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Luteinizing hormone: Evidence for direct action in the CNS

Jeffrey A. Blair [a], Sabina Bhatta [a], Henry McGee [b], Gemma Casadesus [b,*]

[a] School of Biomedical Sciences, Kent State University, Kent, OH, USA
[b] Department of Biological Sciences, Kent State University, Kent, OH, USA

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ABSTRACT

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Hormonal dysfunction due to aging, especially during menopause, plays a substantial role in cognitive decline as well as the progression and development of neurodegenerative diseases. The hypothalamic–pituitary–gonadal (HPG) axis has long been implicated in changes in behavior and neuronal morphology. Most notably, estrogens have proven beneficial in the healthy brain through a host of different mechanisms. Recently, luteinizing hormone (LH) has emerged as a candidate for further investigation for its role in the CNS. The basis of this is that both LH and the LH receptor are expressed in the brain, and serum levels of LH correlate with cognitive deficits and Alzheimer's disease (AD) incidence. The study of LH in cognition and AD primarily focuses on evaluating the effects of downregulation of this peptide. This literature has shown that decreasing peripheral LH, through a variety of pharmacological interventions, reduces cognitive deficits in ovariectomy and AD models. However, few studies have researched the direct actions of LH on neurons and glial cells. Here we summarize the role of luteinizing hormone in modulating cognition, and we propose a mechanism that underlies a role for brain LH in this process.

Introduction

Cognitive function has long been associated with levels of sex steroids, estrogens and androgens, as well as more recently luteinizing hormone (LH). Multiple studies show that the receptors for these hypothalamic–pituitary–gonadal (HPG) axis hormones are found in areas of the brain critical for learning and memory, such as the hippocampus (Ascoli et al., 2002; Roepke et al., 2011). Studies on the role of gender and age-specific changes in hormones, such as estrogens, show a correlation to Alzheimer's disease (AD) incidence. This implicates HPG axis dyshomeostasis as a risk factor for AD (Short et al., 2001; Zandi et al., 2002; Hogervorst et al., 2004; Tsolaki et al., 2005; Butchart et al., 2013; Verdile et al., 2014).

AD is diagnosed by progressive impairments in memory, where attention and memory deficits ultimately lead to debilitated judgment, language skills, and spatial orientation (Cummings et al., 1998). Pathological hallmarks of AD include extracellular senile plaques and intracellular neurofibrillary tangles (Hampel et al., 2012). Aging is the strongest risk factor for AD, and its incidence doubles every five years from ages 65 through 85. The cost of caring for AD has an exorbitant price tag that exceeds $180 billion per year (Stefanacci, 2011). This will only increase given that the number of diagnosed patients is expected to topple over 13 million by 2050 (Hebert et al., 2003). Underlying causal factors for AD remain unknown, and endeavors to pinpoint a molecular cascade underlying the initiation of such a multifactorial disease have been difficult. Up to date, therapeutic strategies aimed at targeting either amyloid-β or tau have been unsuccessful at treating AD; therefore, alternatives need to be considered.

HPG axis in aging

Aging is associated with menopause in women and andropause in men, both of which lead to declines in hormones that comprise the HPG axis. Hormonal changes associated with the dysregulation of the HPG axis are implicated in the pathogenesis of AD. In a healthy brain, gonadotropin-releasing hormone (GnRH) is released from the hypothalamus and acts on its receptor (GnRHR) in the pituitary gland. Once activated, GnRHR stimulates the production and secretion of the gonadotropins, LH and follicle-stimulating hormone, into the bloodstream. LH activates gonadal production of sex steroids, androgens and estrogens, which then provide a negative feedback to the hypothalamus. Drastic decreases in estrogens during aging, due to menopause, remove the negative feedback on gonadotropin production and result in a 3 fold increase in the concentrations of peripheral LH (Cummings et al., 1998; Daniel et al., 2006). Estrogen receptor α (ERα) mediates negative feedback by estrogens on the hypothalamus, ultimately inhibiting LH secretion through p21-activated kinase (Zhao et al., 2009). Importantly for estrogen replacement therapies, the dysregulation of the HPG axis caused by menopause may be due to a diminished ability of estrogens to inhibit the hypothalamus (King et al., 1987; Lloyd et al., 1994; Wise et al., 2002). The decrease in estrogens with aging, the subsequent increase in peripheral luteinizing hormone and the

* Corresponding author at: Kent State University, Department of Biological Sciences, 256 Cunningham Hall, Kent, OH 44242, USA.
E-mail address: gcasades@kent.edu (G. Casadesus).

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diminished ability of estrogens to inhibit the hypothalamus after menopause have been central to our hypothesis that luteinizing hormone is a candidate in the HPG axis to modulate learning and memory.

Estrogens in memory function

Aging related decreases in estrogens result in cognitive deficits, perhaps due to reductions in spine density and reorganization of synapses in brain areas associated with cognition such as the prefrontal cortex and hippocampus (Bloss et al., 2013; Wallace et al., 2006). While the secretion of several hormones progressively decreases with age in both men and women (Arlt and Hewison, 2004), menopause induces an abrupt loss of circulating peripheral ovarian hormones in women. Basal gonadal steroid secretion is maintained after the cessation of ovulation in mice, unlike in human females (Nelson, 2008). Therefore, an ovariectomy, the bilateral removal of ovaries, mimics menopausal ovarian hormone loss in women.

In fact, ovariectomy induces a decline in spine density that parallels those observed during normal aging (Wallace et al., 2006). Loss of estrogens due to ovariectomy leads to deficits in recognition memory tasks (Wallace et al., 2006) as well as novelty seeking, a non-goal-directed exploratory activity (Baeza et al., 2010) and spatial memory tasks (Heikkinen et al., 2004; Monteiro et al., 2005; Daniel and Bohacek, 2010). Additionally, 17β-estrodiol (E2) administration in ovariectomized rats improves spatial/hippocampal function (Luine and Rodriguez, 1994; Luine et al., 1998; Daniel et al., 1997; Dohanich et al., 1994; Dohanich, 2002). E2 treatments, both acute and chronic, are capable of enhancing cognition through alterations in structural and neurochemical aspects of cholinergic, glutaminergic, GABAergic, and monoaminergic systems (Gibbs, 2010; McEwen and Alves, 1999). Work done in vitro by Hojo et al. (2004) demonstrates the importance of NMDA receptor dependent E2 synthesis for the maintenance of spines and synapses in rat hippocampal slices. Similarly, in vivo work of Kato et al. (2013) indicates that activation of cascades involved in memory formation result in increases in hippocampal E2 concentrations. E2 can regulate spines by activating several signaling cascades involving CaMKII, PI3K and PKA/PKC/MAPK (Roepke et al., 2011; McEwen et al., 2012; Srivastava, 2012; Kramar et al., 2013). NMDA receptor induced E2 production in the hippocampus leads to increases in spine density (Kato et al., 2013), providing support for the hypothesis that estrogens synthesized in neurons may contribute to learning and memory through their actions on spines and synapses (Frick, 2012).

Estrogens in clinical trials

Unfortunately, hormone replacement therapy (HRT) has been vastly unsuccessful in ameliorating cognitive deficits in older women (Polo-Kantola et al., 1998). The Women's Health Initiative study found HRT increased the risk of dementia (Rapp et al., 2003; Chlebowski et al., 2010). Interestingly, accounting for differences between the start of menopause and initiation of HRT elucidated that initiation of HRT 10 or more years after menopause increases the risk of AD. On the other hand, initiation of HRT at menopause lowers the risk of AD (Rapp et al., 2003; Zandi et al., 2002). Overall, the clinical trials suggest that a critical period exists between menopause and HRT onset, such that the delay critically impacts its effectiveness. HRT is most effective immediately following menopause but is rendered detrimental when administered with a substantial delay (Sherwin, 2003). These findings parallel the lack of positive results of estrogen administration in rodents, where cognitive (Daniel et al., 2006; Sherwin, 2005) and synaptic deficiencies (Tanapat et al., 2005) were not mitigated when E2 was administered 4–6 months after ovariectomy (Daniel et al., 2006; McLaughlin et al., 2008; Bohacek and Daniel, 2010).

An important question to answer is why a critical time window exists for HRT. One hypothesis in the literature, *the healthy cell bias*, proposes that neuronal health controls the fate of estrogen therapy. Estrogen signaling can be detrimental if activated in unhealthy neurons because of exacerbation of mitochondrial dysfunction and calcium dyshomeostasis (Brinton, 2005; Sohrabji, 2006; Brinton, 2008). We hypothesize that the critical window for estrogen benefits also lies in the ability of estrogens to properly regulate the HPG axis, and thus regulate gonadotropin levels effectively.

Luteinizing hormone in aging and disease

Though HRT failed to consistently ameliorate CNS function and its underlying mechanisms in clinical trials, other HPG axis players are now being evaluated as potential therapeutic targets. One such hormone is LH, which increases 3 fold in women (Chakravarti et al., 1976) and 2 fold in men (Neaves et al., 1984) throughout the aging process. These changes in LH levels correlate with AD progression (Short et al., 2001; Hogervorst et al., 2004; Butchart et al., 2013; Verdile et al., 2014). Furthermore, the loss of sex steroids leads to increased peripheral LH and correlated with a decline in cognition in men (Hyde et al., 2010) and women (Rodrigues et al., 2008). Recently, high levels of peripheral LH were correlated with a pathological marker of neurodegenerative disease, amyloid-β (Verdile et al., 2014). Altogether these data propel the hypothesis that increased levels of peripheral LH lead to deficits in cognition and neurodegeneration.

Peripheral luteinizing hormone in learning and memory

The correlation between increased LH and cognitive decline led to the basic study of peripheral LH effects on learning and memory and associated signaling cascades. It is now known that working memory is impaired in a transgenic mouse model overexpressing LH (Casadesus et al., 2007). In parallel, chronic elevations of peripheral human chorionic gonadotropin (hCG), which shares a receptor with LH, impairs working memory and increases levels of total brain amyloid-β_{40} in a mouse model of AD (Barron et al., 2010). Animal studies using GnRHR antagonists, antide and Cetrorelix, which lower peripheral LH levels through alternate mechanisms, also show benefits on cognition in spatial memory tasks in rats (Ziegler and Thornton, 2010) and mice treated with amyloid-β (Telegdy et al., 2009; Kovacs et al., 2001). These studies suggest that LH may have a significant role in the development of AD.

Leuprolide acetate, a GnRHR super agonist which downregulates LH synthesis, decreases amyloid-β immunoreactivity and improves working memory performance in Y-maze and Morris water maze behavior paradigms in ovariectomized Tg2576 and 3xTg transgenic mouse models of AD (Casadesus et al., 2006; Palm et al., 2014; Bowen et al., 2004). Long-term potentiation (LTP) is responsible for the persistent strengthening of synapses and is associated with CaMKII autophosphorylation. While LTP decreases after ovariectomy, it is rescued with leuprolide acetate treatment, as analyzed by phosphorylation of CaMKII in the hippocampus (Bryan et al., 2010). Leuprolide acetate treatment after ovariectomy also shows an increase in the phosphorylation of the GluR1 subunit of AMPA; therefore, these combined pathways are associated with improvements in learning and memory (Bryan et al., 2010). In this experimental paradigm, leuprolide acetate also affected transcript levels of hippocampal p450 aromatase (Bryan et al., 2010), which in turn can modulate the synthesis of E2 from testosterone. However, there were no changes in the levels of estrogen receptors (Bryan et al., 2010) Altogether, the observed changes may be due to up-regulation of estrogens, but lead toward changes in CREB activation and inhibition of GSK3β (Palaniappan and Menon, 2012; Flynn et al., 2008; Palm et al., 2014).

A link between peripheral and central levels of luteinizing hormone

Changes in behavior correlating to peripheral levels of LH are not an altogether recent hypothesis. LH pulses decrease in frequency but increase in amplitude during sleep (Bagshawe et al., 1968; Lukacs et al.,