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Gender, sex steroid hormones, and Alzheimer's disease

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Abstract

Age-related loss of sex steroid hormones is an established risk factor for the development of Alzheimer's disease (AD) in women and men. While the relationships between the sex steroid hormones and AD are not fully understood, findings from both human and experimental paradigms indicate that depletion of estrogens in women and androgens in men increase vulnerability of the aging brain to AD pathogenesis. We review evidence of a wide range of beneficial neural actions of sex steroid hormones that may contribute to their hypothesized protective roles against AD. Both estrogens and androgens exert general neuroprotective actions relevant to a several neurodegenerative conditions, some in a sex-specific manner, including protection from neuron death and promotion of select aspects of neural plasticity. In addition, estrogens and androgens regulate key processes implicated in AD pathogenesis, in particular the accumulation of β-amyloid protein. We discuss evidence of hormone-specific mechanisms related to the regulation of the production and clearance of β-amyloid as critical protective pathways. Continued elucidation of these pathways promises to yield effective hormone-based strategies to delay development of AD.

Keywords

Alzheimer's disease; β-amyloid; estrogen; progesterone; testosterone

Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disease that is the most common cause of dementia. Neuropathologically, AD is characterized primarily by the extracellular deposition of β-amyloid protein (Aβ) in the form of senile plaques and hyperphosphorylation of the cytoskeletal protein tau within neurons leading to the formation of neurofibrillary tangles within select regions including hippocampus and cortex (Braak and Braak, 1990; Selkoe, 2011). These degenerative lesions are associated with glial activation, neuritic dystrophy and loss of synapses, and neuron death (Selkoe, 2011). Although the causal factors leading to AD-related neurodegeneration and associated dementia remain incompletely defined, the leading hypothesis posits that the key initiating event is the abnormal accumulation of Aβ (Hardy, 2009; Hardy and Selkoe, 2002).

Age is the most significant risk factor for AD. Although the incidence of AD in men and women increases robustly with age (Evans et al., 1989; Rocca et al., 1986), the age-related

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changes underlying this relationship are not known. One significant consequence of normal aging is the depletion of sex steroid hormones (Morley et al., 1997). In this review, we will discuss evidence indicating that age-related declines in sex hormones significantly contribute to AD risk in men and women. Importantly, the relationships between sex hormone depletion and AD risk is gender specific. Evidence suggests that AD pathogenesis is regulated by estrogen and progesterone in females but primarily by androgens in male. Further, female gender may be an inherent risk factor for AD apart from circulating sex hormone levels. Continued elucidation of these issues promises to provide novel insight into the development of AD as well as therapeutic approaches for its prevention and possibly treatment.

Females, menopause, and risk of AD

The mammalian brain is sexually dimorphic, exhibiting significant structural and functional differences between the sexes (Cahill, 2006). Perhaps not surprisingly, the female brain and male brain demonstrate different vulnerabilities to CNS disorders including but not limited to schizophrenia, multiple sclerosis, autism, Parkinson's disease, and AD (Cahill, 2006). Gender differences in vulnerability to neurological disorders might be due to sexual dimorphisms established during development as well as to adult sex differences in circulating and brain levels of the steroid hormones 17β-estradiol (E2), progesterone, testosterone and their metabolites.

AD is more prevalent in women than in men (Andersen et al., 1999; Bachman et al., 1992; Brayne et al., 1995; Farrer et al., 1997). The higher prevalence of AD in women is explained in part by differences in life expectancy between men and women, however incidence of AD is also higher in women (Andersen et al., 1999; Jorm and Jolley, 1998; Ruitenberg et al., 2001). Furthermore, there is evidence that AD pathology (Barnes et al., 2005; Corder et al., 2004; Swaab et al.) and AD-related cognitive decline (Barnes et al., 2005; Buckwalter et al., 1993; Henderson and Buckwalter, 1994; Ruitenberg et al., 2001; Sinforiani et al., 2010) are greater in women than in men. For example, there is a stronger association with the apolipoprotein E ε4 allele in AD in women than in men and this association correlates with greater hippocampal atrophy in women (Farrer et al., 1997; Fleisher et al., 2005).

Transgenic mouse models of AD exhibit sex differences in neuropathology with females showing earlier and more robust changes than males. For example, Aβ accumulation in female Tg2576 mice is significantly higher than in comparably aged males (Callahan et al., 2001; Lee et al., 2002). Similarly, female APP_{swe}xPS1 (Anderson et al., 2003), APP23 (Sturchler-Pierrat and Staufenbiel, 2000), APPswe/PSEN1E9 (Halford and Russell, 2009), and 3xTg-AD (Carroll et al., 2010a; Hirata-Fukae et al., 2008) mice also show higher Aβ levels than age-matched males. Furthermore, females in many transgenic AD mouse models are also reported to show poorer behavioral performance (Carroll et al., 2010a; Clinton et al., 2007; King et al., 1999; Pistell et al., 2008). The observations of greater pathology and behavioral impairment in females across multiple transgenic mouse models suggest that females are inherently more vulnerable than males to AD pathogenesis.

The underlying cause(s) for the increased vulnerability for females to AD-like pathology is unclear. One possible mechanism is that organizational effects of sex steroid hormones during critical periods of neural development result in yet to be identified differences in the female brain conducive to development of AD. It is known that sex steroid hormones exert significant effects on neural development (Bowers et al., 2010; Gore, 2008; Krohmer and Baum, 1989; Slob et al., 1980; Weisz and Ward, 1980) and that manipulations of sex steroid signaling during critical periods result in permanent neural changes (Bakker and Baum, 2008; Isgor and Sengelaub, 2003; McCormick et al., 1998). Consistent with the possibility

that organizational effects of sex steroid contribute to sex differences in vulnerability to AD, a recent study from our group found that neonatal defeminization of female 3xTg-AD mice resulted in regional reductions in Aβ pathology whereas neonatal demasculinization of male 3xTg-AD mice yielded regional increases in Aβ (Carroll et al., 2010a). Also supportive of this hypothesis is that, in transgenic mouse models of AD, the sex differences in pathology typically appear prior to age-related changes in reproductive status and alterations in circulating levels of sex steroid hormones.

Another likely contributor to sex differences in vulnerability to AD pathogenesis is the relatively greater age-related loss in females of the activational effects of sex steroid hormones. Estrogens and progesterone have many neurological benefits that have been widely hypothesized to protect against various aspects of AD pathogenesis (Pike et al., 2009). Because menopause alters the cyclic nature and reduces the circulating levels of E2 and progesterone (Sherman et al., 1976), the neuroprotective actions of these hormones have been widely hypothesized to diminish in the postmenopausal woman (Bonomo et al., 2009; Henderson, 2006b). In comparison, men generally experience a more gradual age-related decline in their primary sex steroid hormone, testosterone (Morley et al., 1997). This difference between how rapidly and significantly the female versus male primary sex hormones decline could explain in part why the incidences of AD are higher in women than in men.

If activational effects of estrogens and progesterone protect against AD, then it follows that depletion of sex steroids should be associated with increased AD risk. In fact, prior work has demonstrated that women with AD have lower circulating (Manly et al., 2000) and brain (Rosario et al., 2011; Yue et al., 2005) levels of E2 than age-matched controls. Further, experimental depletion of sex steroid hormones by ovariectomy (OVX) increases Aβ accumulation in wild-type rodents (Petanceska et al., 2000) and several AD mouse models (Carroll and Pike, 2008; Carroll et al., 2007; Levin-Allerhand et al., 2002; Xu et al., 2006; Yue et al., 2005) in a manner that is significantly prevented or reversed by E2. Interestingly, OVX and E2 treatment were not associated with significant changes in Aβ pathology in some AD models (Golub et al., 2008; Green et al., 2005; Yue et al., 2005) This discrepancy appears to involve differences between circulating and brain levels of sex steroids, which reflect not only gonadal sources but also hormones derived from neurosteroidogenesis. More specifically, Yue and colleagues demonstrated that OVX did not increase Aβ levels in APP23 mice until the strain had been crossed to an aromatase deficient strain which prevents appreciable formation of E2 from extra-gonadal sources (Yue et al., 2005). Thus, the increased vulnerability of female brain to AD pathogenesis appears to involve a combination of organizational effects of sex steroid hormones and the loss of protective activational effects of estrogens and perhaps progesterone.

Neuroprotective actions of estrogens

Estrogens have several established neural actions that are predicted to contribute its theorized protective role against AD. These neuroprotective actions fall into three general categories: (1) improved cognition via regulation of various processes including spine density (Cooke and Woolley, 2005), long-term potentiation (Foy et al., 2010), and neurotransmitter systems (Gibbs, 2010), (2) protection against neuron cell death (Simpkins et al., 2010; Suzuki et al., 2009), and (3) inhibition of select aspects of AD neuropathology including Aβ accumulation and tau hyperphosphorylation (Pike et al., 2009).

Because abnormal accumulation of Aβ is widely theorized to be a primary causal factor in the initiation and/or progression of AD pathogenesis (Hardy, 2009; Hardy and Selkoe, 2002; Selkoe, 2011), the ability of estrogens to reduce Aβ accumulation may be their most

important neuroprotective action against AD (Carroll and Rosario, 2012; Pike et al., 2009). Aβ is a normally occurring peptide that results from the proteolytic processing of the transmembrane amyloid precursor protein (APP). APP is metabolized by one of two pathways, one of which generates Aβ and one that precludes formation of full-length Aβ (O'Brien and Wong, 2011; Thinakaran and Koo, 2008). In the amyloidogenic pathway, APP is cleaved by the protease β-secretase (BACE), which results in the release of the large soluble protein β-APPs and generates a shorter carboxyl terminal fragment that contains the Aβ portion. The carboxyl terminal fragment is further cleaved by γ-secretase to yield Aβ peptides that are predominantly 40 and 42 amino acids in length. Aβ peptides are released from the cell and are normally found in biological fluids in a soluble state at nanomolar levels (Haass et al., 1992; Seubert et al., 1992; Shoji et al., 1992). In the non-amyloidogenic pathway, APP is cleaved within the Aβ domain by α-secretase. This predominant pathway of APP metabolism produces soluble α-APPs but not the 40 and 42 amino acid Aβ peptides. While the production of low levels of soluble Aβ is a normal consequence of APP processing, factors that lead to increased amyloidogenic processing of APP and/or a reduction in the Aβ clearance pathways can lead to accumulation of Aβ. In turn, elevation of Aβ levels promotes assembly of the peptide into toxic oligomers and large insoluble fibrils that can drive neuropathology (Selkoe, 2011).

The initial discovery linking estrogens to an Aβ-lowering role was the observation that E2 can modify APP processing towards increased utilization of the non-amyloidogenic pathway (Gandy, 2003). In several cell systems, E2 promotes the production of α-APPs and, as a consequence, can reduce the amount of Aβ generated (Amtul et al., 2010; Desdouits-Magnen et al., 1998; Jaffe et al., 1994; Manthey et al., 2001; Thakur and Mani, 2005). It is not clear whether E2 specifically activates the non-amyloidogenic APP pathway or alternatively alters APP trafficking such that the amyloidogenic pathway is limited (Greenfield et al., 2002). There is evidence that the process is dependent on ERK1/2 and/or PKC dependent pathways (Desdouits-Magnen et al., 1998; Manthey et al., 2001). Both ERK1/2 and PKC are activated by E2 in a transcription-independent manner. Additionally, recent evidence suggests that E2 can regulate transcription of several components of the secretase enzymes involved in APP processing (Amtul et al., 2010; Bernstein et al., 2010; Nord et al., 2010). It is unclear whether this effect is estrogen receptor dependent, whether it is mediated by classic genomic actions of estrogen, or whether it is instead mediated by downstream transcriptional regulation in the ERK1/2 pathway. Although the mechanism(s) remain to be fully elucidated, the key observation is that in a variety of paradigms E2 alters APP processing to decrease the production of Aβ.

More recently, there is emerging evidence that estrogens and perhaps progesterone can attenuate Aβ accumulation by another strategy: promotion of Aβ clearance. Steady-state levels of Aβ reflect a balance between its production and clearance. One of several important mechanisms that contribute to Aβ clearance is the proteolytic action of Aβ-degrading enzymes (Eckman and Eckman, 2005). E2 increases brain levels and/or activities of the Aβ-degrading enzymes neprilysin (Liang et al., 2009; Xiao et al., 2009) and insulin degrading enzyme (Amtul et al., 2010; Zhao et al., 2011). E2 also increases expression of transthyretin (Amtul et al., 2010; Oliveira et al., 2011; Quintela et al., 2009), which binds and sequesters Aβ, preventing it from aggregating into neurotoxic plaques (Schwarzman et al., 1994).

Hormone therapy and AD risk in postmenopausal women

Given the observations in women and rodent models linking low E2 to AD and the several neuroprotective actions of E2 relevant to AD, the use of estrogen-based hormone therapy (HT) in postmenopausal women would appear to offer significant promise in reducing risk

of AD. Indeed, early evidence from many (Henderson et al., 1994; Hogervorst et al., 1999; LeBlanc et al., 2001; Paganini-Hill, 1996; Zandi et al., 2002), (reviewed in (Craig and Murphy, 2010)) but not all (Haskell et al., 1997) human observational and clinical trials indicated that HT is associated with reduced risk incidence of AD. Despite an abundance of data supporting neuroprotective actions of estrogens against AD, this hypothesis remains controversial. Perhaps most challenging to the hypothesis are the findings from the Women's Health Initiative Memory Study (WHIMS) (Rapp et al., 2003; Shumaker et al., 2003). The WHIMS trial was part of a large-scale, multi-center clinical trial that evaluated outcomes associated with HT consisting of conjugated equine estrogen either alone or with the progestin medroxyprogesterone acetate. Notably, results from WHIMS indicated that HT provided no slowing in cognitive decline in women that developed significant impairment and actually increased the risk dementia.

In the past few years since the WHIMS data were reported, several arguments have been offered to interpret the import of the findings with respect to the potential therapeutic risks and benefits of HT (Gleason et al., 2005; Henderson, 2006a; Maki, 2004). Although beyond the scope of the present review, some key points arising from discussion of WHIMS should be noted. First, the apparent discrepancy between basic research findings showing beneficial E2 neural actions and the WHIMS clinical data highlighting the opposite, have lead some to suggest that key aspects of HT are problematic, including HT formulation (conjugated equine estrogens versus E2), route of administration (oral versus transdermal), and periodicity of hormone delivery (continuous combined versus cyclic) (Gleason et al., 2005; Henderson, 2006a). There are abundant experimental data that appear to validate these arguments. For example, our group recently compared the effects of continuous or cyclic progesterone administration in conjunction with the E2 in ovariectomized female 3xTg-AD mice (Carroll et al., 2010b). Interestingly, the Aβ-lowering actions of E2 were negated when delivered in conjunction with continuous progesterone but improved when delivered with cyclic administration of progesterone. Perhaps the most significant factor contributing to the observed variance in clinical effects of HT is the age at which treatment is initiated. According to the "window of opportunity" hypothesis (Craig and Murphy, 2010; Whitmer et al., 2011), HT is most likely to exert favorable neural effects when administered near the onset of menopause rather than many years later, as was usually the case in WHIMS. In fact, prior work from animal studies demonstrates that many beneficial neural effects of E2 are attenuated in aged females (reviewed in (Pike et al., 2009)). Further, recent clinical data suggest that AD risk is reduced when HT is initiated in midlife but exacerbated by HT delivered in late life (Whitmer et al., 2011). Important new insight into several of these critical issues promises to emerge from two ongoing clinical trials, ELITE and KEEPS.

Males, andropause, and the risk of AD

Although the prevalence and incidence of AD is higher in women, men also experience a robust age-related increase in the risk of AD. In women, an increased risk of AD is significantly affected by normal age-related depletion of the primary female sex steroid hormones, estrogen and progesterone. Similarly, in men, the risk of AD is also significantly affected by normal age-related depletion of the primary male sex steroid hormone, testosterone. Men do not undergo a true andropause that depletes the comparatively rapid change in hormones and reproductive status characteristic of menopause. Rather, normal aging in males involves a gradual decrease in bioavailable testosterone that typically progresses at a rate of ~2% per year (Feldman et al., 2002; Muller et al., 2003). Age-related decreases in circulating testosterone result in a clinical syndrome termed androgen deficiency in aging males (ADAM) that is characterized by increased risk of disease and dysfunction in androgen-responsive tissues including bone, muscle, adipose, and heart (Kaufman and Vermeulen, 2005; Morley et al., 1997).

The brain is an androgen-responsive tissue and is affected by age-related androgen loss. Analyses of brain levels of testosterone and its primary androgen metabolite dihydrotestosterone (DHT) in both rodent (Rosario et al., 2009) and humans (Rosario et al., 2011; Rosario et al., 2004) demonstrate that the brain is particularly vulnerable to age-related androgen loss. Consistent with the observed androgen depletion in brain, ADAM is characterized by neural changes including decreases in mood and libido (Morley et al., 1997) and in some cases, impairments in select aspects of cognition (Janowsky, 2006). Notably, age-related androgen loss has also been associated with increased AD risk. Men with AD exhibit lower circulating (Hogervorst et al., 2003; Hogervorst et al., 2001; Moffat et al., 2004) and brain (Rosario et al., 2011; Rosario et al., 2004) levels of testosterone than age-matched, non-demented men without AD. Importantly, testosterone loss appears to precede clinical (Moffat et al., 2004) and neuropathological (Rosario et al., 2011; Rosario et al., 2004) diagnoses of AD, suggesting that androgen depletion is a precursor event that likely contributes to rather than results from the disease process. Interestingly, testosterone levels in brain are inversely related to soluble brain Aβ in men that show early development of AD-related neuropathology, suggesting a possible mechanism linking testosterone and AD risk (Rosario et al., 2011). Further, brain levels E2 and estrone are neither significantly linked with AD diagnosis in men, nor correlated with brain levels of Aβ, data that indicate sex differences in the relationships between sex steroid hormones and AD risk.

Consistent with the human literature, studies in the 3xTg-AD triple-transgenic mouse model of AD also suggest that androgen depletion promotes AD pathogenesis. Prior work from our group has shown that in young adult (Rosario et al., 2010; Rosario et al., 2006) and middle-aged (unpublished observations) male 3xTg-AD mice, orchiectomy (ORX) induced depletion of endogenous androgens significantly accelerates AD-like pathology, including neural Aβ accumulation and impairment of hippocampal-dependent behavioral performance. Further, treatment of ORX 3xTg-AD mice with testosterone (Rosario et al., 2010) or DHT (Rosario et al., 2010; Rosario et al., 2006) significantly attenuates the increase in pathology. Together, emerging observations in human and experimental paradigms strongly establish a relationship between androgen loss and AD risk.

Neuroprotective actions of androgens

Like estrogens, androgens have numerous neuroprotective actions in brain that may be relevant to its hypothesized protective role against AD. Such beneficial neural actions of androgens include: (1) promotion of neuron growth, axonal regeneration, and synaptic function, (2) protection against neuron cell loss, and (3) regulation of AD-related pathology including Aβ accumulation. In the first case, androgens have a variety of growth-promoting and maturational effects on neurons in a range of paradigms (Arai, 1991; Brannvall et al., 2005; Cooke et al., 1998; Gorski, 1985; Kawashima and Takagi, 1994; Lustig, 1994; Matsumoto, 1991). In addition, androgens are potent facilitators of spine density and synaptic function, including regulation of long-term potentiation in the hippocampus (Garcia-Segura et al., 1994; Hajszan et al., 2008; Hatanaka et al., 2009; MacLusky et al., 2004; Matsumoto, 2001; Matsumoto et al., 1988; Pouliot et al., 1996; Schulz and Korz, 2010). Androgens also accelerate regeneration of axons in damaged motor neurons in certain experimental paradigms (Brooks et al., 1998; Garcia-Ovejero et al., 2002; Gustafsson et al., 1981; Huppenbauer et al., 2005; Jordan et al., 2002; Marron et al., 2005; Yu, 1988). There appear to be sex differences in at least some of these actions. For example, whereas estrogens regulate spine density in females, androgens appear to be more potent than estrogens in male brain in select brain regions (Hajszan et al., 2008; Leranth et al., 2003). Pharmacological and genetic tools indicate that androgen receptor (AR) activation contributes to these actions (Hajszan et al., 2008; MacLusky et al., 2004).

Another androgen action potentially relevant to AD and a number of other neurodegenerative conditions is protection from neuron loss. In many but not all (Cunningham et al., 2009; Gatson and Singh, 2007) culture paradigms, androgens significantly attenuate neural cell injury against a variety of insults, including but not limited to serum deprivation (Brooks et al., 1998; Hammond et al., 2001), oxidative stress (Ahlbom et al., 2001), and Aβ toxicity (Nguyen et al., 2005; Park et al., 2007; Pike, 2001; Zhang, 2004). Similarly, androgens are neuroprotective in some but not all *in vivo* models of neuron death. For example, ORX increases and DHT reduces hippocampal neuron loss caused by kainate lesion (Ramsden et al., 2003b), however androgens exacerbate cell death in an ischemic model of stroke (Li et al., 2006; Yang et al., 2002) and impair or do not improve neuron viability in midbrain dopaminergic neurons (Dluzen, 1996; Johnson et al., 2010). It is unclear why androgen regulation of neuron viability varies across paradigms. One contributing factor may be that androgen-mediated neuroprotection is limited to specific types of cell death that involve apoptosis (Nguyen et al., 2010) but perhaps not some forms of oxidative stress (Cunningham et al., 2011; Dluzen and Ramirez, 1989; Gillies et al., 2004). In addition, variability in androgen neuroprotection may reflect in part differences in androgen-mediated actions across brain regions or neuronal subpopulations (e.g., hippocampal versus nigrostriatal).

In addition to their neurotrophic and neuroprotective actions, androgens may also protect against AD by regulating key factors in pathogenesis including Aβ accumulation. An initial finding (Gandy et al., 2001) that was replicated in subsequent research (Almeida et al., 2004) found that anti-androgen therapy used to treat prostate cancer results in elevated circulating levels of Aβ. Subsequent work from our group found that ORX in adult male rats significantly elevated soluble Aβ levels in brain, an effect prevented by treatment with DHT (Ramsden et al., 2003a). Testosterone also regulates Aβ in cerebrospinal fluid and plasma in ORX male rodents (Wahjoepramono et al., 2008). Importantly, similar results are observed as a result of normal male aging. Specifically, normal age-related depletion of brain levels of DHT that are apparent by age 13 months is associated with correspondingly robust increases in brain levels of Aβ (Rosario et al., 2009). As noted above, ORX increases Aβ accumulation in male 3xTg-AD mice and treatment with testosterone or DHT is protective (Rosario et al., 2010; Rosario et al., 2006).

In parallel to Aβ regulation by estrogens, androgens may reduce Aβ levels by affecting both its production and clearance. Initial work indicated that testosterone reduces Aβ by altering APP processing towards the non-amyloidogenic pathway (Gouras et al., 2000). Since E2 is known to act on APP in a similar manner, perhaps it was not surprising that at least some portion of testosterone regulation of APP metabolism was found to be dependent upon its conversion by aromatase to E2 (Goodenough et al., 2000). However, much of the Aβ-lowering actions of androgens is independent of estrogen pathways. For example, in an aromatase knockout mouse model of AD, elevated testosterone was associated with reduced Aβ burden and decreased expression and activity of the APP metabolizing enzyme β-secretase (McAllister et al., 2010). Consistent with the dual contributions of estrogen and androgen pathways, a recent comparative study on the Aβ-lowering effects of sex steroid hormones found that testosterone, DHT and E2 all significantly reduced Aβ in ORX 3xTg-AD with testosterone being most and E2 least effective (Rosario et al., 2010).

Secondly, androgens also inhibit Aβ accumulation by increasing Aβ clearance. In both neuronal culture (Yao et al., 2008) and animal models (McAllister et al., 2010; Yao et al., 2008) androgen-mediated lowering of Aβ levels has been linked to increased expression of neprilysin, the Aβ-degrading enzyme that appears to be most important to AD risk (Wang et al., 2010). Androgens increase neprilysin expression by an AR-dependent, classic genomic

pathway (Yao et al., 2008) that involves androgen response elements in the neprilysin gene (Shen et al., 2000).

Future directions

As discussed above, there is abundant evidence that sex steroid hormones function as important regulators of AD risk and do so in a way that is at least partially sex specific. Both estrogens and androgens exert a wide range of neuroprotective actions, some of which are relevant to normal brain aging, others that may benefit several neurodegenerative conditions, and still others that appear to be largely specific to AD. Given the strength of the existing research and the current absence of effective preventive and treatment interventions for AD, there continues to be a decided interest in pursuing therapeutic strategies based on gonadal hormones. Results from the pending ELITE and KEEPS trials in postmenopausal women and the Testosterone Trial in aging men promise to shed new insight into the potential of hormone therapies to slow the development of dementia and/or improve cognitive functioning. As progress continues on this front, new research is currently assessing the utility of novel hormone mimetics in AD models. Ongoing work in our lab and others is investigating selective estrogen receptor modulators and selective androgen receptor modulators, a strategy that has demonstrated efficacy in initial studies in AD transgenic mouse models (Carroll and Pike, 2008). With continuing discovery and elucidation of neuroprotective hormone pathways, the development of effective hormone and hormone mimetic therapies for prevention of AD appears increasingly likely.

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Highlights

- age-related estrogen depletion in women is a risk factor for Alzheimer's disease
- age-related androgen depletion in men is a risk factor for Alzheimer's disease
- relationships between hormones and Alzheimer's are often sex-specific
- estrogens and androgens reduce β-amyloid protein to reduce Alzheimer risk