

Steroidogenic Acute Regulatory Protein (StAR): Evidence of Gonadotropin-induced Steroidogenesis in Alzheimer Disease

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Summary

There is mounting evidence that hormones of the hypothalamic-pituitary-gonadal (HPG) axis, especially gonadotropins, play a key role in the pathogenesis of Alzheimer disease (AD) (Webber et al., 2005). Significant elevations of luteinizing hormone (LH) are found in vulnerable neuronal populations in individuals with AD compared to aged control cases (Bowen et al., 2002). Upon binding to its receptor, LH activates a signaling cascade eventually promoting the upregulation of the steroidogenic acute regulatory protein (StAR). In this study, increased levels of StAR were found in AD hippocampus compared to aged matched controls. These findings suggest that LH is able to bind to its receptor and induce potentially pathogenic signaling in AD, and that steroidogenic pathways regulated by LH may play a role in AD.

Introduction

Epidemiological data reporting the predisposition of women to Alzheimer disease (Jorm et al 1998) suggests that age-related changes in hormones of the HPG axis following reproductive senescence, may contribute to the etiology of AD. Recent studies from our group and others have reported increases in circulating gonadotropins, namely LH in individuals with AD compared with

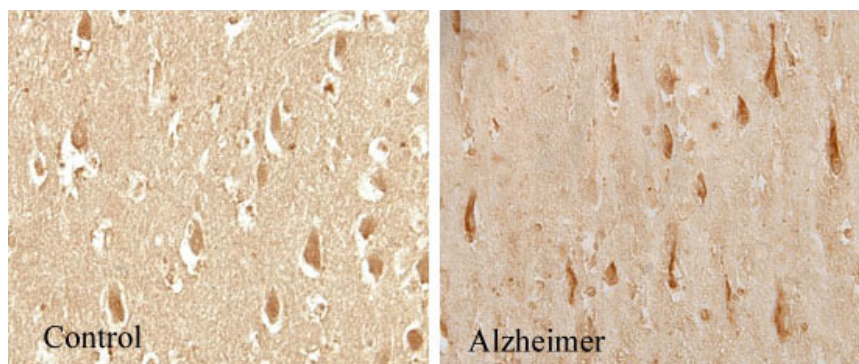
control individuals, and also significant elevations of LH in vulnerable neuronal populations in individuals with AD. The highest density of gonadotropin receptors in the brain are found within the hippocampus, a region devastated in AD [reviewed in (Webber et al., 2005)]. However, while LH is higher in AD patients, the downstream consequences of this are incompletely understood. To clarify this issue, we examined the expression levels of StAR protein, which regulates the first key event in steroidogenesis, namely, the transport of cholesterol into the mitochondria, which is regulated by LH through the cyclic AMP second messenger pathway, in AD and control brain tissue.

Materials and Methods

Hippocampal samples were obtained post mortem from patients (n=16, ages 67-96 years, mean=84.7 years) with clinically and histopathologically confirmed AD, and aged-matched controls (n=12, ages 66-86 years, mean=76.4 years). Tissue was fixed in methacarn (methanol: chloroform: acetic acid; 6: 3: 1 v/v/v) and embedded in paraffin. Immunostaining using the peroxidase-antiperoxidase method with 3-32 -diaminobenzidine as co-substrate was employed. Rabbit polyclonal antisera recognizing StAR (1:100) (Clark et al., 1994) and the human luteinizing hormone receptor (1:50) (GeneTex, Inc., TX, USA) were used. Absorption experiments were performed to verify the specificity of antibody binding.

Results

StAR protein was markedly increased in both the cytoplasm of hippocampal pyramidal neurons as well as in the cytoplasm of other cell types, such as astrocytes, from sixteen AD brains when compared with twelve age-matched controls (Figure). In AD, it also localized to neurofibrillary tangles, neuropil threads and dystrophic neurites. No significant StAR was noted in the cerebral vasculature. To confirm the specificity of StAR immunocytochemistry, several control experiments were performed in parallel. Absorption of StAR antibody with excess immunizing peptide was shown to dramatically decrease immunostaining.



Colocalization using adjacent AD hippocampal serial sections was performed with the human LH receptor. StAR colocalized with LH receptor in both pyramidal neurons as well as in other cells types (data not shown) suggesting that LH, which is known to be increased in AD, is in fact able to bind to its receptor and initiate canonical signaling cascades in the hippocampus.

Discussion and Conclusions

In this study, we demonstrate increased levels of StAR protein in vulnerable neurons as well as in other cell types in individuals with AD when compared to the same cellular populations in normal, aged-matched individuals. We also demonstrate that StAR colocalizes to neurons expressing LH receptor as demonstrated on adjacent serial sections of AD hippocampal tissue. Data from this study not only suggests that LH is able to bind to its receptor and induce signaling cascades in non-gonadal tissue, but also that the steroidogenic consequences of increased LH binding may play a role in AD pathogenesis. With this in mind, it is important to note that the long held notion of the pathogenic effects of decreased sex steroid levels, namely estrogen, on the brain after reproductive senescence is not consistently reflected in studies measuring sex steroid levels in AD compared to age-matched controls. The variability in the results of these studies is thought to be caused in part by the sensitivity of the assay used, as studies that used less sensitive assays reported higher total estrogen levels (Hogervorst et al., 2003) resulting in an overemphasis of the impact of low estrogen levels on the study. Therefore, potentially elevated sex steroid levels resulting from increased StAR expression in AD demonstrated in this study is not necessarily contradictory to epidemiological studies regarding sex steroid levels AD.

Due to the ineffectiveness of hormone replacement therapy in the treatment of AD (Shumaker et al., 2003), it is our hypothesis that age-related changes to gonadotropin levels, namely LH, contribute to AD pathogenesis. While this increase in serum LH in AD would not be expected to result in increased sex steroid production in the gonads due to the loss of function after reproductive senescence, increased neuronal LH in AD would likely induce steroidogenesis in functioning neurons. In support of this notion, reported decreases in steroidogenic enzyme expression, including StAR, in the postmenopausal ovary when compared to the premenopausal ovary (Havelock et al., 2006) are in stark contrast to the increased levels of StAR reported in this study.

In conclusion, this study provides the first connection between gonadotropins and sex steroids in the brain and offers insight into the mechanism of LH-induced pathogenesis in AD. As such, therapeutic approaches targeted at LH may have utility in the treatment of AD. In this regard, decreases in serum LH levels by leuprolide acetate administration lead to decreases in amyloid- β plaque burden and subsequent stabilization of cognition in A β PP transgenic mice (Casadesus et al., 2006).

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