon 4$ allele of the Apolipoprotein E (APOE) gene, and sex - women have a higher incidence of AD than men [6]. The APOE gene encodes a 34 kDa protein that is the major protein component of CNS lipoproteins, involved in lipid transport and redistribution [7]. Even though there is no clear understanding of the role of APOE in AD pathology, the role of APOE4 isoform has been shown to affect synaptic structure, $A\beta$ clearance and transport across blood brain barrier as well as energy metabolism [8]. In mice, APOE4 decrease dendritic spine density and neuronal complexity in various cortical brain regions [9]. In addition, APOE4 mice show impaired learning and memory in the Barnes maze tests [10]. These effects were observed in absence of significant $A\beta$ accumulation suggesting $A\beta$ independent mechanisms contributing to functional impairments in APOE4 carriers.

There is a stronger association of APOE with AD in women than men that correlates well with greater hippocampal atrophy, plaque pathology and cognitive decline [11]. The gradual loss of sex steroid hormones in women may contribute to age associated cognitive decline [12]. A neuroprotective role of natural and synthetic estrogens in the mammalian brain has been established during the past decade. In particular, 17- β -estradiol (β -E2), has commonly been known to play a pivotal role in female reproductive physiology, enhances synaptic plasticity, neurite growth, hippocampal neurogenesis and long-term potentiation [13,14]. β -E2 is also effective in several neural injury and toxicity models. In animal models of AD, β -E2 reduces $A\beta$ pathology and improves cognition [15], although the effectiveness of β -E2 is reduced in the presence of APOE4 [16]. This latter observation is consistent with a role for APOE in modulating the biological effects of estrogen-based therapy.

Early estrogen replacement therapy prior to menopause has been shown to reduce the AD risk in postmenopausal women [17]. However the effects of β -E2 on peripheral targets in both men and women limit its usefulness as a potential therapy for AD. In the past decade concerns have been raised over the safety of long-term 17- β -E2 treatment as

having future therapeutic potential due to feminizing and carcinogenic effects [18].

17- α -E2, an enantiomer of 17- β -E2 has markedly lower feminizing and carcinogenic effects and could provide a potentially safer neuroprotective treatment against AD for aging men and women [19,20]. The role of α -E2 in neuroprotection and physiology is only beginning to unfold and regulatory mechanisms involved in its action and cross-talk with other gonadal hormones is far from clear [21]. Previous neuroprotection studies with feminizing hormones suggest APOE genotype dependent effects in humans and in animal models and current preliminary data support an early neuroprotective role of α -E2 in therapeutic strategies against AD.

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