Stress and Sexuality Divergent Neuropathy in Alzheimers Disease

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Research Abstract

Summary Women have a higher risk for developing Alzheimer’s disease (AD) than men, and 70% of the 5.4 million Americans that have been diagnosed with AD are women. Despite the clear epidemiological evidence for this sex-specific risk increase, the neurobiological basis for

this sexual dimorphism is unclear. Convergent findings from our group and others indicate that stress contributes to the pathogenesis of AD through its effects on corticotropin releasing factor (CRF) transmission. Sexual dimorphism exists at the second messenger level for CRF receptor 1 (CRF1) transmission, in that CRF1-Gs signaling is favored in females while CRF1-?-arrestin-2 signaling is favored in males. This sex bias in CRF1 signaling likely results in different phosphorylation patterns among downstream targets associated with AD neuropathy, and so provide a mechanistic explanation for the difference in the risk of AD between men and women. Consistent with this mechanism, our preliminary data demonstrate that amyloid plaque development is much greater in female than male transgenic mice (APP+/CRF+/tTA+; or TT), in which both human APP and CRF are overexpressed in the forebrain. We now propose to extend these findings by investigating the hypothesis that chronic stress increases the risk of AD neuropathology in female transgenic mice due to sexual dimorphism in CRF1 signaling pathways and sex-specific protein phosphorylation patterns. We will utilize two stress-related AD mouse models (TT mice and isolation-stressed Tg2576 mice) to test our hypothesis. First, we will confirm the increase of amyloid plaque and cognitive deficits in females compared to males determine the degree to which plaque development and cognitive deficits can be prevented in female and male mice by suppressing CRF release or blocking CRF1 transmission. Then, we will interrogate CRF1's downstream effectors in primary cortical and hippocampal neuronal cultures derived from male and female mice, to investigate the degree to which Gs-PKA signaling selectively promotes the development of AD neuropathy during administration of exogenous CRF, CRF1 antagonists, and PKA inhibitors. Further, we will demonstrate the sufficiency of increased Gs-PKA signaling to promote AD pathology using the two mouse models and a virally-mediated DREADD (Designer Receptors Exclusively Activated by Designer Drugs) that is specific for Gs signaling (AAV-CaMKIIa-HArM3D-IRES-mCitrine). Finally, we will perform a quantitative phosphoproteomic assay to identify the sexually dimorphic phosphorylation patterns associated with increased in AD-like neuropathy and CRF1 signaling in both TT mice and stressed Tg2576 mice. This study would be the first to demonstrate the plausibility of a mechanism that could explain the increased risk of AD in women, and thus provide a mechanistic framework and novel targets for treatments that are sex- specific.

Further information available at:

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