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Luteinizing hormone as a key player in the cognitive decline of Alzheimer's disease

Veronica L. Burnham, Janice E. Thornton *

Department of Neuroscience, Oberlin College, 119 Woodland St, Oberlin, OH 44074, USA

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ABSTRACT

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Alzheimer's disease is one of the most prevalent and costly neurological diseases in the world. Although decades of research have focused on understanding Alzheimer's disease pathology and progression, there is still a great lack of clinical treatments for those who suffer from it. One of the factors most commonly associated with the onset of Alzheimer's disease is a decrease in levels of gonadal hormones, such as estrogens and androgens. Despite the correlational and experimental data which support the role of these hormones in the etiology of Alzheimer's disease, clinical trials involving their reintroduction through hormone therapy have had varied results and these gonadal hormones often have accompanying health risks. More recently, investigation has turned toward other hormones in the hypothalamic–pituitary–gonadal axis that are disrupted by age-related decreases in gonadal hormones. Specifically, luteinizing hormone, which is increased with age in both men and women (in response to removal of negative feedback), has surfaced as a potentially powerful player in the risk and onset of Alzheimer's disease. Mounting evidence in basic research and epidemiological studies supports the role of elevated luteinizing hormone in exacerbating age-related cognitive decline in both males and females. This review summarizes the recent developments involving luteinizing hormone in increasing the cognitive deficits and molecular pathology characteristic of Alzheimer's disease.

Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent form of dementia in the world. It is estimated that over 5 million Americans currently suffer from AD (Alzheimer's Association, 2014). Alzheimer's disease disproportionately affects individuals over 65, and has been characterized as a neurodegenerative disorder. Current epidemiological data indicate that Alzheimer's disease affects 11% of individuals above 65 years of age and a third of people over the age of 85 (Hebert et al., 2013). Alzheimer's disease is characterized by large deficits in memory. In addition to progressive memory loss, patients with AD exhibit impaired language and visual–spatial skills (Bäckman et al., 2005). As the disease progresses, patients frequently develop problems such as immobility, malnutrition, and pneumonia which pose severe risks to the elderly (Alzheimer's Association, 2014). Alzheimer's disease is considered to be the sixth leading cause of death in the developed world, though estimates involving death from related health issues consider the risk even greater (Anastasio, 2011; Alzheimer's Association, 2014).

A number of areas in the brain are affected by Alzheimer's disease, including a variety of cortical structures and the hippocampus. The latter is one of the first and most severely affected areas (Braak and Braak, 1997) and the memory loss characteristic of AD is generally thought to be due to neuronal degeneration in the hippocampus (Carli et al., 1997). Although there are some morphological changes that occur in the hippocampus as a result of normal aging, numerous studies have demonstrated particular pathological alterations associated specifically with AD (Ohnishi et al., 2001; Salat et al., 2001; Zeifman et al., 2014). Degradation in the cortices and hippocampus is characterized by a gradual decline in volume of gray matter (Irish et al., 2013; Möller et al., 2013; Ohnishi et al., 2001; Salat et al., 2011). Cortical and hippocampal degradation is precipitated and accompanied by a number of cellular and molecular markers associated with Alzheimer's disease pathology. These include abnormally hyper-phosphorylated neurofibrillary tau tangles, amyloid beta (Aβ) plaque deposits, and neuronal cell death (Niikura et al., 2002; Obulesu and Lakshmi, 2014). There is also decreased neurogenesis and plasticity in hippocampal and cortical regions (Gandy and Dekosky, 2013; Iqbal and Grundke-Iqbal, 2011; Revett et al., 2013) concomitant with decreased levels of the neurotrophic factor BDNF, a key modulator of synaptic plasticity (Palm et al., 2014; Phillips et al., 1991).

The amyloid hypothesis of Alzheimer's disease is the long-standing leading hypothesis for pathology and cause of AD (Hardy and Selkoe, 2002; Hardy, 2009). This hypothesis synthesizes both histopathological and genetic information and primarily posits that deposition of the peptide amyloid-β (Aβ) in the brain sparks a sequence of events that

* Corresponding author.
E-mail address: jan.thornton@oberlin.edu (J.E. Thornton).

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eventually leads to the development of Alzheimer's disease (Hardy and Selkoe, 2002; Hardy, 2009; Karran et al., 2011). The formation of these Aβ deposits involves several steps. Briefly, the β-amyloid precursor protein (APP) is cut in two places by β- and γ-secreatase (Vassar, 2002; Sisodia and St George-Hyslop, 2002). The location of the second cut by γ-secreatase determines whether the short or long form of Aβ is produced. Spontaneous mutation or inherited mutations of the APP gene, or presenilin 1 (PS1) or presenilin 2 (PS2) genes, which are subunits of γ-secretase, result in an increased accumulation of amyloid-β peptides (Morley and Farr, 2014; Scheuner et al., 1996; Zhang et al., 2000). The accumulation of these peptides, particularly the long form, Aβ-42, results in the extracellular deposition of amyloid plaques, which consist of a dense core of β-amyloid protein surrounded by degenerating neurites and activated glia. These plaques are found in AD brains, thought to be toxic (Bentahir et al., 2006; Borchelt et al., 1997; Iwatsubo et al., 1996), and frequently used as biomarkers of the disease. Consistent with this, impaired Aβ clearance pathways (Hawkes et al., 2014), which have been associated with possession of the apolipoprotein E (*APOE*) ε4 allele (Hawkes et al., 2012), confer a significant risk factor for the development of sporadic, non-familial AD (Farrer et al., 1997).

The mechanistic relationships of the hypothesis have been changed over the years, and continue to be debated about today (Benilova et al., 2012; Gilbert, 2014; Hardy and Selkoe, 2002; Morley and Farr, 2014). More recently theories have focused on the possible involvement of synapse loss (Spires-Jones and Hyman, 2014), oxidative stress (Pohanka, 2014), aberrant re-entry of neurons into the cell cycle (Seward et al., 2013), and neuroinflammation (Ferreira et al., 2014). Common to all of the hypotheses, however, are a number of important molecular markers, including APP and Aβ, which are clearly associated with the development of Alzheimer's disease, even if their exact role in the etiology is unknown. Information gleaned from the roles of Aβ, and the various mutations associated with its accumulation and plaque deposition, has been widely utilized to diagnose AD pathology in both humans and animals, and to develop *in vitro* and *in vivo* models that display AD-like symptoms

Brains from AD patients examined post-mortem typically have higher expression of amyloid-β and its associated proteins, compared to age-matched controls (Holsinger et al., 2002; Goedert, 1987), particularly in the hippocampus (Higgins et al., 1988). These depositions are associated with cytotoxic effects, and are thought to lead to or occur simultaneously with synaptic and neuritic injury and degeneration. Ultimately this causes massive cell death and dysfunction, resulting in impaired cognitive functioning and symptoms of dementia (Hardy and Selkoe, 2002) and in the atrophy and degeneration of a number of neural structures, the hippocampus in particular (Apostolova et al., 2012; Sabuncu et al., 2011; Salat et al., 2011). Human AD patients often exhibit an increased rate of hippocampal volume loss, in comparison to age-matched controls (Thompson et al., 2004; Salat et al., 2011). Based on findings in studies of human Alzheimer's disease patients, mice with disruptions in various parts of the amyloid processing pathway have been developed to be used as models of Alzheimer's disease (Webster et al., 2014; Foley et al., 2014). Transgenic mouse models, which overexpress mutated forms of APP, have shown decreases in volume (Gonzalez-Lima et al., 2001), adult neurogenesis (Donovan et al., 2006), and an increase in neuronal loss (Schmitz et al., 2004) in the hippocampus.

Gonadal hormones and Alzheimer's disease

Alzheimer's disease is more prevalent in human females than males (Baum, 2005). Since women typically live longer than men (Ginter and Simko, 2013), it has been hypothesized that longevity may be a major contributor to the gender discrepancy. However, this discrepancy remains even after adjusting for age of individuals (Canadian Study of Health and Aging Working Group, 1994; Andersen et al., 1999).

It has thus been additionally hypothesized that ovarian hormones, specifically estrogens, might play a role. In women, menopause results in extremely decreased estrogen levels throughout the body and in the brain (Coffey al., 1998). This deprivation of estrogen is hypothesized to make neurons more vulnerable to degeneration (Dubal et al., 1999; Garcia-Segura et al., 2001; Pike, 1999) as estrogen has been widely observed to be neuroprotective in rodent and in vitro models (see Arevalo et al., 2014 for review). One study tracked women over a number of years and found that women who used estrogen supplements or underwent menopause later in life had significantly decreased risk of developing Alzheimer's disease (Henderson, 1994). Other research suggests an increase in risk for AD in women who undergo ovariectomy before menopause (Rocca et al., 2007). As such, the usage of estrogen replacement therapies (ERT) has been proposed as a measure to prevent or combat AD-related dementia (Kawas et al., 1997; Mulnard et al., 2000). Although there are a number of studies which report positive results (Craig and Murphy, 2010; Smith et al., 2011; Wharton et al., 2011), there are others which have not found estrogen replacement as an effective treatment for AD prevention (Maki and Henderson, 2012; O'Brien et al., 2014; Zandi, 2002). Moreover, multiple meta-analyses of clinical research studies have shown ERT to be generally ineffective, on the whole (O'Brien et al., 2014; Spooner et al., 2014), However, much of this discrepancy may be because these experiments varied in the timing, length of administration, and type of estrogen used (Henderson, 2014; Maki, 2013; Panay et al., 2013; Wharton et al., 2011; Whitmer et al., 2011). Indeed, trials which used estradiol, the physiological form of estrogen, as opposed to conjugated equine estrogen (CEE), found that estrogen helped stabilize or improve cognition in women with AD (Asthana et al., 2001; Wharton et al., 2011). Thus further inquiry into the specifics of effective estrogen treatment is needed. Unfortunately, estrogen replacement therapy has also been associated with an increase in a number of health risks, particularly the risk of breast cancer (Banks and Canfell, 2010; Green et al., 2012; Narod, 2011). Removal of estrogen therapy results in a significantly decreased risk of breast cancer, further implicating estrogen in enhancing risk. This hypothesis is supported by the presence of estrogen receptors in many breast-cancer tumors (Gruvberger et al., 2001; Lakhani et al., 2005). Additional studies have also found a correlation between estrogen replacement therapy and an increased risk of endometrial cancer (Crosbie et al., 2010). Thus, even if estrogen proves effective against the cognitive loss seen with AD, there is still a great need for the elucidation of other potential gender-specific factors, which might contribute to the greater incidence of AD in women. Hopefully, manipulation of these factors could result in the development of effective treatments with fewer accompanying health risks.

Similar to women, gonadal hormones (i.e. androgens such as testosterone) in men are also decreased throughout the brain and body with aging (Tajar et al., 2012; Nieschlag et al., 2012), a process sometimes referred to as andropause (Vermeulen, 2000). In contrast to women for whom menopause is relatively rapid between the ages of 40–50, in men the androgens begin to decrease earlier but exhibit a much more gradual decline over decades (Ferrini and Barrett-Connor, 1998; Gray et al., 1991). These androgens (which may be aromatized to estrogens) may help to slow the onset of AD (Feldman et al., 2002; Gouras et al., 2000). Consistent with this, men who suffer from Alzheimer's disease have lower physiological levels of the androgen testosterone compared to age-matched individuals without the disease (Hogervorst et al., 2001, 2004; Carcaillon et al., 2013). A number of clinical trials administering testosterone to elderly men resulted in improved cognitive performance (Cherrier et al., 2001, 2005, 2014; Janowsky et al., 1994), though others failed to show significant effects (Haren et al., 2005; Vaughan et al., 2007). Larger trials at earlier stages should be carried out as these differences may be due to variations in timing and/or dose of treatment. For example, total testosterone levels were much lower in the Haren et al. (2005) and Vaughan et al. (2007) studies than in those by Cherrier et al. (i.e. approximately 20 nmol/L vs 40 nmol/L). There is also evidence that testosterone replacement therapy poses alternate health risks, including increase in risk of cardiovascular events (Xu et al., 2013), development of erythrocytosis (Grech et al., 2014) and