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Sex and the development of Alzheimer's disease

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Abstract

Men and women exhibit differences in the development and progression of Alzheimer's disease (AD). The factors underlying the sex differences in AD are not well understood. This review emphasizes the contributions of sex steroid hormones to the relationship between sex and AD. In women, events that decrease lifetime exposure to estrogens are generally associated with increased AD risk, whereas estrogen-based hormone therapy administered near the time of menopause may reduce AD risk. In men, estrogens do not exhibit age-related reduction and are not significantly associated with AD risk. Rather, normal age-related depletions of testosterone in plasma and brain predict enhanced vulnerability to AD. Both estrogens and androgens exert numerous protective actions in the adult brain that increase neural functioning and resilience as well as specifically attenuate multiple aspects of AD-related neuropathology. Aging diminishes the activational effects of sex hormones in sex-specific manners, which is hypothesized to contribute to the relationship between aging and AD. Sex steroid hormones may also drive sex differences in AD through their organizational effects during developmental sexual differentiation of the brain. Specifically, sex hormone actions during early development may confer inherent vulnerability of the female brain to development of AD in advanced age. The combined effects of organizational and activational effects of sex steroids yield distinct sex differences in AD pathogenesis, a significant variable that must be more rigorously considered in future research.

Keywords

Aging; Alzheimer's; estrogen; menopause; sex differences; testosterone

Alzheimer's disease (AD) is an age-related neurodegenerative disorder and the primary cause of dementia. Neuropathologically, AD is characterized primarily by the brain region-specific accumulation of both β-amyloid (Aβ) protein, which aggregates into soluble, toxic oligomers as well as extracellular deposits termed senile plaques, and hyperphosphorylated tau protein, which forms lesions called neurofibrillary tangles and neuropil threads (reviewed in Mucke and Selkoe 2012; Zempel and Mandelkow 2014). Although Aβ and tau are implicated as the primary mediators of AD-related synaptic loss and eventual neuronal death, AD neuropathology involves numerous additional components that contribute to disease progression including chronic gliosis, disrupted blood-brain-barrier, cerebrovascular amyloidosis, and white matter degeneration (reviewed in Vinters 2015). The single most

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significant risk factor for AD is advancing age (Launer et al. 1999), though the age-related changes that underlie this risk are poorly understood. Further, there are numerous genetic, environmental, and modifiable lifestyle factors that significantly affect AD risk (reviewed in Tanzi 2012; Xu et al. 2015). Development of effective prevention and treatment strategies for AD will require understanding how its pathogenesis is affected by the individual and interactive effects of these risk factors.

An extensive yet still woefully incomplete literature indicates that another important regulator of AD risk is sex. Developmental and physiological differences between men and women significantly contribute to the development of several neurological conditions and diseases, including multiple sclerosis, schizophrenia, depression, and autism (reviewed in Cahill 2006). Findings suggest that the vulnerability, clinical manifestation, and neuropathological progression of AD significantly differ between men and women. Initial appreciation of sex differences in AD arose from observations of a female bias in AD prevalence, with recent findings indicating that women comprise nearly two-thirds of AD patients (Hebert et al. 2013). Although most evidence suggests that the incidence of AD is similar among men and women (reviewed in Mielke et al. 2014), women appear to have a higher incidence of AD in old age (Miech et al. 2002). There are also sex differences in the time course of disease progression, which appears to be accelerated in men (Lapane et al. 2001; Stern et al. 1997). In general, women show more robust progression of mild cognitive impairment (Lin et al. 2015) and higher severity of clinical dementia (Barnes et al. 2005; Corder et al. 2004; Irvine et al. 2012) according to most studies (reviewed in Mielke et al. 2014).

Sex also affects the strength of established AD risk factors, though these differences have generally been weakly investigated. For example, the most significant genetic risk factor for late-onset AD is the ε4 allele of the apolipoprotein E gene (*APOE4*) (Saunders et al. 1993; Strittmatter et al. 1993). Notably, *APOE4* is a significantly greater risk AD factor for women than men (Farrer et al. 1997; Payami et al. 1994). Similar female biases in *APOE4* effects are observed in the risk of conversion from cognitively normal to mild cognitive impairment, and from mild cognitive impairment to AD (Altmann et al. 2014) as well as in cognitive dysfunction (Beydoun et al. 2012), brain atrophy (Holland et al. 2013; Liu et al. 2010), and decreased brain connectivity (Damoiseaux et al. 2012). Studies in mice have shown that *APOE4* worsens cognition (Raber et al. 1998) and Aβ pathology (Cacciottolo et al. 2016) more strongly in females than males. Environmental and modifiable lifestyle risk factors of AD also are likely affected by sex. For example, sex and sex steroid hormones contribute to the relationship between obesity in midlife and the development of AD in late life (Moser and Pike 2015). Understanding how sex affects the vulnerability to and progression of AD is essential to developing effective interventions to prevent and treat the disease. In this brief review, sex differences in AD are discussed with an emphasis on the roles of sex steroid hormones, the loss of their protective effects during aging, and their organizing effects during early development.

Females, estrogens, and Alzheimer's

Sex differences in age-related disorders are often significantly linked with the primary sex steroid hormone in women, the estrogen 17β-estradiol. As discussed below, estrogens have a wide range of beneficial actions in brain and other tissues, the loss of which may reasonably be expected to confer increased risk of AD. Consistent with this possibility, some but not all studies suggest that reductions of estrogen in adulthood are associated with increased risk of AD in women. On one hand, there is evidence that longer lifetime estrogen exposure (as indicated by larger number of reproductive years) *increases* dementia risk (Geerlings et al. 2001). Conversely, other studies of lifetime estrogen exposure suggest that dementia risk is associated with reduced estrogen. For example, pregnancies result in an overall decrease in women's lifetime estrogen exposure (Bernstein et al. 1985). In comparison to nulliparous women, childbearing women exhibit increased risk for development of both cognitive impairment and dementia (Beeri et al. 2009; Colucci et al. 2006; McLay et al. 2003; Ptok et al. 2002). The relationship between low estrogen and AD risk is also supported by findings on the interactions between dementia risk and surgical menopause by oophorectomy and/or hysterectomy. Specifically, dementia risk is significantly increased by surgically induced menopause (Bove et al. 2014; Phung et al. 2010; Rocca et al. 2007; Rocca et al. 2011). Importantly, this relationship holds true only when surgical menopause is performed prior to natural menopause, thereby prematurely disrupting the normal, cyclic production of sex steroid hormones. Surgical menopause conducted after natural menopause, the timing of which would not accelerate age-related changes in sex steroid hormones, does not increase dementia risk (Imtiaz et al. 2014; Rocca et al. 2011). Reinforcing the relationship between low estrogens and AD risk are a pair of studies that compared brain levels of estrogen in aged women with and without neuropathologically diagnosed AD. In both studies, women with AD exhibited significantly reduced brain levels of the estrogens 17β-estradiol and/or estrone, an effect that appeared to be strongest in women with mean ages >80 years (Rosario et al. 2011; Yue et al. 2005). Notably, there is a clear sex difference in this relationship: no significant differences in brain levels of estrogens were observed between men with and without AD (Rosario et al. 2011). Collectively, these findings indicate a correlative relationship between low estrogen and AD, perhaps suggesting that reductions in estrogens can increase AD vulnerability specifically in women.

Although estrogen depletion in premenopausal women is a risk factor for subsequent development of AD, the efficacy of estrogen-based hormone therapy (HT) in attenuating AD risk in postmenopausal women remains uncertain. Several retrospective and prospective studies seemed to indicate a protective role of estrogen: HT users exhibited significantly reduced risk of dementia compared to non-users (Kawas et al. 1997; Paganini-Hill and Henderson 1994; Paganini-Hill and Henderson 1996; Tang et al. 1996), with increased benefits associated with prolonged use (Zandi et al. 2002). However the Women's Health Initiative, a large double-blinded, placebo-controlled clinical trial found that HT was associated with *increased* risk of rather than protection from cognitive decline and dementia (Shumaker et al. 2004; Shumaker et al. 2003). Although the efficacy of HT for improving neural outcomes remains controversial, the idea of a "window of opportunity" for HT use has been suggested (Craig and Murphy 2010; Maki 2013). In brief, proponents of this

position suggest that HT must be initiated near the onset of menopause rather than several years following menopause, a timing problem associated with most subjects in the Women's Health Initiative. According to this argument, HT induces neural protection during perimenopause but these outcomes wane with advancing age and may even become deleterious in old age. A few observational studies lend support for the window of opportunity hypothesis. That is, women that began HT in midlife or within the first few years after menopause exhibited significantly reduced AD risk, whereas those that began HT in late life showed either no protection or increased risk (Henderson et al. 2005; Shao et al. 2012; Whitmer et al. 2011). Two recent clinical trials, Early versus Late Intervention Trial with Estradiol (ELITE) (Hodis et al. 2015) and Kronos Early Estrogen Prevention Study (KEEPS) (Wharton et al. 2013), have sought to evaluate the window of opportunity hypothesis by delivering HT to middle-age women near the time of menopause and assessing its effects on cognition. Data from KEEPS find no significant cognitive benefit of HT (Gleason et al. 2015); findings from ELITE have yet to be published. A clinical trial to definitively evaluate the *late-life* outcomes of HT administered during *midlife* is impractical and unlikely, thus a knowledge gap remains concerning the efficacy of HT in reducing AD risk in women. The challenge of future research is to provide insight into the potential neural efficacy of optimized HT use through appropriately designed human and animal studies.

The relationship between estrogens and AD in females has been generally well informed by experimental studies in laboratory animals. Initial work demonstrated that depletion of endogenous sex steroids in wild-type female rodents by ovariectomy (OVX) significantly increased brain levels of soluble Aβ (Petanceska et al. 2000), a finding that has since been repeated (Jayaraman et al. 2012). Similarly, OVX in various transgenic mouse models of AD results in significant acceleration of Aβ pathology and worsening of behavioral performance in comparison to gondally intact female transgenic mice (Carroll et al. 2007; Levin-Allerhand et al. 2002; Xu et al. 2002; Zhao et al. 2011; Zheng et al. 2002). Thus, as predicted by the human literature, low estrogen can create a neural environment in female rodents that promotes AD-like pathogenesis. Also in parallel to findings in humans, estrogen treatment is associated with protection against pathology. OVX non-transgenic (Jayaraman et al. 2012; Petanceska et al. 2000) and AD transgenic (Carroll et al. 2007; Levin-Allerhand et al. 2002; Xu et al. 2002; Zhao et al. 2011; Zheng et al. 2002) female rodents treated with 17β-estradiol exhibit significant lower Aβ accumulation than OVX females treated with placebo. Interestingly, in some AD transgenic strains, neither OVX nor 17β-estradiol significantly alters brain levels of Aβ (Golub et al. 2008; Green et al. 2005; Heikkinen et al. 2004). The likely reason for the discrepant findings is strain differences in neurosteroidogenesis, the brain's inherent ability to produce 17β-estradiol and other sex steroid hormones (Charlier et al. 2015; Porcu et al. 2016). This conclusion is suggested by observations in APP23 mice, in which Aβ levels were not affected by OVX but were significantly increased by reduction of brain 17β-estradiol levels via genetic ablation of aromatase, the enzyme that generates 17β-estradiol from testosterone (Yue et al. 2005). Related findings in 3xTg-AD mice show that pharmacological inhibition of 17β-estradiol synthesis by the aromatase inhibitor anastrozole was more effective than OVX in elevating levels of Aβ in young adult females (Overk et al. 2012). Recent work has demonstrated that the protective efficacy of estrogen in non-transgenic and AD transgenic rodents is regulated

by progesterone (Carroll et al. 2010b; Jayaraman et al. 2012) and may be diminished during aging (Palm et al. 2014), findings that are consistent with the window of opportunity hypothesis. Moving forward, there is a need for animal work to identify how and why aging impacts neural actions of 17β-estradiol and other sex steroids.

Males, androgens, and Alzheimer's

In contrast to women, risk of AD in men is significantly increased by normal, age-related loss of testosterone. Most (Gillett et al. 2003; Hogervorst et al. 2003; Hogervorst et al. 2001; Paoletti et al. 2004; Watanabe et al. 2004) but not all (Pennanen et al. 2004) studies examining the relationship between AD and serum levels of testosterone report lower levels of bioavailable and/or total testosterone in men with AD. These observations suggest that, in parallel to the association between low estrogen in women and increased risk of AD, reduced testosterone levels may promote the development of AD in men. Several lines of evidence are consistent with this possibility. First, longitudinal data indicate that the relationship between low serum testosterone and AD risk is apparent at least ten years prior to the clinical diagnosis of dementia, suggesting testosterone depletion is an early component of AD risk in men (Moffat et al. 2004). Second, in comparison to neuropathologically normal men, those with both early and late stages of AD neuropathology exhibit significantly reduced brain levels of testosterone, suggesting that testosterone loss in brain occurs early in the disease process (Rosario et al. 2011; Rosario et al. 2004). This relationship appears to be sex-specific since brain levels of testosterone are not significantly different in women with AD (Rosario et al. 2011). Interestingly, in men with early AD-related pathology, brain levels of testosterone are inversely correlated with soluble Aβ (Rosario et al. 2011). Finally, a recent comparison of prostate cancer patients found that those receiving androgen deprivation therapy were significantly more likely to develop AD (Nead et al. 2016). The use of androgen deprivation therapy was previously demonstrated to increase plasma levels of Aβ (Gandy et al. 2001). Although the relationship between testosterone and AD risk remains to be completely elucidated, available evidence is most consistent with the idea that decreased testosterone in men but not women increases the development of AD.

Limited work in male rodents indicates that testosterone negatively regulates AD-related pathology. In male rats, the normal age-related decrease in brain levels of androgens significantly correlates with age-related increases in soluble Aβ (Rosario et al. 2009). Depletion of endogenous testosterone by orchiectomy (ORX) significantly increases soluble Aβ in brain (Ramsden et al. 2003). This ORX-induced increase in Aβ is reversed by the non-aromatizable androgen dihydrotestosterone but not by 17β-estradiol (Ramsden et al. 2003), suggesting that androgens are more important than estrogens for the regulation of Aβ in males. Testosterone is similarly implicated as a negative regulator of Aβ in transgenic mouse models of AD. In male 3xTg-AD mice, ORX is associated with increased Aβ accumulation in several brain regions (Rosario et al. 2010; Rosario et al. 2006), though in one study this effect failed to meet statistical significance (Overk et al. 2012). Treatment with the androgens testosterone or dihydrotestosterone significantly decreased Aβ levels in ORX 3xTg-AD mice (George et al. 2013; Rosario et al. 2010; Rosario et al. 2006). Also consistent with a protective role of testosterone is the finding that elevation of endogenous

testosterone resulting from knockdown of the testosterone metabolizing enzyme aromatase results in decreased Aβ accumulation in male APP23 mice (McAllister et al. 2010). In summary, convergent findings from human and animal studies generally agree that testosterone depletion promotes development of AD. Translation of this relationship into an androgen-based intervention to prevent AD is supported by animal research but has yet to be rigorously investigated at the clinical level. A key challenge moving forward will be to determine whether testosterone-based therapy can reduce AD risk in men while avoiding the pitfalls that have plagued HT use in women.

Alzheimer's disease and the activational effects of sex steroids

The classic view of the relationship between sex steroid hormones and AD is that the normal age-related depletion of estrogens in women and androgens in men results in a loss of neuroprotective hormone effects, which in turn might contribute to an increased risk of disease. The actions of sex steroid hormones can be broadly classified into organizational effects, which refer to the long-lasting or permanent roles of hormones in sexual differentiation and development, and activational effects, which are the more transient actions of sex hormones in the adult (Arnold and Breedlove 1985). Thus, it is the loss of activational effects of estrogens and androgens that occur as a consequence of normal aging that are thought to contribute to a spectrum of senescent changes that underlie the essential role of aging in AD pathogenesis.

Women and men exhibit qualitative differences in the age-related loss of activational effects of sex steroid hormones. This sex difference is a critical component in the relationships between sex steroids and AD. The primary factor underlying diminished activational effects of estrogens in women is the depletion of estrogen after menopause. Menopause occurs in midlife with a mean age of onset of 51 years. The losses of ovarian and menstrual cycles that characterize the menopause transition occur over a several year period and involve a variety of endocrine changes (Finch 2014; Harlow et al. 2012). The primary driving force of female reproductive senescence appears to be the exhaustion of primary follicles and oocytes, which begins in early life. Decreases in the overall number and recruitment of follicles ultimately lead to cessation of the ovarian cycle and significant reduction in estrogen production (reviewed in Finch 2014). Notably, the cyclic fluctuations in estrogen and progesterone levels that accompany normal cycles are also lost with aging, changes that may have significant consequences in tissue responses to these hormones.

In contrast to the menopause transition, male reproductive aging occurs gradually over several decades with comparatively modest age changes in sex steroid levels. Male reproductive aging, often colloquially referred to as andropause, typically begins during the fourth decade of life. It is characterized by a gradual decrease in testosterone, with total testosterone decreasing at a rate of <1% per year and bioavailable testosterone at 2–3% per year (Feldman et al. 2002; Gray et al. 1991; Muller et al. 2003). Underlying this age-related testosterone decrease are both atrophy of the testosterone-producing Leydig cells in the testes and progressive dysfunction of the hypothalamic-pituitary-gonadal axis that regulates testosterone production (reviewed in Kaufman and Vermeulen 2005). Testosterone depletion leads to a net loss in activational effects of androgens with age that increases risks of

impaired function and disease in tissues throughout the body (Kaufman and Vermeulen 2005; Morley 2001) as well as increased risk of mortality (Muraleedharan and Jones 2014). Although 17β-estradiol is synthesized from testosterone, aging men do not exhibit significant decreases in plasma (Muller et al. 2003) or brain (Rosario et al. 2011; Rosario et al. 2004) levels of 17β-estradiol. Thus, decreases in sex steroid hormones and their activational effects during reproductive aging significantly vary between women and men, with distinct sex differences in the time course, the magnitude, and the identity of the sex hormones.

Brain levels of sex steroid hormones reflect not only gonadal hormone production, but also the brain's synthesis of estrogens, androgens, and other neuroactive hormones through the process of neurosteroidogenesis (reviewed in Melcangi et al. 2008). Thus, besides menopause and andropause, age-related changes in neurosteroidogenesis are expected to significantly regulate brain levels of sex steroids. In addition to decreases in brain levels of estrone and 17β-estradiol in women and testosterone in men (Rosario et al. 2011), the AD brain exhibits decreases in a number of neurosteroids (Naylor et al. 2010; Schumacher et al. 2003; Weill-Engerer et al. 2002). It remains to be determined whether the relationship between neurosteroids and AD represent changes in pathways that contribute to AD pathogenesis or merely correlate with the disease. Expression of enzymes involved in neurosteroid synthesis also show changes in AD, including increased aromatase (Luchetti et al. 2011). Sex differences in neurosteroids in both normal and pathological aging are not well described. In male rodents, recent work indicates that normal aging is associated with decreased expression of several enzymes that contribute to testosterone synthesis (Munetomo et al. 2015), which suggests possible age-related changes in steroid synthesis. Comparison of young adult and aged non-transgenic and 3xTg-AD male mice reveals changes in levels of numerous neurosteroids by aging and or AD-related transgenes (Caruso et al. 2013). Regulation of neurosteroids may have therapeutic potential for AD as indicated by findings with the neurosteroid allopregnanolone (Irwin et al. 2011) and ligands that activate translocator protein 18kD (Barron et al. 2013), a key positive regulator of neurosteroidogenesis (reviewed in Rupprecht et al. 2010). Important knowledge gaps remain in our understanding of how aging and sex affect neurosteroidogenesis.

Estrogens, progestogens, and androgens exert a wide range of activational effects in brain that increase neural health and resistance to AD and other neurodegenerative diseases. As discussed above, estrogens and androgens directly regulate Aβ accumulation, perhaps the critical factor in AD pathogenesis (Hardy 2006; Hardy 2009). By activating cell signaling pathways that are dependent upon estrogen and androgen receptors, sex steroid hormones inhibit the production and/or enhance the degradation and clearance of Aβ (Pike et al. 2009). Similarly, sex steroids inhibit two other key components of AD pathology, tau phosphorylation and glial activation (Alvarez de la Rosa et al. 2005; Morgan and Finch 2015; Vegeto et al. 2008; Zhang et al. 2008). There are several reviews that discuss the mechanisms underlying the protective actions of sex steroids (Brinton et al. 2008; Engler-Chiurazzi et al. 2016; Pike et al. 2009; Singh and Su 2013).

Sex steroid hormones also act more generally to increase brain function and resilience. For example, estrogens and progestogens independently and interactively act on neurons and

glia in the absence and presence of pathology to beneficially regulate learning and memory, neuroplasticity, and neuron survival, as already extensively reviewed (Brinton 2009; Brinton et al. 2008; De Nicola et al. 2013; Duarte-Guterman et al. 2015; Simpkins et al. 2012). Androgens also promote aspects of cognition, neuroprotection, and synaptic plasticity (Cherrier 2009; Galea 2008; MacLusky et al. 2006; Pike et al. 2008). There are a few points worth noting in the context of this discussion. First, neural effects of sex hormones often exhibit sex-specific actions. For example, hippocampal spine density in non-transgenic rodents is increased by 17β-estradiol in females (Woolley and McEwen 1992), but androgens and not 17β-estradiol increase spines in males (Leranth et al. 2003). Second, the decrease in beneficial activational effects of sex steroids involves not only decreased hormone levels, but also diminished responsiveness to at least some sex hormone actions, a concept most clearly described for estrogen (Adams et al. 2001; Bake and Sohrabji 2004; Jezierski and Sohrabji 2001; Stone et al. 2000). In rodent studies, altered neural estrogen responsiveness occurs during early reproductive senescence that is consistent in many ways with human perimenopause (Yin et al. 2015). Finally, for women, the loss of cyclic fluctuations in hormones after menopause may adversely affect interactions between estrogen and progesterone in regulation of neural outcomes. In female rodents, optimal neural effects of 17β-estradiol and progesterone are typically observed with treatment regimens that include discontinuous exposure to one or both hormones (Azcoitia et al. 1999; Barron et al. 2015; Carroll et al. 2010b; Gibbs 1996; Gibbs 2000; Jayaraman et al. 2012). In contrast, protective actions of 17β-estradiol can be attenuated by continuous co-treatment with progesterone (Carroll et al. 2007; Carroll et al. 2008; Carroll et al. 2010b; Wong et al. 2009). The numerous sex differences in age-related declines of sex hormone activational effects almost certainly contribute to sex-specific vulnerability to the development of cognitive decline and AD.

Alzheimer’s disease and the organizational effects of sex steroids

Although activational effects of sex steroid hormones are generally thought to be the primary mediator of sex differences in the development and progression of AD, emerging evidence suggests that organizational effects also play an important role. The presence of the Y chromosome, specifically the *Sry* gene, drives the male pattern of sexual differentiation during early development (reviewed in Morris et al. 2004). With the formation of testes, males produce testosterone that, both directly (via activation of androgen receptors) and after aromatase-mediated conversion to 17β-estradiol, mediates sexual differentiation of the brain during critical prenatal and early postnatal periods (Morris et al. 2004). Some aspects of sexual differentiation of the brain continue up through puberty (reviewed in Juraska et al. 2013). Sexual differentiation of the brain during development yields a variety of permanent structural and functional differences between the adult male and female brain (Juraska et al. 2013; Morris et al. 2004). These differences appear to include altered vulnerability to a range of neurological disorders (Cahill 2006). Thus, there is no *a priori* reason to assume that sex differences in AD might not result from a combination of developmental organizational effects and age-related loss of activational effects.

Comparison of sex differences in transgenic mouse models of AD supports the position that organizational effects of sex steroid hormones confer females with increased vulnerability to

AD. Among the several studies that have evaluated sex differences in the levels of neuropathology in various AD transgenic models, most (Cacciottolo et al. 2016; Callahan et al. 2001; Carroll et al. 2010a; Hirata-Fukae et al. 2008; Wang et al. 2003) but not all (Clinton et al. 2007; Devi and Ohno 2015) reported significantly increased pathology in females (reviewed in Dubal et al. 2012). Importantly, neuropathology in AD transgenics typically begins in young adulthood, prior to the onset of reproductive senescence and age-related decreases in sex hormone levels and their activational effects. Thus, organizational rather than activational effects of sex hormones likely contribute to the observed sex differences. What these studies do not address is the possibility that XY chromosomal differences rather than hormone-driven sexual differentiation also contribute to sex differences in AD, a possibility that has yet to be thoroughly investigated (Dubal et al. 2012). One strategy to evaluate the role of organizational effects is by experimental manipulation of sexual differentiation. Maleness and femaleness exist along a spectrum rather than a strict binary separation (reviewed in Ainsworth 2015). The relative position along this spectrum can be altered by acutely controlling hormone exposure during critical developmental periods. Using this approach in 3xTg-AD mice, which exhibit a female bias in pathology, neonatal females were masculinized by testosterone treatment and neonatal males were feminized by pharmacological inhibition of androgen receptors (Carroll et al. 2010a). Upon reaching adulthood, the masculinized females exhibited a brain-region specific reduction in Aβ accumulation whereas the feminized males showed increased Aβ (Carroll et al. 2010a). These data suggest that developmental changes that create a relatively more feminine adult brain yield a neural environment that is more permissive to AD pathogenesis. The extent to which these findings extrapolate to humans is unknown. Collectively, these findings suggest the possibility that the female brain may be inherently more vulnerable to development of AD.

Conclusion

AD is one of several neurological diseases characterized by significant sex differences. The development of AD and its neuropathological and clinical progressions differ between men and women. Further, the penetrance of both genetic and environmental risk factors for AD can vary according to sex. These findings provide valuable opportunities to both understand the disease and develop effective and perhaps sex-specific interventions. How sex affects AD remains incompletely defined. There is compelling yet incomplete evidence that the sex-specific, age-related depletion of estrogens in women and androgens in men are significant factors in the association between age and AD. Sex steroid hormones exert a wide range of neuroprotective actions in adults, termed sex hormone activational effects, which diminish with age-related losses in hormones and hormone responsiveness. In addition, emerging evidence suggests that developmental effects of sex steroid hormones that lead to sexual differentiation of the brain, termed organizational effects, yield a female brain that may be inherently more vulnerable to AD pathogenesis. Given the importance of sex in AD, it is imperative that future research in AD not merely control for sex differences, but rather evaluate sex as an essential variable of the disease.

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References

Adams MM, Shah RA, Janssen WG, Morrison JH. Different modes of hippocampal plasticity in response to estrogen in young and aged female rats. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98(14):8071–8076. [PubMed: 11427724]

Ainsworth C. Sex redefined. Nature. 2015; 518(7539):288–291. [PubMed: 25693544]

Altmann A, Tian L, Henderson VW, Greicius MD, Alzheimer's Disease Neuroimaging Initiative I. Sex modifies the APOE-related risk of developing Alzheimer disease. Annals of neurology. 2014; 75(4): 563–573. [PubMed: 24623176]

Alvarez de la Rosa M, Silva I, Nilsen J, Perez MM, Garcia-Segura LM, Avila J, Naftolin F. Estradiol prevents neural tau hyperphosphorylation characteristic of Alzheimer's disease. Ann N Y Acad Sci. 2005; 1052:210–224. [PubMed: 16024764]

Arnold AP, Breedlove SM. Organizational and activational effects of sex steroids on brain and behavior: a reanalysis. Hormones and behavior. 1985; 19(4):469–498. [PubMed: 3910535]

Azcoitia I, Fernandez Galaz C, Sierra A, Garcia Segura LM. Gonadal hormones affect neuronal vulnerability to excitotoxin-induced degeneration. Journal of Neurocytology. 1999; 28(9):699–710. [PubMed: 10859573]

Bake S, Sohrabji F. 17beta-estradiol differentially regulates blood-brain barrier permeability in young and aging female rats. Endocrinology. 2004; 145(12):5471–5475. [PubMed: 15471968]

Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. Arch Gen Psychiatry. 2005; 62(6):685–691. [PubMed: 15939846]

Barron AM, Brown MA, Morgan TE, Pike CJ. Impact of continuous versus discontinuous progesterone on estradiol regulation of neuron viability and sprouting after entorhinal cortex lesion in female rats. Endocrinology. 2015; 156(3):1091–1099. [PubMed: 25514084]

Barron AM, Garcia-Segura LM, Caruso D, Jayaraman A, Lee J-W, Melcangi RC, Pike CJ. Ligand for translocator protein reverses pathology in a mouse model of Alzheimer's disease. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2013; 33(20):8891–8897. [PubMed: 23678130]

Beeri MS, Rapp M, Schmeidler J, Reichenberg A, Purohit DP, Perl DP, Grossman HT, Prohovnik I, Haroutunian V, Silverman JM. Number of children is associated with neuropathology of Alzheimer's disease in women. Neurobiology of aging. 2009; 30(8):1184–1191. [PubMed: 18079025]

Bernstein L, Pike MC, Ross RK, Judd HL, Brown JB, Henderson BE. Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. Journal of the National Cancer Institute. 1985; 74(4):741–745. [PubMed: 3857369]

Beydoun MA, Boueiz A, Abougergi MS, Kitner-Triolo MH, Beydoun HA, Resnick SM, O'Brien R, Zonderman AB. Sex differences in the association of the apolipoprotein E epsilon 4 allele with incidence of dementia, cognitive impairment, and decline. Neurobiology of aging. 2012; 33(4): 720–731 e724. [PubMed: 20619505]

Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, De Jager PL. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology. 2014; 82(3):222–229. [PubMed: 24336141]

Brinton RD. Estrogen-induced plasticity from cells to circuits: predictions for cognitive function. Trends Pharmacol Sci. 2009; 30(4):212–222. [PubMed: 19299024]

Brinton RD, Thompson RF, Foy MR, Baudry M, Wang J, Finch CE, Morgan TE, Pike CJ, Mack WJ, Stanczyk FZ, Nilsen J. Progesterone receptors: form and function in brain. Frontiers in neuroendocrinology. 2008; 29(2):313–339. [PubMed: 18374402]

Cacciottolo M, Christensen A, Moser A, Liu J, Pike CJ, Smith C, LaDu MJ, Sullivan PM, Morgan TE, Dolzhenko E, Charidimou A, Wahlund LO, Wiberg MK, Shams S, Chiang GC, Finch CE. The

APOE4 allele shows opposite sex bias in microbleeds and Alzheimer's disease of humans and mice. Neurobiology of aging. 2016; 37:47–57. [PubMed: 26686669]

Cahill L. Why sex matters for neuroscience. Nature reviews Neuroscience. 2006; 7(6):477–484. [PubMed: 16688123]

Callahan MJ, Lipinski WJ, Bian F, Durham RA, Pack A, Walker LC. Augmented senile plaque load in aged female beta-amyloid precursor protein-transgenic mice. Am J Pathol. 2001; 158(3):1173–1177. [PubMed: 11238065]

Carroll JC, Rosario ER, Chang L, Stanczyk FZ, Oddo S, LaFerla FM, Pike CJ. Progesterone and estrogen regulate Alzheimer-like neuropathology in female 3xTg-AD mice. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2007; 27(48):13357–13365. [PubMed: 18045930]

Carroll JC, Rosario ER, Kreimer S, Villamagna A, Gentzschein E, Stanczyk FZ, Pike CJ. Sex differences in beta-amyloid accumulation in 3xTg-AD mice: Role of neonatal sex steroid hormone exposure. Brain research. 2010a; 1366:233–245. [PubMed: 20934413]

Carroll JC, Rosario ER, Pike CJ. Progesterone blocks estrogen neuroprotection from kainate in middle-aged female rats. Neuroscience letters. 2008; 445(3):229–232. [PubMed: 18790007]

Carroll JC, Rosario ER, Villamagna A, Pike CJ. Continuous and cyclic progesterone differentially interact with estradiol in the regulation of Alzheimer-like pathology in female 3xTransgenic-Alzheimer's disease mice. Endocrinology. 2010b; 151(6):2713–2722. [PubMed: 20410196]

Caruso D, Barron AM, Brown MA, Abbiati F, Carrero P, Pike CJ, Garcia-Segura LM, Melcangi RC. Age-related changes in neuroactive steroid levels in 3xTg-AD mice. Neurobiology of aging. 2013; 34(4):1080–1089. [PubMed: 23122920]

Charlier TD, Cornil CA, Patte-Mensah C, Meyer L, Mensah-Nyagan AG, Balthazart J. Local modulation of steroid action: rapid control of enzymatic activity. Frontiers in neuroscience. 2015; 9:83. [PubMed: 25852459]

Cherrier MM. Testosterone effects on cognition in health and disease. Front Horm Res. 2009; 37:150–162. [PubMed: 19011295]

Clinton LK, Billings LM, Green KN, Caccamo A, Ngo J, Oddo S, McGaugh JL, LaFerla FM. Age-dependent sexual dimorphism in cognition and stress response in the 3xTg-AD mice. Neurobiology of disease. 2007; 28(1):76–82. [PubMed: 17659878]

Colucci M, Cammarata S, Assini A, Croce R, Clerici F, Novello C, Mazzella L, Dagnino N, Mariani C, Tanganelli P. The number of pregnancies is a risk factor for Alzheimer's disease. European journal of neurology: the official journal of the European Federation of Neurological Societies. 2006; 13(12):1374–1377.

Corder EH, Ghebremedhin E, Taylor MG, Thal DR, Ohm TG, Braak H. The biphasic relationship between regional brain senile plaque and neurofibrillary tangle distributions: modification by age, sex, and APOE polymorphism. Ann N Y Acad Sci. 2004; 1019:24–28. [PubMed: 15246987]

Craig MC, Murphy DG. Estrogen therapy and Alzheimer's dementia. Ann N Y Acad Sci. 2010; 1205:245–253. [PubMed: 20840280]

Damoiseaux JS, Seeley WW, Zhou J, Shirer WR, Coppola G, Karydas A, Rosen HJ, Miller BL, Kramer JH, Greicius MD, Alzheimer's Disease Neuroimaging I. Gender modulates the APOE epsilon4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2012; 32(24):8254–8262. [PubMed: 22699906]

De Nicola AF, Coronel F, Garay LI, Gargiulo-Monachelli G, Gonzalez Deniselle MC, Gonzalez SL, Labombarda F, Meyer M, Guennoun R, Schumacher M. Therapeutic effects of progesterone in animal models of neurological disorders. CNS & neurological disorders drug targets. 2013; 12(8): 1205–1218. [PubMed: 24040821]

Devi L, Ohno M. Effects of BACE1 haploinsufficiency on APP processing and Abeta concentrations in male and female 5XFAD Alzheimer mice at different disease stages. Neuroscience. 2015; 307:128–137. [PubMed: 26314636]

Duarte-Guterman P, Yagi S, Chow C, Galea LA. Hippocampal learning, memory, and neurogenesis: Effects of sex and estrogens across the lifespan in adults. Hormones and behavior. 2015; 74:37–52. [PubMed: 26122299]

Dubal DB, Broestl L, Worden K. Sex and gonadal hormones in mouse models of Alzheimer's disease: what is relevant to the human condition? Biology of sex differences. 2012; 3(1):24. [PubMed: 23126652]

Engler-Chiurazzi EB, Brown CM, Povroznik JM, Simpkins JW. Estrogens as neuroprotectants: Estrogenic actions in the context of cognitive aging and brain injury. Progress in neurobiology. 2016

Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. Jama. 1997; 278(16):1349–1356. [PubMed: 9343467]

Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002; 87(2):589–598. [PubMed: 11836290]

Finch CE. The menopause and aging, a comparative perspective. The Journal of steroid biochemistry and molecular biology. 2014; 142:132–141. [PubMed: 23583565]

Galea LA. Gonadal hormone modulation of neurogenesis in the dentate gyrus of adult male and female rodents. Brain Res Rev. 2008; 57(2):332–341. [PubMed: 17669502]

Gandy S, Almeida OP, Fonte J, Lim D, Waterrus A, Spry N, Flicker L, Martins RN. Chemical andropause and amyloid-beta peptide. Jama. 2001; 285(17):2195–2196.

Geerlings MI, Ruitenberg A, Witteman JC, van Swieten JC, Hofman A, van Duijn CM, Breteler MM, Launer LJ. Reproductive period and risk of dementia in postmenopausal women. Jama. 2001; 285(11):1475–1481. [PubMed: 11255424]

George S, Petit GH, Gouras GK, Brundin P, Olsson R. Nonsteroidal selective androgen receptor modulators and selective estrogen receptor beta agonists moderate cognitive deficits and amyloid-beta levels in a mouse model of Alzheimer's disease. ACS chemical neuroscience. 2013; 4(12): 1537–1548. [PubMed: 24020966]

Gibbs RB. Fluctuations in relative levels of choline acetyltransferase mRNA in different regions of the rat basal forebrain across the estrous cycle: effects of estrogen and progesterone. The Journal of neuroscience: the official journal of the Society for Neuroscience. 1996; 16(3):1049–1055. [PubMed: 8558233]

Gibbs RB. Effects of gonadal hormone replacement on measures of basal forebrain cholinergic function. Neuroscience. 2000; 101(4):931–938. [PubMed: 11113342]

Gillett MJ, Martins RN, Clarnette RM, Chubb SA, Bruce DG, Yeap BB. Relationship between testosterone, sex hormone binding globulin and plasma amyloid beta peptide 40 in older men with subjective memory loss or dementia. Journal of Alzheimer's disease: JAD. 2003; 5(4):267–269. [PubMed: 14624021]

Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, Brinton EA, Cedars MI, Lobo RA, Merriam GR, Neal-Perry G, Santoro NF, Taylor HS, Black DM, Budoff MJ, Hodis HN, Naftolin F, Harman SM, Asthana S. Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS medicine. 2015; 12(6):e1001833. discussion e1001833. [PubMed: 26035291]

Golub MS, Germann SL, Mercer M, Gordon MN, Morgan DG, Mayer LP, Hoyer PB. Behavioral consequences of ovarian atrophy and estrogen replacement in the APPswe mouse. Neurobiology of aging. 2008; 29(10):1512–1523. [PubMed: 17451844]

Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 1991; 73(5):1016–1025. [PubMed: 1719016]

Green PS, Bales K, Paul S, Bu G. Estrogen therapy fails to alter amyloid deposition in the PDAPP model of Alzheimer's disease. Endocrinology. 2005; 146(6):2774–2781. [PubMed: 15731362]

Hardy J. Has the amyloid cascade hypothesis for Alzheimer's disease been proved? Current Alzheimer research. 2006; 3(1):71–73. [PubMed: 16472206]

Hardy J. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. Journal of neurochemistry. 2009; 110(4):1129–1134. [PubMed: 19457065]

Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. Climacteric: the journal of the International Menopause Society. 2012; 15(2):105–114. [PubMed: 22338612]

Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology. 2013; 80(19):1778–1783. [PubMed: 23390181]

Heikkinen T, Kalesnykas G, Rissanen A, Tapiola T, Iivonen S, Wang J, Chaudhuri J, Tanila H, Miettinen R, Puolivali J. Estrogen treatment improves spatial learning in APP + PS1 mice but does not affect beta amyloid accumulation and plaque formation. Experimental neurology. 2004; 187(1):105–117. [PubMed: 15081593]

Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA, Group MS. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. J Neurol Neurosurg Psychiatry. 2005; 76(1):103–105. [PubMed: 15608005]

Hirata-Fukae C, Li HF, Hoe HS, Gray AJ, Minami SS, Hamada K, Niikura T, Hua F, Tsukagoshi-Nagai H, Horikoshi-Sakuraba Y, Mughal M, Rebeck GW, LaFerla FM, Mattson MP, Iwata N, Saido TC, Klein WL, Duff KE, Aisen PS, Matsuoka Y. Females exhibit more extensive amyloid, but not tau, pathology in an Alzheimer transgenic model. Brain research. 2008; 1216:92–103. [PubMed: 18486110]

Hodis HN, Mack WJ, Shoupe D, Azen SP, Stanczyk FZ, Hwang-Levine J, Budoff MJ, Henderson VW. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause (New York, NY). 2015; 22(4):391–401.

Hogervorst E, Combrinck M, Smith AD. Testosterone and gonadotropin levels in men with dementia. Neuroendocrinol Lett. 2003; 24(3–4):203–208. [PubMed: 14523358]

Hogervorst E, Williams J, Biudge M, Barnetson L, Combrinck M, Smith AD. Serum total testosterone is lower in men with Alzheimer's disease. Neuro Endocrinol Lett. 2001; 22(3):163–168. [PubMed: 11449190]

Holland D, Desikan RS, Dale AM, McEvoy LK, Alzheimer's Disease Neuroimaging I. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. AJNR Am J Neuroradiol. 2013; 34(12): 2287–2293. [PubMed: 23828104]

Imtiaz B, Tuppurainen M, Tiihonen M, Kivipelto M, Soininen H, Hartikainen S, Tolppanen AM. Oophorectomy, hysterectomy, and risk of Alzheimer's disease: a nationwide case-control study. Journal of Alzheimer's disease: JAD. 2014; 42(2):575–581. [PubMed: 24898656]

Irvine K, Laws KR, Gale TM, Kondel TK. Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. Journal of clinical and experimental neuropsychology. 2012; 34(9):989–998. [PubMed: 22913619]

Irwin RW, Wang JM, Chen S, Brinton RD. Neuroregenerative mechanisms of allopregnanolone in Alzheimer's disease. Frontiers in endocrinology. 2011; 2:117. [PubMed: 22654847]

Jayaraman A, Carroll JC, Morgan TE, Lin S, Zhao L, Arimoto JM, Murphy MP, Beckett TL, Finch CE, Brinton RD, Pike CJ. 17b-Estradiol and progesterone regulate expression of b-amyloid clearance factors in primary neuron cultures and female rat brain. Endocrinology. 2012; 153:5467–5479. [PubMed: 22962256]

Jezierski MK, Sohrabji F. Neurotrophin expression in the reproductively senescent forebrain is refractory to estrogen stimulation. Neurobiology of aging. 2001; 22(2):309–319. [PubMed: 11182481]

Juraska JM, Sisk CL, DonCarlos LL. Sexual differentiation of the adolescent rodent brain: hormonal influences and developmental mechanisms. Hormones and behavior. 2013; 64(2):203–210. [PubMed: 23998664]

Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocrine reviews. 2005

Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A, Bacal C, Lingle DD, Metter E. A prospective study of estrogen replacement therapy and the risk of developing

Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology. 1997; 48(6):1517–1521. [PubMed: 9191758]

Lapane KL, Gambassi G, Landi F, Sgadari A, Mor V, Bernabei R. Gender differences in predictors of mortality in nursing home residents with AD. Neurology. 2001; 56(5):650–654. [PubMed: 11245718]

Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology. 1999; 52(1):78–84. [PubMed: 9921852]

Leranth C, Petnehazy O, MacLusky NJ. Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. JNeurosci. 2003; 23(5):1588–1592. [PubMed: 12629162]

Levin-Allerhand JA, Lominska CE, Wang J, Smith JD. 17Alpha-estradiol and 17beta-estradiol treatments are effective in lowering cerebral amyloid-beta levels in AbetaPPSWE transgenic mice. Journal of Alzheimer's disease: JAD. 2002; 4(6):449–457. [PubMed: 12515896]

Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM. Marked gender differences in progression of mild cognitive impairment over 8 years. Alzheimer's & dementia: translational research & clinical interventions. 2015; 1(2):103–110.

Liu Y, Paajanen T, Westman E, Wahlund LO, Simmons A, Tunnard C, Sobow T, Proitsi P, Powell J, Mecocci P, Tsolaki M, Vellas B, Muehlboeck S, Evans A, Spenger C, Lovestone S, Soininen H, AddNeuroMed C. Effect of APOE epsilon4 allele on cortical thicknesses and volumes: the AddNeuroMed study. Journal of Alzheimer's disease: JAD. 2010; 21(3):947–966. [PubMed: 20693633]

Luchetti S, Bossers K, Van de Bilt S, Agrapart V, Morales RR, Frajese GV, Swaab DF. Neurosteroid biosynthetic pathways changes in prefrontal cortex in Alzheimer's disease. Neurobiology of aging. 2011; 32(11):1964–1976. [PubMed: 20045216]

MacLusky NJ, Hajszan T, Prange-Kiel J, Leranth C. Androgen modulation of hippocampal synaptic plasticity. Neuroscience. 2006; 138(3):957–965. [PubMed: 16488544]

Maki PM. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. Menopause (New York, NY). 2013; 20(6):695–709.

McAllister C, Long J, Bowers A, Walker A, Cao P, Honda S, Harada N, Staufenbiel M, Shen Y, Li R. Genetic targeting aromatase in male amyloid precursor protein transgenic mice down-regulates beta-secretase (BACE1) and prevents Alzheimer-like pathology and cognitive impairment. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2010; 30(21):7326–7334. [PubMed: 20505099]

McLay RN, Maki PM, Lyketsos CG. Nulliparity and late menopause are associated with decreased cognitive decline. The Journal of neuropsychiatry and clinical neurosciences. 2003; 15(2):161–167. [PubMed: 12724456]

Melcangi RC, Garcia-Segura LM, Mensah-Nyagan AG. Neuroactive steroids: state of the art and new perspectives. Cell Mol Life Sci. 2008; 65(5):777–797. [PubMed: 18038216]

Miech RA, Breitner JC, Zandi PP, Khachaturian AS, Anthony JC, Mayer L. Incidence of AD may decline in the early 90s for men, later for women: The Cache County study. Neurology. 2002; 58(2):209–218. [PubMed: 11805246]

Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clinical epidemiology. 2014; 6:37–48. [PubMed: 24470773]

Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, Resnick SM. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004; 62(2):188–193. [PubMed: 14745052]

Morgan TE, Finch CE. Astrocytic estrogen receptors and impaired neurotrophic responses in a rat model of perimenopause. Frontiers in aging neuroscience. 2015; 7:179. [PubMed: 26483679]

Morley JE. Androgens and aging. Maturitas. 2001; 38(1):61–71. discussion 71–63. [PubMed: 11311591]

Morris JA, Jordan CL, Breedlove SM. Sexual differentiation of the vertebrate nervous system. Nature neuroscience. 2004; 7(10):1034–1039. [PubMed: 15452574]

Moser VA, Pike CJ. Obesity and sex interact in the regulation of Alzheimer's disease. Neuroscience and biobehavioral reviews. 2015 Dec 18. [Epub ahead of print].

Mucke L, Selkoe DJ. Neurotoxicity of amyloid beta-protein: synaptic and network dysfunction. Cold Spring Harbor perspectives in medicine. 2012; 2(7):a006338. [PubMed: 22762015]

Muller M, den Tonkelaar I, Thijssen JH, Grobbee DE, van der Schouw YT. Endogenous sex hormones in men aged 40–80 years. Eur J Endocrinol. 2003; 149(6):583–589. [PubMed: 14641001]

Munetomo A, Hojo Y, Higo S, Kato A, Yoshida K, Shirasawa T, Shimizu T, Barron A, Kimoto T, Kawato S. Aging-induced changes in sex-steroidogenic enzymes and sex-steroid receptors in the cortex, hypothalamus and cerebellum. The journal of physiological sciences: JPS. 2015; 65(3): 253–263. [PubMed: 25715777]

Muraleedharan V, Jones TH. Testosterone and mortality. Clinical endocrinology. 2014; 81(4):477–487. [PubMed: 25041142]

Naylor JC, Kilts JD, Hulette CM, Steffens DC, Blazer DG, Ervin JF, Strauss JL, Allen TB, Massing MW, Payne VM, Youssef NA, Shampine LJ, Marx CE. Allopregnanolone levels are reduced in temporal cortex in patients with Alzheimer's disease compared to cognitively intact control subjects. Biochimica et biophysica acta. 2010; 1801(8):951–959. [PubMed: 20488256]

Nead KT, Gaskin G, Chester C, Swisher-McClure S, Dudley JT, Leeper NJ, Shah NH. Androgen Deprivation Therapy and Future Alzheimer's Disease Risk. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2016; 34(6):566–571. [PubMed: 26644522]

Overk CR, Lu PY, Wang YT, Choi J, Shaw JW, Thatcher GR, Mufson EJ. Effects of aromatase inhibition versus gonadectomy on hippocampal complex amyloid pathology in triple transgenic mice. Neurobiology of disease. 2012; 45(1):479–487. [PubMed: 21945538]

Paganini Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol. 1994; 140(3):256–261. [PubMed: 8030628]

Paganini Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med. 1996; 156(19):2213–2217. [PubMed: 8885820]

Palm R, Chang J, Blair J, Garcia-Mesa Y, Lee HG, Castellani RJ, Smith MA, Zhu X, Casadesus G. Down-regulation of serum gonadotropins but not estrogen replacement improves cognition in aged-ovariectomized 3xTg AD female mice. Journal of neurochemistry. 2014; 130(1):115–125. [PubMed: 24601954]

Paoletti AM, Congia S, Lello S, Tedde D, Orru M, Pistis M, Pilloni M, Zedda P, Loddo A, Melis GB. Low androgenization index in elderly women and elderly men with Alzheimer's disease. Neurology. 2004; 62(2):301–303. [PubMed: 14745075]

Payami H, Montee KR, Kaye JA, Bird TD, Yu CE, Wijsman EM, Schellenberg GD. Alzheimer's disease, apolipoprotein E4, and gender. Jama. 1994; 271(17):1316–1317. [PubMed: 8158809]

Pennanen C, Laakso MP, Kivipelto M, Ramberg J, Soininen H. Serum testosterone levels in males with Alzheimer's disease. Journal of neuroendocrinology. 2004; 16(2):95–98. [PubMed: 14763994]

Petanceska SS, Nagy V, Frail D, Gandy S. Ovariectomy and 17beta-estradiol modulate the levels of Alzheimer's amyloid beta peptides in brain. Experimental gerontology. 2000; 35(9–10):1317–1325. [PubMed: 11113610]

Phung TK, Waltoft BL, Laursen TM, Settnes A, Kessing LV, Mortensen PB, Waldemar G. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. Dementia and geriatric cognitive disorders. 2010; 30(1):43–50. [PubMed: 20689282]

Pike CJ, Carroll JC, Rosario ER, Barron A. Protective actions of sex steroid hormones in Alzheimer's disease. Front Neuroendocrinol. 2009; 30:239–258. [PubMed: 19427328]

Pike CJ, Nguyen TV, Ramsden M, Yao M, Murphy MP, Rosario ER. Androgen cell signaling pathways involved in neuroprotective actions. Hormones and behavior. 2008; 53(5):693–705. [PubMed: 18222446]

Porcu P, Barron AM, Frye CA, Walf AA, Yang SY, He XY, Morrow AL, Panzica GC, Melcangi RC. Neurosteroidogenesis Today: Novel Targets for Neuroactive Steroid Synthesis and Action and Their Relevance for Translational Research. Journal of neuroendocrinology. 2016; 28(2)

Ptok U, Barkow K, Heun R. Fertility and number of children in patients with Alzheimer's disease. Archives of women's mental health. 2002; 5(2):83–86.

Raber J, Wong D, Buttini M, Orth M, Bellosta S, Pitas RE, Mahley RW, Mucke L. Isoform-specific effects of human apolipoprotein E on brain function revealed in ApoE knockout mice: increased susceptibility of females. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95(18):10914–10919. [PubMed: 9724804]

Ramsden M, Nyborg AC, Murphy MP, Chang L, Stanczyk FZ, Golde TE, Pike CJ. Androgens modulate beta-amyloid levels in male rat brain. Journal of neurochemistry. 2003; 87(4):1052–1055. [PubMed: 14622134]

Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, Melton LJ 3rd. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 2007; 69(11):1074–1083. [PubMed: 17761551]

Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen treatment, and cognitive aging: clinical evidence for a window of opportunity. Brain research. 2011; 1379:188–198. [PubMed: 20965156]

Rosario ER, Carroll J, Pike CJ. Testosterone regulation of Alzheimer-like neuropathology in male 3xTg-AD mice involves both estrogen and androgen pathways. Brain research. 2010; 1359:281–290. [PubMed: 20807511]

Rosario ER, Carroll JC, Oddo S, LaFerla FM, Pike CJ. Androgens regulate the development of neuropathology in a triple transgenic mouse model of Alzheimer's disease. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2006; 26(51):13384–13389. [PubMed: 17182789]

Rosario ER, Chang L, Beckett TL, Carroll JC, Paul Murphy M, Stanczyk FZ, Pike CJ. Age-related changes in serum and brain levels of androgens in male Brown Norway rats. Neuroreport. 2009; 20(17):1534–1537. [PubMed: 19829160]

Rosario ER, Chang L, Head EH, Stanczyk FZ, Pike CJ. Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. Neurobiology of aging. 2011; 32(4):604–613. [PubMed: 19428144]

Rosario ER, Chang L, Stanczyk FZ, Pike CJ. Age-related testosterone depletion and the development of Alzheimer disease. Jama. 2004; 12:1431–1432.

Rupprecht R, Papadopoulos V, Rammes G, Baghai TC, Fan J, Akula N, Groyer G, Adams D, Schumacher M. Translocator protein (18 kDa) (TSPO) as a therapeutic target for neurological and psychiatric disorders. Nature reviews Drug discovery. 2010; 9(12):971–988. [PubMed: 21119734]

Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology. 1993; 43(8):1467–1472. [PubMed: 8350998]

Schumacher M, Weill-Engerer S, Liere P, Robert F, Franklin RJ, Garcia-Segura LM, Lambert JJ, Mayo W, Melcangi RC, Parducz A, Suter U, Carelli C, Baulieu EE, Akwa Y. Steroid hormones and neurosteroids in normal and pathological aging of the nervous system. Progress in neurobiology. 2003; 71(1):3–29. [PubMed: 14611864]

Shao H, Breitner JC, Whitmer RA, Wang J, Hayden K, Wengreen H, Corcoran C, Tschanz J, Norton M, Munger R, Welsh-Bohmer K, Zandi PP, Investigators CC. Hormone therapy and Alzheimer disease dementia. Neurology. 2012; 79(18):1846–1852. [PubMed: 23100399]

Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. Jama. 2004; 291(24):2947–2958. [PubMed: 15213206]

Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN 3rd, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-Smoller S, Wactawski-Wende J. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women' Health Initiative Memory Study: a randomized controlled trial. Jama. 2003; 289(20):2651–2662. [PubMed: 12771112]

Simpkins JW, Singh M, Brock C, Etgen AM. Neuroprotection and estrogen receptors. Neuroendocrinology. 2012; 96(2):119–130. [PubMed: 22538356]

Singh M, Su C. Progesterone, brain-derived neurotrophic factor and neuroprotection. Neuroscience. 2013; 239:84–91. [PubMed: 23036620]

Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, Marder K, Sano M, Devanand D, Albert SM, Bylsma F, Tsai WY. Predicting time to nursing home care and death in individuals with Alzheimer disease. Jama. 1997; 277(10):806–812. [PubMed: 9052710]

Stone DJ, Rozovsky I, Morgan TE, Anderson CP, Lopez LM, Shick J, Finch CE. Effects of age on gene expression during estrogen-induced synaptic sprouting in the female rat. Experimental neurology. 2000; 165(1):46–57. [PubMed: 10964484]

Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance MA, Enghild J, Salvesen GS, Roses AD. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America. 1993; 90(5):1977–1981. [PubMed: 8446617]

Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, Andrews H, Mayeux R. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet. 1996; 348(9025):429–432. [PubMed: 8709781]

Tanzi RE. The genetics of Alzheimer disease. Cold Spring Harbor perspectives in medicine. 2012; 2(10)

Vegeto E, Benedusi V, Maggi A. Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. Frontiers in neuroendocrinology. 2008; 29(4):507–519. [PubMed: 18522863]

Vinters HV. Emerging concepts in Alzheimer's disease. Annual review of pathology. 2015; 10:291–319.

Wang J, Tanila H, Puolivali J, Kadish I, van Groen T. Gender differences in the amount and deposition of amyloidbeta in APPswe and PS1 double transgenic mice. Neurobiology of disease. 2003; 14(3):318–327. [PubMed: 14678749]

Watanabe T, Koba S, Kawamura M, Itokawa M, Idei T, Nakagawa Y, Iguchi T, Katagiri T. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. Metabolism. 2004; 53(4):476–482. [PubMed: 15045695]

Weill-Engerer S, David JP, Sazdovitch V, Liere P, Eychenne B, Pianos A, Schumacher M, Delacourte A, Baulieu EE, Akwa Y. Neurosteroid quantification in human brain regions: comparison between Alzheimer' and nondemented patients. J Clin Endocrinol Metab. 2002; 87(11):5138–5143. [PubMed: 12414884]

Wharton W, Gleason CE, Miller VM, Asthana S. Rationale and design of the Kronos Early Estrogen Prevention Study (KEEPS) and the KEEPS Cognitive and Affective sub study (KEEPS Cog). Brain research. 2013; 1514:12–17. [PubMed: 23603409]

Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. Annals of neurology. 2011; 69(1):163–169. [PubMed: 21280086]

Wong AM, Rozovsky I, Arimoto JM, Du Y, Wei M, Morgan TE, Finch CE. Progesterone influence on neurite outgrowth involves microglia. Endocrinology. 2009; 150(1):324–332. [PubMed: 18772232]

Woolley CS, McEwen BS. Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat. J Neurosci. 1992; 12(7):2549–2554. [PubMed: 1613547]

Xu H, Greenfield JP, Cai D, Leung LW, Kassik K, Rodriguez Boulan E, Greengard P. Hormonal control of cerebral amyloidogenesis in Alzheimer's diseases. Journal of neurochemistry. 2002; 81(Suppl 1):82.

Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Zhao QF, Li JQ, Wang J, Yu JT. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2015; 86(12): 1299–1306. [PubMed: 26294005]

Yin F, Yao J, Sancheti H, Feng T, Melcangi RC, Morgan TE, Finch CE, Pike CJ, Mack WJ, Cadenas E, Brinton RD. The perimenopausal aging transition in the female rat brain: decline in bioenergetic systems and synaptic plasticity. Neurobiology of aging. 2015; 36(7):2282–2295. [PubMed: 25921624]

Yue X, Lu M, Lancaster T, Cao P, Honda S, Staufenbiel M, Harada N, Zhong Z, Shen Y, Li R. Brain estrogen deficiency accelerates Abeta plaque formation in an Alzheimer's disease animal model.

Proceedings of the National Academy of Sciences of the United States of America. 2005; 102(52):19198–19203. [PubMed: 16365303]

Zandi PP, Carlson MC, Plassman BL, Welsh Bohmer KA, Mayer LS, Steffens DC, Breitner JC. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. Jama: the Journal of the American Medical Association. 2002; 288(17):2123–2129. [PubMed: 12413371]

Zempel H, Mandelkow E. Lost after translation: missorting of Tau protein and consequences for Alzheimer disease. Trends in neurosciences. 2014; 37:721–732. [PubMed: 25223701]

Zhang QG, Wang R, Khan M, Mahesh V, Brann DW. Role of Dickkopf-1, an antagonist of the Wnt/beta-catenin signaling pathway, in estrogen-induced neuroprotection and attenuation of tau phosphorylation. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2008; 28(34):8430–8441. [PubMed: 18716201]

Zhao L, Yao J, Mao Z, Chen S, Wang Y, Brinton RD. 17beta-Estradiol regulates insulin-degrading enzyme expression via an ERbeta/PI3-K pathway in hippocampus: relevance to Alzheimer's prevention. Neurobiology of aging. 2011; 32(11):1949–1963. [PubMed: 20053478]

Zheng H, Xu H, Uljon SN, Gross R, Hardy K, Gaynor J, Lafrancois J, Simpkins J, Refolo LM, Petanceska S, Wang R, Duff K. Modulation of A(beta) peptides by estrogen in mouse models. Journal of neurochemistry. 2002; 80(1):191–196. [PubMed: 11796757]

Significance

The development and progression of Alzheimer's disease are characterized by significant sex differences. Understanding the role of sex differences in Alzheimer's disease is essential for not only identifying those most at risk but also developing interventions to prevent and treat the disease. This review highlights the roles of sex steroid hormones in this relationship, emphasizing sex differences in hormone actions and their importance during both development and aging.