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Luteinizing Hormone: Evidence for direct action in the CNS

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Abstract

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.

Graphical Abstract

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In the aged female brain estrogen replacement after ovariectomy does not improve cognitive function or associated underlying mechanisms such as dendritic spine density changes. Drugs that reduce peripheral levels of LH, which surge after ovariectomy or during menopause, rescue ovariectomy-dependent cognitive dysfunction, increases signaling events associated with synaptic plasticity. The LH receptor is localized to cognition-associated areas and its functionality is described both at a level of function and plasticity. Brain-derived LH protein levels are present in cognition associated areas and reduced by ovariectomy. These levels are normalized by drugs that reduce peripheral LH levels and this normalization of brain-LH positively correlates with markers of neuroplasticity and cognitive improvement.

Keywords

luteinizing hormone; leuprolide acetate; ovariectomy; estrogen; HPG axis; memory

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 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., 2012; 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 top out 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-release 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 (ER α) 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 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, 17 β -estradiol (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, glutamatergic, 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., 2012; 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 auto-phosphorylation. 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 GSK3 β (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., 1995). Furthermore, it has long been proposed that high levels of hCG typical during the first and third trimester of pregnancy are associated with changes in sleep (Berkowitz et al., 1981). Electroencephalograms of rats injected intraperitoneally with hCG show increased high and low amplitude sleep while decreasing

the active awake phase (Toth et al., 1994). Furthermore, peripheral hCG injections decreased walking and increased rest periods (Toth et al., 1994); therefore showing LHR activation is associated with wakefulness.

Along with the direct and peripheral effects of hCG, we have recently discovered that LH is produced in the brain (Figure 1). It is expressed in cognition modulating areas such as the hippocampus, the cingulate cortex and midbrain structures such as the thalamus and superior colliculi (Figure 1A), and it co-localizes with neuronal markers such as NeuN in pyramidal neurons (Figure 1B). Electron microscopy shows that LH appears to be encapsulated in vesicles (Figure 1C). Importantly, we have shown that LH mRNA levels are reduced in hippocampi of AD patients compared to controls, and in ovariectomized 3xTg AD mice LH immunoreactivity in the superior colliculus is decreased (Palm et al., 2014). Downregulation of peripheral LH using leuprolide acetate normalizes brain LH to levels observed in SHAM operated mice (Palm et al., 2014). Therefore, there seems to be an inverse relationship of LH expression between the brain and bloodstream. How the underlying mechanisms are associated with this inverse relationship are unknown, but we identified that LH levels in the superior colliculus were positively correlated with cognitive function (Palm et al., 2014). This suggests that levels of brain LH may, at least partially, regulate cognitive function (Figure 2). Importantly, this could explain why ovariectomy, especially in the absence of estrogen effectiveness, or states that involve high peripheral LH, such as polycystic ovarian syndrome lead to cognitive deficits (Barnard et al., 2007).

Luteinizing hormone receptor in nervous tissue

Importantly, LHR is found in the CNS (Oliver et al., 1977, Apaja et al., 2004, Hämäläinen et al., 1999). LHR mRNA transcripts are found not only in the testis, ovary, and placenta of Sprague-Dawley rats but also in the trigeminal ganglion, thalamus, olfactory bulb, and pituitary (Apaja et al., 2004). Localization of mRNA by *in situ* hybridization shows the receptor is present in the hippocampal formation, hypothalamus, cerebellum, choroid plexus, and ependymal cells of both the ventricles and cortex (Lei et al., 1993). Not only is the mRNA present, but LHR protein levels can be analyzed via immunoprecipitation to reveal both a mature (90 kDa) and an immature (73 kDa) species (Apaja et al., 2004). The immature form shifts in molecular mass after endoglycosidase H treatment, indicating a high level of mannose. The mature form is resistant to endoglycosidase H treatment and only shifted molecular mass upon N-glycosidase F treatment, indicating N-linked oligosaccharide glycosylation (Apaja et al., 2004).

LHR is expressed both in adults and in heads of embryonic day 14.5 and 19.5 rats (Apaja et al., 2004), suggesting a potential role for LHR in development. To this end, rat primary neuronal and glial cultures express mRNA transcripts and protein (Al-Hader et al., 1997a; Al-Hader et al., 1997b). Interestingly, in glial cells LHR expression increases with an increase in glial proliferation (Al-Hader et al., 1997b), and activation of LHR with hCG increases the number of neurite-bearing cells in primary neuronal cultures (Al-Hader et al., 1997a). This treatment also increases prostaglandin D2, while decreasing prostaglandin E2 (Al-Hader et al., 1997b). Prostaglandin E2 slows glial proliferation, while prostaglandin D2

promotes proliferation. Hence, LHR may modulate glial cell populations in the brain through this process.

Luteinizing hormone receptor signaling mechanisms

The physiology of LHR, shared by human chorionic gonadotropin and LH, and its signaling are well characterized in the reproductive literature (Menon et al., 2012). LHR activation stimulates ovulation and production of the corpus luteum. It is also essential in the male reproductive system, where it is responsible for the release of testosterone, ultimately controlling spermatogenesis. LHR is a class A, GPCR characterized as rhodopsin-like and is leucine rich (McFarland et al., 1989; Loosfelt et al., 1989; Menon et al., 2012). Furthermore, LHR is in a subgroup with the FSH receptor, the thyrotropin receptors and orphan receptors which have yet to be assigned ligands.

Canonically, stimulation of LHR with LH or hCG will cause its phosphorylation, and G α s activation of adenylyl cyclase stimulating the cAMP/PKA pathway (Marsh, 1976). More recently, other pathways were discovered to be activated by LHR stimulation (Salvador et al., 2002). In primary bovine luteal cells, activation of LHR increases S6K1 phosphorylation, which is known to drive cell growth and metabolism downstream of mTOR (Hou et al., 2010). It was previously observed that LHR stimulation increased levels of β -catenin and inhibited GSK3 β (Roy et al., 2009; Palm et al., 2014). The inhibition of GSK3 β halts tuberous sclerosis complex activation which normally inhibits mTOR signaling. Therefore, LH stimulation increases mTOR signaling, putting luteal cells at risk for aberrant cell proliferation and metabolism (Hou et al., 2010). Interestingly, it has also been shown in granulosa cells that LHR induced inhibition of GSK3 β is associated with a decrease in MAP2d phosphorylation, a protein with no known function but is closely related to protrusion stabilization protein, MAP2b (Flynn et al., 2008). MAP2d, one of the lesser studied microtubule associated proteins, is expressed throughout the adult rat CNS (Ferhat et al., 1994) and high levels are found in the astrocytes of the neurohypophyseal system (Matsunaga et al., 2002).

Aside from the canonical cAMP/PKA pathway, LHR also activates IP3 in granulosa cells (Davis et al., 1986; Dimino et al., 1987). Phospholipase C is upregulated upon LHR activation in a cAMP-independent manner, and this action is physiologically relevant for follicle maturation (Donadeu et al., 2011; Herrlich et al., 1996). In addition to G α s, LHR also time-dependently promotes G α q/11, G α 13, and G α i activation as well as calcium mobilization (Rajagopalan-Gupta et al., 1998; Gunderman et al., 1992). The link between LHR and G α q/11 activation has been studied with genetic manipulations to reveal a deficit in IP3 activation, ultimately leading to impaired follicular rupture. However, LHR signaling in this pathway does not affect the majority of reproductive actions of LHR (Breen et al., 2013).

LHR can evoke signaling that has been well linked to learning and memory. GSK3 β , which is inhibited by leuprolide acetate treatment (Palm et al., 2014), increases AD pathology and produces memory impairments (Hooper et al., 2008). The mTOR cascade is associated with synaptic plasticity and autism spectrum disorder (Hoeffler and Klann, 2010). Phospholipase C signaling, which ultimately leads to IP3 receptor activation, is known to diminish LTP and

facilitate LTD in neurons of the CA1 region of the hippocampus (Taufiq et al., 2005) and is involved in neurite outgrowth (Nishimura et al., 2008; Spencer et al., 2008) as well as spatial memory (McOmish et al., 2008).

Direct action of luteinizing hormone receptor activation in the CNS

Limited information is available on the direct action of LHR in the brain. LHR is expressed and functional in the CNS of *Xenopus laevis*, where it affects courtship songs as a part of reproductive behavior (Yang et al., 2006). In rodents LHR is involved in pheromone-driven social behavioral between male and female mice and changes in expression of hippocampal neurogenesis (Mak et al., 2007), a neuroplasticity mechanism associated with the regulation of cognitive function (Zhao et al., 2008). Lukacs et al. (1995) injected rats intracerebroventricularly with hCG at high doses and showed that there was a decrease in overall activity. In parallel, rats peripherally injected with hCG showed a similar response in the open field test. Taste neophobia, an innate fear of new food, in rodents was attenuated by peripheral and central hCG injections (Lukacs et al., 1995). However, in a learning and memory paradigm, the T-maze, no differences were observed with the exception of stereotypic behavior, which was decreased in hCG treated animals (Lukacs et al., 1995). Together these experiments may reflect that at the doses administered hCG affects overall activity in rodents rather than anxiety or learning and memory. These studies show that extragonadal expression of LHR not only occurs, but is functional and may play a role in the control of higher processes by the nervous system.

Conclusion

The HPG axis has well known involvements in cognitive deficits that arise as a result of hormonal dysregulation due to the aging process. Despite the important role of estrogens on cognition and neuroplasticity, the known critical period for its benefits following menopause or ovariectomy reduces the ability of these hormones to become an important therapeutic tool for age-related cognitive dysfunction and AD. Here, we have highlighted the important role of luteinizing hormone in cognitive decline and neurodegeneration. As such, we provide an additional potential player and thus a novel therapeutic target for cognitive dysfunction and AD. The latter is supported by a study demonstrating that administration of leuprolide acetate is beneficial in a subgroup of female AD patients (Bowen et al. 2014). We have also provided a potential mechanism through which leuprolide acetate may exert its effects. That is, through its ability to downregulate peripheral LH, brain LH is normalized and able to signal through LHR normally. The fact that LHR regulates signaling cascades that are critically important for cognition and is able to regulate structural changes in neuronal cultures further supports the role of LH in cognition.

Loss of HPG axis sensitivity, and resulting increased inability of estrogens to regulate LH synthesis may be involved in the loss of estrogen effectiveness beyond a critical window. Alternatively, LH may regulate cognition and neuroplasticity in an independent fashion, which we propose could be mediated through endogenous production of LH and LHR signaling. Both of these aspects need to be carefully studied. Nevertheless, the growing literature demonstrating a role of luteinizing hormone in learning and memory invites the

field to view HPG axis regulation of cognition more plural rather than simply restricting research to understanding the CNS function regulation by sex steroids.

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Figure 1. LH Expression and Localization

LHβ expression (NHP Program Harbor-UCLA Medical Center, Torrance, CA) in a coronal mouse brain slice (A). LHβ immunoreactivity co-localizes with the neuronal marker NeuN. LHβ (green), NeuN (red), Nuclei are stained with DAPI (blue) (B). Electron microscopy demonstrates that LHβ is contained in vesicles of sizes corresponding to secretory vesicles (C).

Figure 2. Mechanism of action for luteinizing hormone modulating learning and memory

In the aged female brain estrogen replacement after ovariectomy does not improve cognitive function or associated underlying mechanisms such as dendritic spine density changes.

Drugs that reduce peripheral levels of LH, which surge after ovariectomy or during menopause, rescue ovariectomy-dependent cognitive dysfunction and increase signaling events associated with synaptic plasticity. The LH receptor is localized to cognition-associated areas and it is described both at a level of function and plasticity. Brain-derived LH protein levels are present in cognition associated areas and are reduced by ovariectomy. The drugs that reduce peripheral LH levels also normalize brain-LH levels and these positively correlate with markers of neuroplasticity and cognitive improvement.