Impact of estrogen loss and replacement on GluN2B containing NMDARs, synaptic plasticity, and learning and memory in females using a novel transgenic rat model of Alzheimer’s Disease

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Research Abstract
? DESCRIPTION (provided by applicant): Alzheimer’s disease targets two-thirds more women than men, likely a result of hormone loss during menopause. Clinical and preclinical data support beneficial roles of 17??estradiol (E2) and its replacement post-menopause on neuronal function, amyloid and tau pathology, and cognition. However, it is unknown how E2 improves or maintains synaptic processes underlying cognitive function throughout early asymptomatic and symptomatic disease progression. Abnormal activation of extrasynaptic GluN2B-containing NMDARs and loss of synaptic GluN2Bcontaining NMDAR as a consequence of increased soluble toxic A???and increased activity of the tyrosine phosphatase STEP are believed to mediate synaptic deficits in presymptomatic AD. The increased activation of extrasynaptic GluN2B-containing NMDARs appears to mediate spine loss and LTP deficits in hippocampus in transgenic AD mice. Therefore, minimizing aberrant extrasynaptic GluN2B-NMDAR activation early in the disease is critical to delaying its onset and slowing its progression. Importantly, proestrous-like levels of plasma E2 not only increases spine density and LTP, it selectively increases synaptic current mediated by GluN2Bcontaining NMDARs that are critical for the E2-enhanced learning and memory. These beneficial effects of E2 could directly oppose the negative effects of increased soluble A?o, but whether E2 can stimulate these synaptic changes in the context of accumulating AD pathology is an open question. We will use a novel transgenic rat model of AD, TgF334-AD, and brain slice electrophysiology combined with learning and memory behavior to test the overarching hypothesis that that proestrous-like E2 replacement can heighten synaptic function in OVX Tg females by increasing synaptic and decreasing extrasynaptic GluN2B-containing NMDARs along with their associated signaling molecules, which will be linked to increased synaptic plasticity and learning and memory.

Further information available at:

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