Review

Gonadotropins: A cohesive gender-based etiology of Alzheimer disease

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Abstract

While there is ample experimental evidence supporting the role of estrogen in the pathogenesis of Alzheimer disease, recent inconclusive data regarding hormone replacement therapy (HRT), specifically, the unexpected results of the Women’s Health Initiative (WHI) Memory Study has raised serious questions regarding the protective effects of estrogen. Because of this and other inconsistencies in the estrogen hypothesis, we propose that another hormone of the hypothalamic–pituitary–gonadal axis, luteinizing hormone, is a major factor in the pathogenesis of Alzheimer disease. Specifically, we suspect that the increase in gonadotropin concentrations, and not the decrease in steroid hormone (e.g., estrogen) production following menopause/andropause, is a primary causative factor for the development of Alzheimer disease. In this review, we examine how the gonadotropins may play a central and determining role in modulating the susceptibility to, and progression of, Alzheimer disease.

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1. Alzheimer disease

Alzheimer disease (AD) is clinically characterized by progressive memory loss, impairments in behavior, language and visual–spatial skills and ultimately, death. AD is not only the leading cause of senile dementia, but it is also the most prevalent neurodegenerative disease worldwide, and is subsequently, an increasingly alarming national health problem in the United States where recent studies report that over four million Americans are currently afflicted with the disease. Total national costs of caring for AD patients have been estimated to be in excess of US$ 100 billion per year (Ernst and Hay, 1994), and this figure will undoubtedly rise since it is estimated that by 2050, fourteen million Americans will be afflicted with this debilitating disease (Hebert et al., 2003).

Despite the fact that AD affects up to 15% of people over the age of 65 and nearly half of all individuals by the age of
It is, in fact, the gonadotropins, which are the members of the hypothalamic–pituitary–gonadal axis that regulate sex steroid production, and not the sex steroids themselves, namely estrogen, which may be playing a central role in the pathogenesis of AD (Bowen et al., 2000, 2002, 2004a, 2004b, 2005; Bowen, 2001; Casadesus et al., 2004, 2005; Smith et al., 2003; Webber et al., 2004, 2005a, 2005b; Zhu et al., 2004a, 2004b).

The hormones of the hypothalamic–pituitary–gonadal axis include gonadotropin-releasing hormone, luteinizing hormone (LH), follicle-stimulating hormone, estrogen, progesterone, testosterone, activin, inhibin, and follistatin. Each of these hormones is involved in regulating reproductive function by participating in a complex feedback loop that is initiated by the hypothalamic secretion of gonadotropin-releasing hormone (Genazzani et al., 1992) that stimulates the anterior pituitary to secrete the gonadotropins, luteinizing hormone and follicle-stimulating hormone. These gonadotropins then bind to receptors on the gonads and stimulate oogenesis/spermatogenesis, as well as the production of the sex steroids. Sex steroids complete the negative feedback loop by decreasing gonadotropin secretion from the hypothalamus and pituitary gland. Activin and inhibin, which are members of the TGFβ family of proteins, also are involved in the complex feedback loop of the hypothalamus–pituitary–gonadal axis (Welt et al., 2002); however, our current focus is on the gonadotropins described above.

Menopause/andropause shift the balance of the hypothalamic–pituitary–gonadal axis feedback loop described above, and this shift results in an increase in the production of gonadotropins along with the bioavailability of activin and a decrease in gonadal inhibin production. In women, these changes can be attributed to the loss of negative feedback by estrogen and inhibin (Couzinet and Schaison, 1993), and result in a 3- to 4-fold increase in the concentration of serum luteinizing hormone and a 4- to 18-fold increase in the concentration of serum follicle-stimulating hormone (Chakravarti et al., 1976). Likewise, men also experience a greater than 2- and 3-fold increase in luteinizing hormone and follicle-stimulating hormone, respectively, as their reproductive function deteriorates during andropause (Neaves et al., 1984); however, this increase is notably smaller than the increase of gonadotropin levels in women following reproductive senescence. While both menopause and andropause refer to the decrease in sex steroids upon reproductive senescence in women and men, respectively, the rate at which these changes take place are drastically different, with menopause occurring very abruptly while the process of andropause is a gradual phenomenon (Boyar et al., 1972). It is, in fact, this gender-based difference in the rate and intensity of hormonal changes due to reproductive aging which serves as the basis for hypotheses regarding the role of sex steroids, and also the gonadotropins, in AD. Surprisingly, the effects of increased circulating gonadotropins due to the loss of negative feedback on the aging brain are largely unexplored.

2. The hypothalamic–pituitary–gonadal axis

Epidemiological studies with regard to gender differences in AD have often resulted in conflicting data (Fratiglioni et al., 1997; Letenneur et al., 1994), yet most studies support the higher prevalence (Breitner et al., 1988; Jorm et al., 1987; McGonigal et al., 1993; Rocca et al., 1991) and incidence (Jorm and Jolley, 1998) of AD in women. Because this gender-based predisposition towards females is specific to AD and is not found in other dementias such as Parkinson’s, where men have a higher prevalence and progression of disease, investigators have been focusing on the roles of the sex steroids estrogen; and to a lesser extent, testosterone, in the pathogenesis of AD. This has led to a number of lines of evidence suggesting that estrogen deficiency, following menopause, may contribute to the etiology of AD in women. Despite the large body of evidence supporting the protective role of estrogen in AD; there have been several recent contradictory studies demonstrating an increase in estrogen levels in patients with AD when compared with controls (Hogervorst et al., 2003), and studies reporting no improvement in cognitive function upon estrogen plus progesterin treatment (Rapp et al., 2003). Such inconsistent data and unanswered mechanistic questions not only reveal our incomplete understanding of the fundamental characteristics of AD, but also cast serious doubt on the role of sex steroids in the disease process. There are, however, a number of other hormones involved in the hypothalamic–pituitary–gonadal axis that along with estrogen and testosterone, regulate reproductive function, and receptors for these other hormones are also expressed in many nonreproductive tissues including, most notably, the brain (Apaja et al., 2004). Considering this fact and the reported incomplete protection of hormone replacement therapy, we hypothesize that it is, in fact, the gonadotropins, which are the members of the hypothalamic–pituitary–gonadal axis that regulate sex steroid production, and not the sex steroids themselves, namely estrogen, which may be playing a central role in the pathogenesis of AD (Bowen et al., 2000, 2002, 2004a, 2004b, 2005; Bowen, 2001; Casadesus et al., 2004, 2005; Smith et al., 2003; Webber et al., 2004, 2005a, 2005b; Zhu et al., 2004a, 2004b).

3. Gonadotropins in Alzheimer disease

There is growing evidence supporting a role for gonadotropins, particularly luteinizing hormone, in the pathogenesis of AD, beginning with the finding of a 2-fold
increase in circulating gonadotropins in individuals with AD compared with age-matched control individuals (Bowen et al., 2000; Short et al., 2001). Despite the increase of both luteinizing hormone as well as follicle-stimulating hormone in the serum of AD patients, which would implicate both gonadotropins in the disease process, only luteinizing hormone receptors, and not follicle-stimulating hormone receptors have been detected in the brain, the highest density of which are found within the hippocampus (Lei et al., 1993), a region devastated in Alzheimer disease. Furthermore, luteinizing hormone, but not follicle-stimulating hormone, was significantly elevated in vulnerable neuronal populations in individuals with Alzheimer disease compared to aged control cases (Bowen et al., 2002). Notably, such increases in neuronal luteinizing hormone appear to be a very early change in disease history serving to predict neuronal populations at risk of degeneration and death. In fact, elevations in luteinizing hormone parallel the ectopic expression of cell cycle and oxidative markers that represent one of the initiating pathological changes preceding neuronal degeneration by decades (Harris et al., 2000; McShea et al., 1997, 1999; Nunomura et al., 2001; Ogawa et al., 2003a, 2003b; Raina et al., 2000; Zhu et al., 1999, 2000, 2004a, 2004b). Furthermore, while luteinizing hormone did not alter amyloid-β protein precursor (AβPP) expression in a recent study using M17s, a neuroblastoma cell line (Bowen et al., 2004a, 2004b), luteinizing hormone did alter AβPP processing toward the amyloidogenic pathway as evidenced by increased secretion and insolubility of amyloid-β (Aβ), decreased αAβPP secretion, and increased AβPP-C99 levels. This same study also reported a 3.5- and 1.5-fold reduction in total brain Aβ1–42 and Aβ1–40 concentrations, respectively, in C57Bl/6J mice treated with leuprolide acetate, a potent gonadotropin-releasing hormone agonist shown to effectively lower serum levels of the gonadotropins, luteinizing hormone and follicle-stimulating hormone (Bowen et al., 2004a, 2004b). This data, which supports a role for luteinizing hormone in AβPP processing contributing to disease pathogenesis in vivo and in vitro, not only offers support to the mounting evidence implicating luteinizing hormone as the initiating pathological factor in AD (Bowen et al., 2000, 2002, 2004a, 2004b, 2005; Bowen, 2001; Casadesus et al., 2004, 2005; Smith et al., 2003; Webber et al., 2004, 2005a, 2005b; Zhu et al., 2004a, 2004b), but also provides a novel explanation for the surprising results of the Women’s Health Initiative (WHI) Memory Study, which bears mentioning.

4. WHI memory study

Questions regarding the “critical period” in hormone replacement therapy (HRT)-based protection against AD, suggests that falling serum levels of steroid hormones that accompany menopause/andropause cannot sufficiently explain patterns of AD susceptibility. It was recently shown that HRT, in the form of conjugated equine estrogen plus progestin, administered as a therapeutic agent in a WHI clinical trial was shown to increase the risk for probable dementia in postmenopausal women aged 65 years or older (Shumaker et al., 2003). The investigators responsible for this study hypothesize that the negative effect of estrogen and progestin may be linked to the increased risk of stroke that was also reported in the estrogen/progestin treatment group, as the relationship between microinfarcts in the brain and susceptibility to AD is likely related, yet currently not well characterized. While this may indeed partially explain the results of the WHI clinical trial, it is only when the role of the other hormones of the hypothalamic–pituitary–gonadal axis during the climacteric years and beyond is taken into account that the results of the WHI clinical trial can be fully and accurately explained. For instance, it is crucial when interpreting the results of this study to recognize that the hormones of the hypothalamic–pituitary–gonadal axis have been in disequilibrium for decades in all of the women who participated in the WHI clinical trial, aged 65 years and older; therefore, if a lack of estrogen does indeed play a role in AD pathogenesis, these women have been exposed to this disease-promoting hormonal environment for years, if not decades, by the time the estrogen/progestin treatment was administered. For this reason, along with the high prevalence of obesity among the participants of this study, it has been argued that this was not a true primary prevention study as it is highly likely that the patients involved in this study are beyond preventative measures (Bhavnani, 2003). This argument is supported by the fact that reports of probable dementia appeared within the first year of the study in both the treatment and placebo groups. It is likely predictable that the administration of estrogen/progestin in these aged women was not only unable to restore the proper functioning of the hypothalamic–pituitary–gonadal axis, but also that the influx of exogenous hormones actually served to exacerbate the disease process. Thus, any accurate interpretation of the results of the WHI clinical trial of estrogen plus progestin treatment in aged women must take into account the other hormones of the hypothalamic–pituitary–gonadal axis and the effect of reproductive senescence on this axis (Webber et al., 2005a, 2005b).

5. Therapeutic considerations: gonadotropin-releasing hormone antagonists

As previously mentioned, treatment with leuprolide acetate, a potent gonadotropin-releasing hormone agonist shown to effectively lower serum levels of the gonadotropins, luteinizing hormone and follicle-stimulating hormone, through gonadotropin-releasing hormone receptor desensitization, resulted in a 3.5- and 1.5-fold reduction in total brain Aβ1–42 and Aβ1–40 concentrations, respectively, in C57Bl/6J mice (Bowen et al., 2004a, 2004b). Because of the similar role of luteinizing hormone in AD pathogenesis and the ability of leuprolide acetate to not only decrease Aβ concentrations, but also serum luteinizing hormone concentrations, leuprolide acetate is strong candidate for the treatment, and perhaps, prevention of AD. Currently, leuprolide acetate is used as a treatment for prostate cancer; and the observation was made that men who were suffering from Alzheimer disease and who were also taking this drug experienced a diminution of their neurological symptoms (Bowen et al., 2000; Bowen, 2001). While the use of leuprolide in premenopausal women has resulted in memory loss and depression...
(Varney et al., 1993), these adverse reactions are due to the sec-
ondary abrupt loss of estrogen production since memory and
mood returned to normal after estrogen replacement (Sherwin
and Tulandi, 1996). Since women with AD are postmenopausal
and already have lost their ability to produce estrogen, leuprolide
would be predicted to have no effect on their estrogen produ-
cation, and furthermore, patients would be predicted to benefit
from leuprolide-induced decreases in luteinizing hormone reduc-
ing its pathogenic affects (Bowen, 2001; Bowen et al., 2004a,
2004b, 2005; Casadesus et al., 2004, 2005; Smith et al., 2003;
Webber et al., 2004, 2005a, 2005b; Zhu et al., 2004a, 2004b). The
results of clinical trials of leuprolide acetate for the treat-
ment of AD are eagerly anticipated.

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