Proteomic Studies of Protein Pathways for the Estrogen Therapeutic Window in AD

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Proteomic Studies of Protein Pathways for the Estrogen Therapeutic Window in AD

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Research Abstract

? DESCRIPTION (provided by applicant): Benefits and risks have been reported for the use of hormone therapy to prevent chronic disease, including Alzheimer’s disease (AD). While the Women’s Health Initiative (WHI) found no protective effect of hormone therapy on the cognitive

function of women whose treatment was initiated far past the onset of menopause, the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study showed that women receiving treatment around 50-63 years of age were at reduced risk for AD. A Kaiser Permanente study further defined this, showing reduced risk of AD with midlife treatment, versus increased risk of AD with late treatment. Together, these and other studies have led to the hypothesis of a ""critical initiation window"" for the beneficial effects of estrogen on the brai and that estrogen may need to be administered at perimenopause or earlier to observe a beneficial effect on the cardiovascular and neural system. Our work supports this, by demonstrating that early and long term estrogen treatment improves cognitive function and reduce A? accumulation in AD mouse models with surgical menopausal or brain estrogen deficiency, while there is no effect of late (and short-term) estrogen treatment on AD neuropathogenesis. Furthermore, our published data show reduced brain estrogen at autopsy in AD versus control female brains. The differences in brain estrogen levels between female AD and healthy individuals provide some level of explanation of why only 13-15% of aged females developed AD, even though every woman loses endogenous estrogen after menopause in advanced age. However, very little is known about the molecular mechanisms underlying the ""critical initiation window"" and whether different protein networks are responsible for brain estrogen deficiency- associated risk of AD in females. Our goal is to use proteomics to identify target protein pathways responsible for the estrogen therapeutic window in AD, to study the function of these target proteins in various transgenic animal models in vivo and determine the signaling pathways of each target protein in vitro. We will also directly explore the relationship f these target proteins and pathways to estrogen-responsive proteins known to contribute to AD, such as the ?-site APP cleavage enzyme, and the A? degradation enzymes nerilysin (NEP) and insulin degrading enzyme (IDE). The outcome of this proposed study will provide molecular network-level insights into the ""critical initiation window"" theory, and identify specific target proteins of therapeutic responsiveness that may lead to improved treatment strategies and optimal estrogen therapy.

Further information available at:

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