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Gonadotropins and Alzheimer's disease: the link between estrogen replacement therapy and neuroprotection

Kate M. Webber[1], Richard Bowen[2], Gemma Casadesus[1], George Perry[1], Craig S. Atwood[1] and Mark A. Smith[1]

[1]Institute of Pathology, Case Western Reserve University, 2085 Adelbert Road, Cleveland, Ohio 44106, USA; [2]Voyager Pharmaceutical Corporation, 8540 Colonnade Center Drive, Suite 409 Raleigh, North Carolina 27615, USA

Abstract. The search for a definitive gender bias in Alzheimer's disease has resulted in a multitude of epidemiological findings that point to a higher prevalence and incidence of Alzheimer's disease in women. Due to this reported predisposition of women to Alzheimer's disease, the sex steroid estrogen has become the primary focus of research in this field, however, inconclusive data regarding estrogen replacement therapy has lead some researchers to further investigate the role of the other hormones of the hypothalamic-pituitary-gonadal (HPG) axis that have been, for the most, part overlooked. The hormones of the HPG axis, such as the gonadotropin, (luteinizing hormone and follicle-stimulating hormone), are involved in regulating reproductive function *via* a complex feedback loop. We propose that it is in fact the increase in gonadotropin concentrations and not the decrease in steroid hormone (e.g., estrogen) production following menopause/andropause that results in an increased risk of Alzheimer's disease. Furthermore, when the role of gonadotropins is taken into account, the data obtained from recent epidemiological studies and randomized trials suggesting the ineffectiveness estrogen may indeed be misinterpreted. In this review, we examine how hormones of the hypothalamic-pituitary-gonadal axis, in particular the gonadotropins, play a central and determining role in modulating the susceptibility to and progression of Alzheimer's disease. Based on this, we suggest that therapeutic interventions targeted at gonadotropins could both prevent disease in those patients currently asymptomatic or halt, and even reverse, disease in those currently afflicted.

Review

The correspondence should be addressed to M.A. Smith, Email: mas21@po.cwru.edu

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INTRODUCTION

Recent epidemiological studies and clinical trials regarding estrogen replacement therapy and neuroprotection have resulted in inconclusive data that has provided more questions than answers. This is largely due to the fact that estrogen does not act alone within the body and is in fact involved in a complex feedback loop with the other hormones of the hypothalamic-pituitary-gonadal axis, including the gonadotropin luteinizing hormone. When the role of the gonadotropins, namely luteinizing hormone, are taken into account, the failure of these recent studies to show a link between estrogen replacement therapy and neuroprotection is predictable on a mechanistic level. Gonadotropins not only play a role in the pathogenesis of Alzheimer's disease, they can also serve as a target for therapeutic intervention and could both prevent and even possibly reverse the conditions of Alzheimer's disease.

BACKGROUND AND EPIDEMIOLOGY OF ALZHEIMER'S DISEASE

Alzheimer's disease, the leading cause of senile dementia, is clinically characterized by progressive memory loss, impairments in behavior, language and visual-spatial skills and ultimately, death. Unfortunately, at present, therapeutic management of the disease is primarily targeted toward palliative treatment of symptoms rather than forestalling the progression of the disease. As such, even with state of the art pharmaceutical intervention, continued and progressive cognitive decline in patients is inevitable. The major obstacle in managing the disease and designing a rationale for therapeutic targets is our incomplete understanding of the pathogenesis of the disease.

The pathological hallmarks of Alzheimer's disease, which include amyloid-β plaques and neurofibrillary tangles among others, have been well documented; however, the etiologic events that lead to the generation of these pathological hallmarks are not understood. Nonetheless, a number of hypotheses have been touted as explaining Alzheimer's disease, with the amyloid hypothesis gaining most attention due to the findings that early onset Alzheimer's disease result from mutations in either the amyloid β protein precursor or presenilin-1 and 2, proteins involved in the processing of amyloid-β (Selkoe 1997). However, perturbation of these elements in cell or animal models does not result in the multitude of biochemical and cellular changes found in the disease. For example, there is little to no neuronal loss in transgenic rodent models that overexpress amyloid β protein precursor despite large depositions of amyloid-β protein (Irizarry et al. 1997). More importantly, however, there is now considerable evidence that amyloid-β is a consequence, rather than causative factor, in disease pathogenesis (Obrenovich et al. 2002, Perry et al. 2000, Rottkamp et al. 2002). This has led to a consideration of other theories to explain the mechanism of disease that include tau phosphorylation (Avila 2000, Trojanowski et al. 1999, Zhu et al. 2002), oxidative stress (Perry et al. 1998, Pogocki 2003), metal ion dysregulation (Perry et al. 2002) and inflammation (Atwood et al. 2001). However, while these aspects are all associated with Alzheimer's disease and almost certainly play a role in the disease process; not one of these theories is sufficient to explain the entire spectrum of abnormalities found in the disease. In fact to date, while we know that age, gender, genetics and environment all play a role in the disease, there has been no single mechanistic hypothesis, aside from that discussed herein that explains all of the known features and risk factors for the disease.

THE ROLE OF HORMONE REPLACEMENT THERAPY IN ALZHEIMER'S DISEASE

Previous epidemiological studies concerning gender differences in Alzheimer's disease have often resulted in conflicting data (Fratiglioni et al. 1997 vs. 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 Alzheimer's disease in women. Because this gender-based predisposition is specific to Alzheimer's disease and not to other dementias, investigators have been focusing on the role of the sex steroid estrogen in the pathogenesis of the disease. This has led to a number of lines of evidence suggesting that estrogen deficiency, following menopause, may contribute to the etiology of Alzheimer's disease in women. In this regard, a positive correlation has been shown to exist between Alzheimer's disease and decreased estrogen levels following menopause (levels below that of men), such that women who maintain relatively high endoge-

nous estrogen levels after menopause exhibit a decreased prevalence of Alzheimer's disease (Manly et al. 2000). Further evidence supporting the protective effects of estrogen in Alzheimer's disease demonstrates a decreased incidence (Henderson et al. 1994) and a delay in the onset (Tang et al. 1996) of Alzheimer's disease among women on hormone replacement therapy (HRT) following menopause (Kawas et al. 1997). However, recent conflicting data reports an increased risk for probable dementia in postmenopausal women sixty-five years and older who are placed on HRT therapy, specifically estrogen plus progestin (Schumaker et al. 2003). A comparable study further suggests that estrogen plus progestin therapy did not improve cognitive function when compared with placebo in postmenopausal women aged 65 and older (Rapp et al. 2003).

The discrepancy between these findings is due largely in part to the time in which the HRT regiment was initiated in the postmenopausal women, and subsequently the methodology of the different studies. In the earlier epidemiological studies, women were placed on the HRT regiment shortly after or during menopause, while in the more recent randomized trials, prolonged postmenopausal women, no younger than sixty five years old, were placed on a HRT regiment. HRT protection against Alzheimer's disease has been suggested to be effective only when administered during a "critical period" that constitutes the climacteric years (as in the epidemiological studies), and yet almost completely ineffective when administered during the latent preclinical stage of Alzheimer's disease that usually occurs much later in life (Resnick and Henderson 2002) (Fig.1). The notion of a "critical period" infers that estrogen HRT must be administered early enough to counter the loss of negative feedback by estrogen during menopause (Couzinet and Schaison 1993), which consequently results in a three- to four-fold increase in the concentration of serum luteinizing hormone and a four- to eighteen-fold increase in the concentration of serum follicle-stimulating hormone in women (Chakravarti et al. 1976). Surprisingly, the effects of increased circulating gonadotropins due to the loss of negative feedback on the aging brain are largely unexplored. However, these high levels of serum gonadotropins, namely luteinizing hormone and follicle-stimulating hormone, have been present for an upwards of ten years in the sixty five year old postmenopausal women included in the recent randomized trials, so it is highly unlikely that the influx of estrogen introduced by the HRT would be

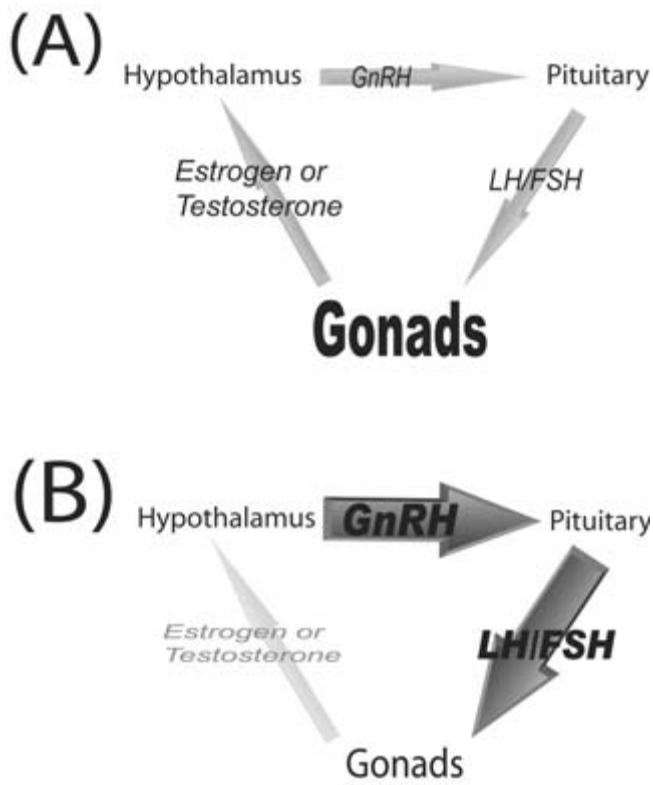

Fig. 1. Both estrogen and testosterone production are under the control of the hypothalamic-pituitary-gonadal (HPG) axis. HPG stimulates sex steroid production by increasing the secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus, which stimulates the pituitary to secrete LH and FSH (A). Following menopause/andropause (B) there are increases in circulating LH and FSH levels resulting from the loss of negative feedback by estrogen and testosterone on the HPG (Couzinet and Schaison 1993).

able to return the hormone levels to a pre-menopausal state. Furthermore, elevated levels of the gonadotropins combined with increased levels of estrogen achieved through HRT, appear to have a synergistic effect resulting in the reported increased risk for probable dementia. This directly implicates the gonadotropins, mainly luteinizing hormone, in general dementia and we further hypothesize that luteinizing hormone contributes specifically to the pathogenesis of Alzheimer's disease.

ALZHEIMER'S DISEASE IS ASSOCIATED WITH ELEVATED SERUM GONADOTROPINS

In order to further dissect the role of gonadotropins in Alzheimer's disease, we investigated circulating go-

nadotropin levels in individuals with Alzheimer's disease compared with age-matched control individuals, and we discovered a two-fold increase in circulating gonadotropins (Bowen et al. 2000, Short et al. 2001). More importantly, since, the highest density of gonadotropins receptors in the brain are found within the hippocampus (Al-Hader et al. 1997a,b, Lei et al. 1993), a region devastated in Alzheimer's disease, and gonadotropins are known to cross the blood brain barrier (Lukacs et al. 1995), we speculate that elevated gonadotropins, particularly luteinizing hormone, may be a driving pathogenic force in Alzheimer's disease (Bowen et al. 2002). In support of such a notion, we found significant elevations of luteinizing hormone in vulnerable populations in individuals with Alzheimer's 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 (Nunomura et al. 2001, Ogawa et al. 2003). Along the same lines, the reactivation of the mitotic signaling pathways ERK and MAPK shown to occur early in Alzheimer's pathogenesis (Perry et al. 1999, Zhu et al. 2001, 2002) is also known to be upregulated by gonadotropins, including luteinizing hormone (Harris et al. 2002). Since luteinizing hormone is a powerful mitogen (Harris et al. 2002), it is likely, given the temporal and spatial overlap with mitotic changes in Alzheimer's disease (Bowen et al. 2002, our unpublished observations), that elevations in luteinizing hormone are responsible for inappropriate cell cycle re-entry in neurons (Fig. 2) (Bowen et al. 2002, Raina et al. 2000) that accompany the onset of disease. Obviously this does not preclude the involvement of the other hormones of the hypothalamic-pituitary-gonadal axis that also exhibit significant changes in serum concentrations later in life.

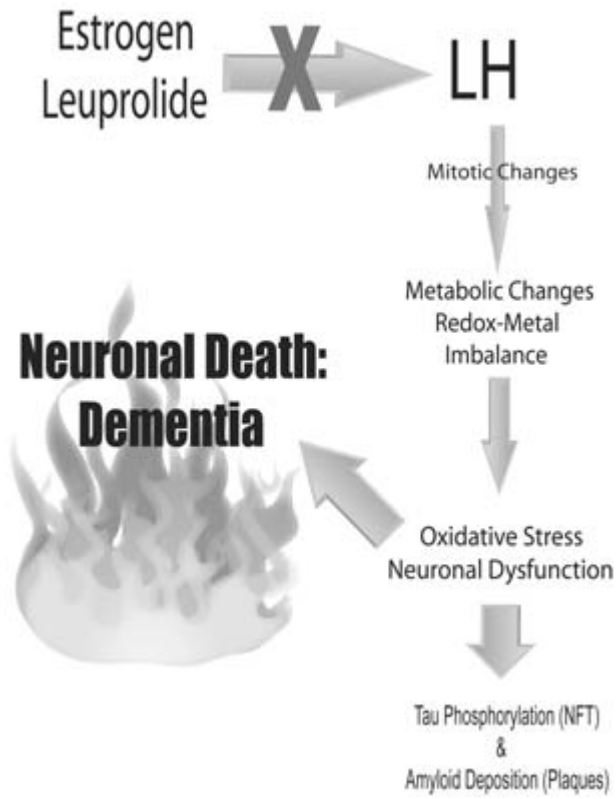

Fig. 2. Proposed sequence of events that culminate in AD. Luteinizing hormone is believed to initiate mitotic events in susceptible LH-receptor bearing neurons which subsequently leads to a variety of cellular changes including metabolic, metallic and oxidative alterations. Together, these changes mediate the hallmarks of Alzheimer's disease that include neurofibrillary tangles, amyloid-β plaques and neuronal death. The lowering of LH through therapeutic intervention could potentially circumvent this process and block the degenerative cascade that occurs in AD.

THERAPEUTIC CONSIDERATIONS: GONADOTROPIN-RELEASING HORMONE ANTAGONISTS

The reason that estrogen replacement therapy has not been shown to be effective in the treatment of Alzheimer's disease (Mulnard 2000, Mulnard et al. 2000) is likely because it does not restore the hypothalamic-pituitary-gonadal axis to its premenopausal state since the gonadotropin stimulating effect of activin is still increased due to the loss of inhibin after menopause. In addition, even the "normal" concentrations of luteinizing hormone exhibited earlier in life may be detrimental late in life. Therefore, leuprolide acetate, a gonadotropin-releasing hormone agonist which has been shown to suppress luteinizing hormone to undetectable levels by down regulating pituitary gonadotropin-releasing hormone receptors, might be an effective method of treatment for Alzheimer's disease. 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 secondary abrupt loss of estrogen production since memory and mood returned

to normal after estrogen replacement (Sherwin and Tulandi 1996). Since women with Alzheimer's disease are postmenopausal and already have lost their ability to produce estrogen, leuprolide would be predicted to have no effect on their estrogen production, and therefore their memory. The results of clinical trials of leuprolide acetate for the treatment of Alzheimer's disease are anticipated early 2004.

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