Evidence for the role of gonadotropin hormones in the development of Alzheimer disease

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Differences in the prevalence and age of onset of Alzheimer disease (AD) in men and women, together with observations that hormone replacement therapy (HRT) prevented the development of AD, caused many to hypothesize that estrogen deficiency contributes to AD. However, recent trials did not show any benefit of HRT in preventing or alleviating the disease. To address this and other inconsistencies in the estrogen hypothesis, we propose another hormone of the hypothalamic-pituitary-gonadal axis, luteinizing hormone (LH), as a major factor in AD pathogenesis. Women with AD have elevated levels of this hormone when compared with controls, and previous studies by Rao and colleagues demonstrate LH receptor expression in brain regions that, in humans, are vulnerable to degeneration in AD. In fact, our recent work shows that LH is present in increased quantities in brain regions susceptible to degeneration in AD indicating a potential mechanistic interplay. In cell culture and *in vivo*, LH increases the amyloidogenic processing of amyloid-β protein precursor, an aspect linked to neurodegeneration in AD. Given that amyloid-β plaques and cognitive decline are cardinal features of AD, the findings presented above provide a strong case for the involvement of LH in disease pathogenesis. In this regard, we found that pharmacologic suppression of LH using leuprolide acetate reduces amyloid-β plaque formation and improves cognitive function in a murine model of AD. Given these findings, a phase II/III trial of leuprolide acetate, which suppresses LH release, is currently ongoing for the treatment of AD.