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Review

Protective actions of sex steroid hormones in Alzheimer's disease

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ABSTRACT

Risk for Alzheimer's disease (AD) is associated with age-related loss of sex steroid hormones in both women and men. In post-menopausal women, the precipitous depletion of estrogens and progestogens is hypothesized to increase susceptibility to AD pathogenesis, a concept largely supported by epidemiological evidence but refuted by some clinical findings. Experimental evidence suggests that estrogens have numerous neuroprotective actions relevant to prevention of AD, in particular promotion of neuron viability and reduction of β -amyloid accumulation, a critical factor in the initiation and progression of AD. Recent findings suggest neural responsiveness to estrogen can diminish with age, reducing neuroprotective actions of estrogen and, consequently, potentially limiting the utility of hormone therapies in aged women. In addition, estrogen neuroprotective actions are also modulated by progestogens. Specifically, continuous progestogen exposure is associated with inhibition of estrogen actions whereas cyclic delivery of progestogens may enhance neural benefits of estrogen. In recent years, emerging literature has begun to elucidate a parallel relationship of sex steroid hormones and AD risk in men. Normal age-related testosterone loss in men is associated with increased risk to several diseases including AD. Like estrogen, testosterone has been established as an endogenous neuroprotective factor that not only increases neuronal resilience against AD-related insults, but also reduces β -amyloid accumulation. Androgen neuroprotective effects are mediated both directly by activation of androgen pathways and indirectly by aromatization to estradiol and initiation of protective estrogen signaling mechanisms. The successful use of hormone therapies in aging men and women to delay, prevent, and or treat AD will require additional research to optimize key parameters of hormone therapy and may benefit from the continuing development of selective estrogen and androgen receptor modulators.

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1. Introduction

As expertly described in the accompanying review articles, sex steroid hormones are potent regulators of neuron survival in multiple CNS regions and across a variety of circumstances ranging from normal development to neural injury. A compelling, and as yet largely unrealized, promise of sex steroid hormones is the translation of their neuroprotective properties into efficacious strategies for the treatment and or prevention of age-related neurodegenerative disorders such as Alzheimer's disease (AD). Despite this unfulfilled therapeutic potential, abundant experimental, epidemiological and clinical evidence suggest that neural actions androgens, estrogens, and perhaps even progestogens can reduce the risk for AD.

AD is an age-related neurological disease that is the leading cause of dementia. Neuropathologically, AD is characterized by brain region-specific deposition of β -amyloid protein (A β) which creates senile plaques, hyperphosphorylation of the cytoskeletal

protein tau that forms lesions called neurofibrillary tangles and neuropil threads, glial activation which is associated with inflammatory responses, and both synaptic and neuronal loss [3,37,139,140,196]. Although the mechanisms of AD pathogenesis remain to be fully resolved, the leading hypothesis posits that the disease is initiated and driven by prolonged elevation of A β levels [140]. A β is a proteolytic byproduct of the metabolism of amyloid precursor protein, a widely expressed protein with numerous functions ranging from axonal transport to gene transcription [336]. As a consequence of amyloid precursor protein expression, A β is normally found as a soluble protein at low levels in fluids and tissues throughout the body. In theory, alterations in either the production or clearance of A β that sway A β homeostasis towards increased neural levels will promote the development of AD [140]. The accumulation of A β encourages its abnormal assembly into oligomeric species that exhibit an altered structural conformation and can induce a range of neurodegenerative effects [136]. Consequently, enormous effort has been expended on identifying factors that regulate A β accumulation and or affect its neurodegenerative properties. One such class of factors is sex steroid hormones.

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In this review, we will discuss the neuroprotective properties of sex steroid hormones as they relate to AD pathogenesis, focusing largely on their effects on A β accumulation and its associated neurodegeneration. Estrogens are the most thoroughly studied steroid hormones in terms of AD. We will cover the epidemiological and clinical evidence that suggests depletion of ovarian hormones at menopause increases the risk of AD in post-menopausal women, a danger some studies suggest may be mitigated by estrogen-based hormone therapy (HT). Consistent with a protective role against AD, experimental studies demonstrate that estrogens not only reduce neuron loss induced by AD-related insults but also act to reduce A β levels. However, in the Women's Health Initiative (WHI) trial, the most exhaustive clinical evaluation of HT thus far, HT was associated with increased rather than decreased risk of AD. Analysis of experimental work reveals several key limitations of estrogen's neuroprotective actions that may contribute to this clinical observation, including loss of neural estrogen responsiveness with age and interactions with progestogens that may limit estrogen neuroprotection. A more recent and still emerging literature suggests a parallel relationship in men with their primary sex steroid hormone, testosterone. That is, normal age-related testosterone is associated with increased risk of AD in aging men. Like estrogens, androgens also exert neuroprotective properties relevant to AD, including promotion of survival in neurons challenged with AD-related insults and reduction of A β levels. Finally, we consider future directions in this field, emphasizing the clinical potential of sex steroid hormones in prevention rather than treatment of AD and the emerging promise of selective estrogen receptor and androgen receptor modulators.

2. Menopause, hormone therapy, and Alzheimer's disease

Converging lines of evidence indicate a potentially important role of estrogens in regulating AD pathogenesis. Preliminary clues suggesting this possibility stemmed from reports of sex differences in AD risk, with women showing higher prevalence and incidence. Although sex differences in AD are difficult to interpret due to gender differences in life expectancy, many studies of various cohorts indicate that women are at greater risk of AD [9,17,39,93,101,137,180,221,281,290]. Further, there is some evidence that AD pathogenesis may be more severe in women as indicated by sex differences in cognitive deficits and neuropathology [21,49,66,150], although other studies indicate men have higher levels of tau pathology [293,294]. Further, there is a stronger association between the apolipoprotein E ϵ 4 allele and sporadic AD in women compared to men [66,84,165] and the ϵ 4 allele has been shown to be associated with greater hippocampal atrophy and memory impairments in women compared to men [98]. When considered together, these epidemiological and neuropathological studies indicate sex differences in AD, suggesting that women may be more vulnerable to AD than men.

Several transgenic mouse models exhibit sex differences in AD-like neuropathology that appears to parallel that observed in human AD cases. For example, at both 15 and 19 mo of age, female Tg2576 mice display a higher plaque load burden and higher levels of both soluble and insoluble A β 40 and A β 42 than age-matched males [51]. Similarly, female APP_{Swe}xPS1 transgenic mice have higher A β load burden and plaque number than age-matched males [350]. The same pattern of greater A β deposition in female versus male mice is also observed in the 3xTg-AD triple transgenic mouse [156]. These studies in transgenic mouse models of AD suggest that the female brain may be more vulnerable to AD pathogenesis.

The increased risk of AD in women is presumed to be associated with the precipitous loss of estrogens and progesterone at menopause. Consistent with this position, plasma levels of the estrogen

17 β -estradiol (E₂) [212] are reported to be lower in women with AD in comparison to age-matched controls. If the depletion of ovarian hormones at menopause contributes to women's increased risk of AD, then one would predict that estrogen-based hormone therapy (HT) would be effective in the prevention and or treatment of AD. This critical issue remains unresolved with persuasive arguments both for and against the use of HT for AD. An early study of this issue found that AD risk was lower in women who used HT relative to nonusers and this risk decreased significantly as both dose and duration of HT use increased [247]. Similarly, findings from several other case control and prospective studies suggest that post-menopausal women with a history of HT use were at reduced risk of AD [52,151,184,248,329,351,382]. Further, a meta-analysis of studies found that HT was associated with decreased risk of cognitive dysfunction [158,197,241,305]. Collectively, these studies suggest a potential protective role of estrogen against the development of AD.

Despite indications of benefits, the potential protective of HT against AD remains controversial. Arguing against a protective role, several studies found that HT use was not associated with reduced risk of AD (reviewed in [146]) or failed to yield significant cognitive benefits [7,22,34,40,119,152,228,266,349,369]. One possible explanation for this discrepancy is suggested by findings from the Cache County Study, which demonstrated that the association between HT use and reduced risk of AD was strengthened in long-term HT users [382]. Interpretations of these findings include the concept that HT may have a largely preventive role against AD and or the hypothesis that early initiation of HT is essential as women who took HT for longer periods likely began treatment nearer the time of menopause.

The notion that estrogen-based HT can effectively reduce the risk of AD and improve age-related deficits in cognition has been challenged by findings from the Women's Health Initiative Memory Study (WHIMS). WHIMS was a randomized, multi-center, double-blind, placebo-controlled study of ~4500 women between 65 and 79 yrs of age that evaluated effects of HT consisting of conjugated equine estrogen (CEE) alone or CEE with the progestin medroxyprogesterone acetate (MPA). This study reported that neither CEE nor CEE + MPA significantly improved cognition versus placebo in women showing cognitive decline associated with normal aging [91,273] or dementia [312,311]. In the CEE alone arm, there was no significant difference in dementia incidence between HT or placebo groups although there was a non-significant trend towards increased risk in the HT group [91,312]. In the CEE + MPA arm, they found that women receiving HT had a higher risk of probable dementia [311]. HT use was also associated with increased incidence of stroke and breast cancer, suggesting that the risks of HT may outweigh its benefits. Further, the important differences between the CEE alone arm and the CEE + MPA arm raise several issues about the inclusion of a progestin component.

Although the WHIMS findings raise serious concerns over HT use, many challenge the interpretation that these data dismiss the potential efficacy of HT in reducing the risk of AD [75,118,149,209,265,276]. A variety of issues have been identified that may have affected HT outcomes in the WHIMS compared to the many observational studies such as differences in methodological techniques, outcome measures, hormone exposures, menopausal symptoms, and the timing of hormone use [149]. In particular, neural sensitivity to sex steroid hormones may diminish during the menopause transition, resulting in a critical window in which to initiate HT in order to realize benefits (reviewed in [75]). Because HT was initiated many years after menopause in the WHIMS study, the study's design may have inadvertently focused on an age group in which estrogen is minimally active in brain and thus was unlikely to detect potential cognitive benefits. In addition, as suggested by prior epidemiological and clinical find-

ings, estrogen may be most effective in preventing rather than treating AD. In this case, the relatively advanced age of WHIMS subjects would also be biased against positive outcomes. Additional issues include HT formulation, route of administration, and treatment regime (e.g., cyclic versus continuous hormone delivery). In order to unravel this conundrum, a greater understanding of the neuroprotective actions of estrogens and progestogens are needed, as well as their limitations in the context of aging.

In the following sections, we examine the neuroprotective effects of estrogen, focusing on its abilities to increase neuronal resilience against AD insults and to antagonize AD pathogenesis by reducing A β accumulation. Importantly, we also discuss experimental evidence that addresses how these protective actions of estrogen are affected by the concerns raised by WHIMS.

3. Estrogen neuroprotection and Alzheimer's disease insults

An established neural action of estrogens that may contribute to a protective role against AD is promotion of neuron viability. Estrogen is neuroprotective against a variety of insults in several cell culture and rodent paradigms of injury and neurodegenerative disease. Of particular interest is the ability of estrogen to protect against neuronal loss induced by A β , which is thought to be primary neurodegenerative agent in AD. Reports from several groups demonstrate that estrogen can protect cultured neurons and neural cell lines from A β mediated toxicity [26,124,132,135,222,259].

Estrogen may potentially protect against A β -induced neurotoxicity at several steps in the degenerative process. The leading theory of A β toxicity posits a pathologic assembly of A β involving adoption of a β -sheet conformation, resulting in a change in protein structure that is associated with a toxic gain of function (reviewed in [347]). Consistent with this working hypothesis of A β neurotoxicity, our prior work has shown that A β is toxic only in an assembled state [263,261]. Assembled A β in the form of soluble oligomers and insoluble fibrils can induce neuronal death [72,348,373] degeneration of neurites [169,262] and synaptic disruption [145,182,288,348] leading to impaired learning and memory [61,198]. Interaction of A β assemblies with neurons initiates a cascade of upstream signaling mechanisms associated with cell death, including calcium dysregulation [216,356], oxidative stress [25,123,214], and activation of pro-inflammatory pathways promoting chronic gliosis [89,264]. Most evidence suggests that the plethora of upstream signaling cascades elicited by A β ultimately mediate neurotoxicity by downstream activation of neuronal apoptosis pathways [71,73]. In particular, we find that A β -induced neuronal apoptosis involves activation of JNK signaling and consequent dysregulation of the Bcl-2 family of apoptosis-related proteins [374].

Since neuronal apoptosis is an important downstream mediator of A β neurotoxicity, regulation of apoptosis is predicted to be a key mechanism of estrogen protection from A β . Consistent with this hypothesis, estrogen has been implicated in the regulation of Bcl-2 family members in neurons [86,110,191,234,254,259,316,320]. The Bcl-2 family includes both proteins that promote cell survival (e.g., Bcl-2, Bcl-x_L, and Bcl-w) and others that antagonize it (e.g., Bax, Bad, Bak, Bik, Bid, BNIP3, and Bim) (reviewed in [12,70]). We have found that physiological levels of E₂ inhibit neuronal apoptosis at least in part by increasing expression of anti-apoptotic Bcl-x_L [259,320] and Bcl-w [375] while down-regulating expression of the pro-apoptotic Bim [375]. The observed effects of E₂ on A β mediated apoptosis were found to be mediated ER-dependent mechanisms, since the anti-apoptotic effects of E₂ were blocked by pre-treatment with an ER antagonist [259, 375]. Supporting this, it has been previously demonstrated that both ER α and ER β are crucial in regulating Bcl-2 expression and neuronal survival

[388] and recently it has been shown that E₂ can also increase Bcl-2 through Akt-dependent CREB activation [381].

Interestingly, estrogen dependent regulation of the Bcl-2 family of proteins has also been implicated in neuroprotection against excitotoxicity, a form of neuronal injury implicated in AD neurodegeneration (reviewed in [29,280]). Evidence suggests that in AD, A β toxicity and glutamate excitotoxicity may cooperatively activate pathways leading neuronal death. Glutamate-induced excitotoxic injury is potentiated by A β . In cell culture paradigms, the combination of sub-lethal concentrations of glutamate combined with sub-lethal levels A β yields robust neuronal loss [189,215]. Such degenerative interactions are predicted to occur in AD because the AD brain exhibits both A β accumulation and evidence of glutamate injury. Whether upstream and or downstream pathways of A β and glutamate action are responsible for their synergistic toxic effects is unclear. Glutamate excitotoxicity leads to calcium dysregulation and oxidative stress, and excitotoxic neuron death is mediated in part by apoptosis (reviewed in [64]).

Several studies have demonstrated that estrogen reduces excitotoxic neuronal death induced by glutamate agonists in cell culture [43,236,275,317,315,319]. For example, Dorsa and colleagues found that estrogen inhibited neuronal death in murine cortical cultures following excitotoxic insult, an effect that could be pharmacologically blocked with the ER antagonist, tamoxifen [315]. Further, Brinton and colleagues found estrogen to promote intracellular Ca²⁺ accumulation in neuronal cultures treated glutamate at physiological doses, while inhibiting intracellular Ca²⁺ accumulation following treatment with excitotoxic glutamate doses [236]. Similar observations of estrogen neuroprotection following excitotoxic challenge have been reported by several groups [124,275,354].

Estrogen has also been shown to regulate the extent of excitotoxic injury in rodent models [15,14,55,286]. For example, administration of exogenous E₂ to ovariectomized (OVX) rats has been reported to protect against kainate-induced neuronal loss [14]. Additionally, depletion of endogenous estrogen levels may increase susceptibility to excitotoxicity, with pronounced kainate-induced neural loss observed in intact rats during proestrus or following OVX [15]. Similarly, we observe neuroprotection against kainate lesion following administration of estrogen to OVX rats [55,286].

Interestingly, estrogen neuroprotection against excitotoxic injury shares mechanistic similarities with protection against A β -induced apoptosis. That is, estrogen regulation of the Bcl-2 family is implicated in protective actions against glutamate-related injury [232,234,316,388]. Brinton and colleagues found that estrogen mediated neuroprotection against glutamate excitotoxicity by promoting mitochondrial Ca²⁺ sequestration, and this was associated with increased expression of Bcl-2 [232]. Estrogen dependent modulation Bcl-2 following excitotoxicity may be mediated by rapid, non-genomic ER-dependent signaling mechanisms [387,388]. Estrogen activates an ER-dependent Src/ERK/CREB signaling pathway that leads to upregulation of Bcl-2 [364]. In contrast, others suggest that estrogen may regulate Bcl-2 family expression through a direct genomic mechanism. Supporting this we have described an estrogen responsive element (ERE) on the Bcl-x gene [259], while others describe EREs on Bcl-2 [83,256]. These pathways are summarized in Fig. 1.

In addition to regulation of the Bcl-2 family of proteins, estrogen has also been implicated in neuroprotection against many other prominent features of the AD-neurodegenerative cascade including inflammation and oxidative stress. Many studies indicate that A β may be contribute to AD-related oxidative stress [25,123,214] and deposition of A β may activate microglia and promote inflammation [291,338]. Abundant evidence indicates that estrogen is a potent inhibitor of oxidative damage [340] and hydrogen peroxide mediated neuronal death [27,26,124]. Estrogen mediates these antioxi-

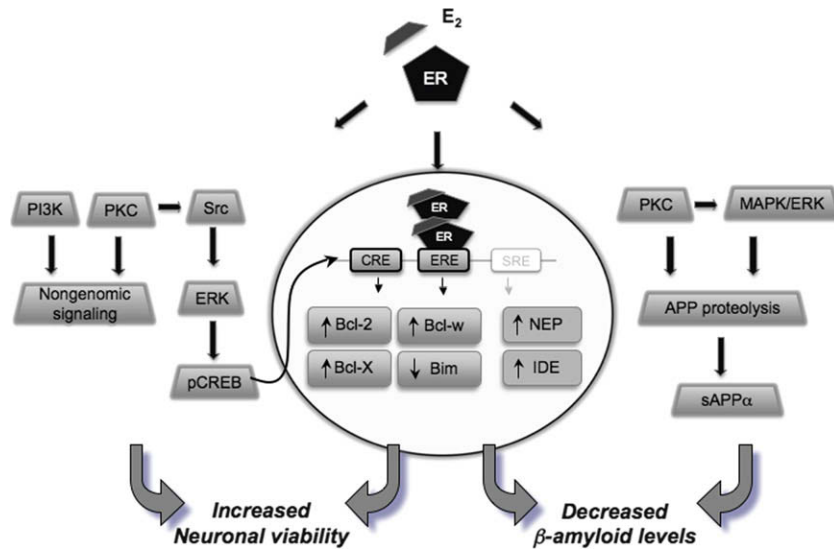


Fig. 1. Estrogens activate neuroprotective pathways that may attenuate Alzheimer's disease. Estrogens including 17 β -estradiol (E₂) reduce neuronal apoptosis by (i) non-genomic signaling cascades, including activation of PI3 K, protein kinase C (PKC) and Src/ERK pathways, and (ii) genomic pathways utilizing CREB response elements (CRE) and estrogen response elements (ERE) on members of the Bcl-2 family of genes including Bcl-2, Bcl-x, Bcl-w, and Bim. Similarly, estrogens decrease levels of the AD-related protein A β by (i) non-genomic signaling that promotes non-amyloidogenic processing of the A β precursor protein (APP), and perhaps (ii) classic genomic mechanisms that may involve ERE, CRE, and other steroid response elements (SRE) on the A β -catabolizing enzymes neprilysin (NEP) and insulin degrading enzyme (IDE).

dant effects through ER-independent mechanisms, acting as a free radical scavenger owing to its phenolic structure [279,278,324,325]. However, these neuroprotective effects are only elicited at supraphysiological estrogen dosages [27,202], thereby limiting the clinical relevance of these neuroprotective actions of estrogens. In contrast, the anti-inflammatory actions of estrogen are mediated by ER-dependent mechanisms and may provide preventative or therapeutic benefit to a range of neurodegenerative diseases where neuroinflammation is a major degenerative process. Pluripotent effects of estrogen have been described on glial function and activation. Estrogen may suppress reactive gliotic responses associated with traumatic injury and neurodegeneration [109,111], while also promoting the neuroprotective properties of astrocytes by increasing arborization and promoting synaptogenesis [80,323]. Interestingly, estrogen has been found to attenuate microglial activation only when estrogen treatment was given to the cultures prior to inflammatory insult, indicating estrogen does not have the capacity to modulate inflammatory reactions once microglial activation has been initiated [341]. This suggests the anti-inflammatory benefits of estrogen may be limited to prevention of AD rather than treatment.

Another potentially significant neuroprotective action of estrogen that is highly relevant to AD and related neurodegenerative disorders is inhibition of pathological tau hyperphosphorylation. Both estrogen and progesterone can modulate activities of kinases and phosphatases involved in regulating levels of tau phosphorylation. Specifically, E₂ and P4 regulate tau phosphorylation through the glycogen synthase kinase-3 β (GSK-3 β) pathway [8,122]. Estrogen can reduce GSK-3 β activity [122], and progesterone can decrease expression of both tau and GSK-3 β . Estrogen can also lower tau hyperphosphorylation through the wnt signaling pathway and a gene called dickkopf-1 [386] as well as through the protein kinase A pathway [204]. These results demonstrate some of the first insights into the mechanism behind estrogen neuroprotection in tau-related disorders.

The described neuroprotective actions of estrogen against AD-related insults are largely mediated by activation of estrogen receptors (ER). It has been well established that both ER subtypes are widely distributed in the brain, including in brain regions

affected in AD such as the hippocampus, frontal cortex, and amygdala [144,310,309]. Recently, changes in the subcellular distribution of ERs in hippocampal neurons have been implicated in AD pathogenesis [205]. Specifically, the shift of ER α from the nucleus to the cytoplasm may decrease the development of AD pathology in humans [155] and transgenic mice [181]. In addition, recent studies have demonstrated that ER α levels in the frontal cortex correlated with mini-mental state examination scores in women with end-stage AD [185] and that specific allele differences in ER α are correlated with an increased risk for AD in women with Down syndrome [296]. Also, ER β immunoreactivity is reportedly increased in the hippocampus compared to age-matched controls [292]. Taken together, these studies suggest that the expression of ER α / β in the AD brain may play an integral role in the neuroprotective actions of E₂. These effects are discussed in several recent reviews [38,240].

Both ER subtypes ER α and ER β are implicated in mediating estrogen neuroprotection, although their relative contributions have been incompletely defined. Selective expression of ER α versus ER β in neural cell lines has suggested a more important role of ER α in mediating neuroprotection in some studies [187] but significant contributions from both ER α and ER β in others [97,203,218]. Cell culture studies utilizing selective ER α (propylpyrazole triol, PPT), and ER β agonists (diarylpropionitrile; DPN) to study estrogen neuroprotection typically report similar levels of protection from both agonists, although some evidence suggests greater activity of the ER α agonist PPT [28]. Our studies in primary neuron culture indicate comparable levels of neuroprotection against A β from E₂, PPT, and DPN, suggesting potential contributions from both ER α and ER β in estrogen neuroprotection [67]. However, our data also suggested potential differences between ER subtypes in terms of protective mechanisms, with PPT but not DPN inducing PKC-dependent neuroprotection [67]. Similarly, Brinton and colleagues find that PPT and DPN closely mimic E₂ protection from glutamate excitotoxicity, including activation of ERK signaling and upregulation of Bcl-2 expression [387,388]. They also reported differences between the agonists in which DPN effects showed greater calcium dependence [387]. Collectively, available evidence suggests that both ER α and ER β likely contribute to neuroprotection against

AD-related insults but that each may mediate protection by preferentially activate different signaling pathways.

4. Estrogen regulation of β -amyloid accumulation

In addition to increasing neuronal resistance to AD-related insults, estrogen may also protect against AD by preventing the key initiator of AD pathogenesis, accumulation of $A\beta$. Steady state levels of $A\beta$ are influenced by opposing pathways of $A\beta$ production and $A\beta$ clearance, both of which appear to be regulated by estrogen. Estrogen regulation of $A\beta$ was first suggested by cell culture experiments focused on $A\beta$ production. Early studies demonstrated that estrogen modulates processing of amyloid precursor protein (APP), the transmembrane parent protein of $A\beta$ [106].

The majority of APP is metabolized by two competing pathways, the amyloidogenic and non-amyloidogenic pathways. In the amyloidogenic pathway, thought to occur following endocytosis of cell-surface APP, APP is first cleaved by β -secretase (BACE) to liberate β -APPs. The C-terminal fragment (C99/ β -CTF) is left embedded in the membrane and is cleaved by the γ -secretase enzyme liberating the $A\beta_{40}/A\beta_{42}$ peptides. It is thought that another fragment is also released termed the APP intracellular domain (AICD), which can translocate to the nucleus and activate gene transcription. In the non-amyloidogenic pathway, which is the predominant pathway, APP is cleaved within the $A\beta$ domain by α -secretase to liberate a neuroprotective, secreted form of APP (α -APPs). A C-terminal fragment (C83/ α CTF) is left embedded in the membrane for further cleavage into non-amyloidogenic fragments [297,343].

Estrogen appears to regulate $A\beta$ levels at least in part by promoting the non-amyloidogenic cleavage of APP, precluding production of the $A\beta$ peptide. In the human kidney 293 cell line, E_2 has been shown to reduce the level of $A\beta$ peptide in a concentration-dependent manner [59]. Further, some preliminary results suggest that in a clinical setting, short-term E_2 treatment is able to reduce plasma levels of $A\beta$ in post-menopausal women naïve to HT [20], although the significance of plasma $A\beta$ in terms of both AD pathogenesis and diagnostic value remains controversial.

How estrogen regulates APP processing is not clear, although multiple pathways have been implicated. First, most data suggest that estrogen increases the α -secretase pathway of APP processing [171,213,366,385]. There is evidence that estrogen can promote the α -secretase pathway via activation of extracellular-regulated kinases 1 and 2 (ERK1 and ERK2) signaling [213], a well-established estrogen signaling pathway [319,335,353]. The action of estrogen on the ERK components of mitogen-activated protein kinase (MAPK) signaling pathway and APP generation are rapid and may be ER independent [213]. Estrogen may also regulate APP processing through protein kinase C (PKC)-dependent pathways. PKC signaling is a strong activator of non-amyloidogenic APP processing [74,190,242]. Further, estrogen is a significant activator of PKC in both neuron culture [69,68] and in brain [11,268,299]. Consistent with this possibility, a recent cell culture study has shown that estrogen activation of α -secretase APP processing is blocked by PKC inhibitors [385]. However, not all studies demonstrate such straightforward results. For example, an *in vitro* study demonstrated that E_2 is capable of increasing the production of sAPP α but not reducing the release of $A\beta$ in cortical neurons over-expressing APP_{swe} [344].

Some evidence also suggests that estrogen may promote non-amyloidogenic APP processing by altering APP trafficking. Specifically, Greenfield et al. reported that estrogen promoted the secretion of APP containing vesicles from the primary site of amyloidogenic APP processing, the trans golgi nucleus, thereby decreasing available APP substrate for $A\beta$ formation [134]. In addition

to promoting the non-amyloidogenic APP processing pathway, estrogen has also been implicated in the modulation of APP levels through the regulation of alternative splicing [333] and APP over-expression post-injury [307], thereby altering substrate for APP processing and subsequent $A\beta$ production.

Importantly, subsequent studies demonstrated that estrogen also functions as a regulator of $A\beta$ in animal models. For example, the depletion of endogenous estrogen by OVX in guinea pigs increased the levels of soluble $A\beta$ in brain, an effect partially reversed by E_2 treatment [258]. This estrogen action may be sex-dependent since androgen but not E_2 treatment reduced elevated $A\beta$ levels resulting from orchietomy (ORX) of adult male rats [271]. A similar pattern of E_2 regulation of $A\beta$ has been observed in several transgenic mouse models of AD. That is, OVX is associated with increased $A\beta$ and E_2 treatment with reduced $A\beta$ levels in Tg2576 [380,390], APP_{swe} [199], Tg2576xPS1 [368,390], and 3xTg-AD [53,54] mice. The mechanism by which estrogen regulates $A\beta$ *in vivo* has yet to be elucidated. In the APP_{swe} transgenic mouse model of AD, E_2 treatment was associated with increased sAPP α , indicating increased α -secretase APP processing [199]. However, in wild type guinea pigs, experimental manipulation of estrogen status was not associated with corresponding changes in sAPP α levels [258]. Increased levels and activity of BACE observed in aromatase knock-out mice also suggests a potential role for estrogen in the regulation of secretase expression and/or activity [380]. Further work will be needed to elucidate whether estrogen regulation of $A\beta$ in animals involves APP processing and, if so, to define the relevant upstream signaling components (e.g., MAPK, PKC).

Curiously, estrogen levels are associated with $A\beta$ accumulation only in some but not all transgenic mouse models of AD [120,133,148,380]. In the Tg2576, PDAPP, and APP_{swe}xPS1 mouse models, OVX was not associated with increased $A\beta$ levels and E_2 treatment did not reduce $A\beta$ levels. Discrepancies in the effects of estrogen on $A\beta$ levels across transgenic mouse models may reflect several differences, ranging from molecular design of the transgenic lines to variability in methodological parameters such as the timing and dosing of hormone manipulations. One potentially important methodological difference across the studies is their varying techniques for $A\beta$ quantification, each of which preferentially measures different pools of $A\beta$ ranging from soluble monomeric $A\beta$ to oligomeric and deposited forms. Whether estrogen differentially regulates these various $A\beta$ pools is currently unknown. In our laboratory, we found that estrogen decreases $A\beta$ accumulation in the 3xTg-AD mouse model as assessed by the immunoreactive load method [53,54], which detects relatively insoluble intra- and extra-cellular $A\beta$. Future studies will be needed to determine exactly which $A\beta$ pool(s) estrogen is capable of regulating and whether this contributes to observed differences in estrogen actions across models.

Discrepancies between studies on the role of estrogen as a regulator of $A\beta$ accumulation also may indicate differences in brain levels of estrogen. Recent work suggests that OVX has limitations as a strategy to fully deplete brain estrogens. For example, in the estrogen-responsive element-luciferase mouse model, which was engineered to express the non-mammalian luciferase protein in response to classical ER activation, OVX resulted in relatively high brain estrogen activity in comparison to other body regions [65]. In evaluating the role of brain estrogens in $A\beta$ regulation, Yue et al. [380] found that in the APP₂₃ transgenic mouse model OVX alone was not sufficient to remove all brain estrogen and did not result in elevated $A\beta$ levels. However, they reported elevated $A\beta$ levels after preventing E_2 formation in brain by crossing the APP₂₃ mice with aromatase knock-out mice [380]. Thus, brain levels of sex steroid hormones, which are affected not only by gonadal hormone production but also by *de novo* steroid hormone synthesis in brain (i.e., neurosteroidogenesis), may be the critical factor in

regulation of brain A β accumulation. This hypothesized importance of brain hormone levels is supported by the finding that brain levels of E₂ are lower in female AD patients in comparison to age-matched control cases [380], a finding we have recently replicated [287]. In addition, it has recently been shown that long-term OVX in female mice significantly lowers E₂ levels in the hippocampus while increasing serum levels of A β [105]. Thus, estrogen regulation of A β may depend primarily upon brain estrogen levels, which may be dependent on both ovarian and brain steroid production.

In addition to modulating the production of A β , estrogen may also promote A β clearance. One mechanism of A β clearance is through microglial degradation [282]. Estrogen has been shown to promote microglial phagocytosis [47,267] and E₂ treatment increases microglial internalization of A β in microglia of both murine [143] and human origin [200]. Estrogen treatment has also been found to reduce A β accumulation in rats following intracerebroventricular A β injection [143]. Correspondingly, increased A β burden and impaired microglial A β clearance has been reported in an estrogen deficient transgenic mouse model of AD [380]. Estrogen has also been implicated in the regulation of levels of two major A β degrading enzymes, insulin degrading enzyme and neprilysin. Both of these enzymes are significant regulators of A β levels and their regulation and activities are implicated in AD pathogenesis [331,337]. A few recent studies suggest that estrogen depletion by OVX can decrease neprilysin activity in female rat brain, an effect reversed by E₂ replacement [163]. Thus, estrogens may influence A β clearance through regulation of neprilysin, although this pathway may involve an androgen responsive element on the neprilysin gene [365]. Estrogen pathways of A β -lowering are illustrated in Fig. 1. Given the significance of A β accumulation to AD pathogenesis, future studies must clearly define the role of estrogen in regulating both A β production and clearance pathways and how they are affected by differences in E₂ brain levels.

5. Aging effects on estrogen responsiveness

Whether the described neuroprotective effects of estrogen prove to have therapeutic relevance to age-related neural diseases including AD will depend in part on the brain's responsiveness to estrogen with advancing age. One of the primary criticisms of WHIMS and other clinical studies of estrogen-based HT is that the intervention may have been initiated beyond a critical window of opportunity [118,265,276]. This notion refers to the possibility that the aging brain may lose responsiveness to sex steroid hormones after an extensive period of low hormone levels, such as occurs following menopause. According to this argument, HT may exert estrogenic effects only if begun near the time of menopause. Since most participants in the WHIMS study were many years beyond menopause, the critical window hypothesis could explain in part the absence of beneficial neural actions of HT. Consistent with this position, several clinical studies have noted that HT is associated with positive neural effects in women showing menopause symptoms (e.g., flushing), suggesting retained estrogen responsiveness [154,153,157,306,305]. Although this issue remains to be fully evaluated, results from the Multi-Institutional Research on Alzheimer Genetic Epidemiology study show that HT was associated with reduced AD risk only in post-menopausal women that initiated treatment at a relatively younger age [154].

The critical window notion of an age-related loss in brain responsiveness to estrogen is supported by studies in animal models. One experimental approach to address this issue is the "gap paradigm" in which OVX animals are treated with E₂ replacement after short versus long periods of time, a design that assesses the effects of prolonged hormone deprivation on subsequent hormone

exposure. In general, results from gap studies indicate diminished estrogen responses following many months of hormone absence. For example, E₂ and E₂ plus progesterone replacement was associated with improved spatial memory on the delayed match task when administered within 3 months post-OVX, but not when hormone treatment was delayed 10 months post-OVX [115]. Further, E₂ given immediately after OVX in rats improved spatial memory performance on radial arm maze while E₂ given after 5 months of OVX did not [78]. Recently, it was reported that E₂ given immediately after OVX but not after a 5 months delay was able to increase hippocampal ChAT protein levels in middle-aged OVX wild type rats [35]. Although this topic requires further work to elucidate the key factors and underlying mechanism(s), the data generated thus far suggest that in laboratory animals, the brain can show reduced hormone responsiveness after an extended period of hormone depletion.

Another approach to evaluate the role of aging in neural estrogen responsiveness has been to simply compare the effects of estrogen in young adult versus aging female rodents. This type of study is critical in determining the efficacy of female sex steroid hormones before and after the onset of reproductive senescence, the result of normal reproductive aging in female rodents (reviewed in [58]). While reproductive aging in rodents does not mimic menopause, rodents do experience a pattern of estrus cycle irregularity followed by reproductive senescence that is similar in some respects with the perimenopause period in women [95]. Age-related reproductive changes in female rodents typically become apparent between 9 and 11 months of age, depending upon species and strain. For example, the age-related estrus cycle changes have been well characterized in the C57Bl6 mouse strain [95]. Like women, these female mice demonstrate a large range of variability in cycle irregularity and hormone levels during middle and old age. These mice experience cycle cessation between 11 and 16 mo of age during which a substantial proportion enter a period of persistent vaginal cornification lasting 2–4 months. After this variable period, all mice enter an irreversible final stage of permanent diestrus characterized by low E₂ and progesterone levels and elevated luteinizing hormone levels [114], ovarian follicle depletion, and loss of reproductive capability [126].

In estrogen neuroprotection studies, middle-aged female rodents undergoing reproductive senescence show diminished effects in some studies but retained protection in others. First, several reports suggest that the neural effects of OVX and E₂ treatment are diminished in aging female rodents. Studies by Sohrabji and colleagues suggest that reproductive senescence in middle-aged female rats reduces protective estrogen actions. For example, in assessing estrogen regulation of neurotrophin expression, they found that E₂ treatment in OVX young adult female rats (age 3 mo) increased levels of BDNF, trkA, and trkB in olfactory bulb and diagonal band of Broca, whereas E₂ treatment of middle-aged (17 months) OVX reproductively senescent, female rats showed either no increase or decreased expression of neurotrophins [175]. Similar studies by this research group found that, in comparison to young adult female rats, reproductively senescent female rats show several alterations in estrogen-mediated effects including cytokine and growth factor responses following injury [176,237] and blood-brain-barrier permeability [18]. In another paradigm, Finch and colleagues reported differences between young adult (3 mo) and middle-aged (18 mo) female rats on estrogen regulation of compensatory neuronal sprouting following entorhinal cortex lesion. In comparison to young rats, older rats no longer exhibited an OVX-induced decrease in sprouting and showed differences in regulation of GFAP mRNA [321]. However, some neural actions of estrogen appear to remain relatively robust during aging. For example, E₂ treatment in middle-aged OVX rats enhanced performance on hippocampal-dependent spatial

memory tasks [78] as well as altered the hippocampal expression of several genes [1].

In neural injury paradigms, there is evidence of both retained and altered estrogen neuroprotection. In reproductively senescent female rats, both E_2 and progesterone reduced infarct size in a model of stroke injury [5]. Wise and colleagues reported similar neuroprotective effects of E_2 treatment in OVX young (3–4 mo) and middle-aged (9–12 mo) rats in the middle cerebral artery occlusion (MCAO) model of stroke [85,360]. In our laboratory, we have found that reproductively senescent female rats show evidence of altered but not completely diminished estrogen neuroprotection. In young adult (3 mo) female rats, an excitotoxic lesion to hippocampus induced by systemic application of the glutamate agonist kainate is significantly worsened in animals OVX for 2 weeks prior to the lesion. In a similar paradigm, we find that E_2 treatment, initiated at the time of OVX, significantly increases the number of viable hippocampal neurons following kainate lesion [286]. However, in reproductively senescent (14 mo) rats, OVX was not associated with further cell loss, although E_2 replacement still resulted in a significant increase in neuron survival [55]. In a model of spinal cord injury, the effects of E_2 treatment in young (2 mo) versus middle-aged (12 mo) sham-OVX and OVX female rats were investigated. Treatment with E_2 protected against several indices of injury in both young and aging OVX rats, however in ovary-intact rats E_2 neuroprotection was lost in middle-aged rats [60].

Interestingly, emerging data suggest that patterns of reproductive aging in female rats may contribute to altered estrogen responsiveness with age. A recent study compared estrogen protection using the MCAO stroke model in middle-aged female rats stratified by their stage of reproductive aging: reproductively senescent rats that had entered a persistent acyclic state, and rats with normal but lengthened cycles. In comparison to the middle-aged cycling rats, the reproductively senescent rats exhibited larger lesions and no longer showed reduced lesion size following E_2 treatment [298]. Our recent data also suggest that responsiveness to estrogen protection vary according to status of reproductive aging. In the kainate lesion model, we observed that E_2 was most protective in rats showing an acyclic state of persistent vaginal cornification compared to rats with present, albeit irregular cycles [55]. Thus, although additional studies are necessary to define the relationships, it is reasonable to hypothesize that patterns of reproductive aging affect estrogen neuroprotection. Such findings are consistent with the “critical window” hypothesis of HT and have important implications for the future of clinical use of estrogen-based therapies.

Why the brain shows is less responsive to estrogen with age is unclear, but age-related decreases in ER expression as well as E_2 binding to ERs in aged rat brain have been reported [58,289,361]. Estrogen actions also show age-related changes in other estrogen responsive tissues, including uterus, bone and heart. For example, the uterus becomes less responsive to estrogen with increasing age, showing smaller OVX-induced decreases in uterine weight [367] and uterotrophic effects of estrogen only when treated soon after OVX [78]. Further, while most studies demonstrate that the trophic effects of E_2 on bone extend through middle-age, some studies suggest that as aging progresses, this effect is altered from an $ER\alpha/\beta$ -mediated effect to only an $ER\alpha$ mediated one [168]. Interestingly, increased $ER\alpha$ predominance has also been suggested to underlie age changes in neural estrogen responsiveness [19].

Taken together, available experimental research suggests that although estrogen neuroprotection is often observed in aging rats, it can also be significantly diminished. Still uncertain is how the many AD-related facets of estrogen neuroprotection may be impacted by aging. Additional studies are necessary to determine

the extent to which observed age-related changes in estrogen responsiveness may be delayed, prevented and or reversed. This phenomenon has important implications for the future of HT in post-menopausal women. Ongoing clinical and animal studies promise to shed new insight into this issue in the next few years.

6. Progesterone interactions with estrogen in regulation of Alzheimer's disease

Estrogen actions must also be considered with respect to the second major class of ovarian hormones, progestogens. Progesterone has long been recognized as a regulator of estrogen, particularly in the female reproductive system (reviewed in [130]), where it often antagonizes estrogen action. Clinically, progestogens are typically a key element of HT that are thought to minimize deleterious effects of estrogen. Perhaps most importantly, in experimental paradigms progesterone can inhibit human endometrial cancer cell growth [77,79] and in clinical studies progestogens are associated with reduced risk of endometrial cancer [129,257].

In clinical studies of AD and dementia, most results indicate similar outcomes with both estrogens alone (ie., CEE) and estrogens in combination with progestogens (ie., CEE + MPA). In the WHIMS trial, a comparison between the CEE alone and CEE + MPA arms of the study raised the question that the clinical efficacy of HT may be dependent upon the hormone constituents within. Both the CEE and CEE + MPA arms failed to demonstrate a protective effect and both actually increased the risk of dementia compared to women receiving placebo [311]. Notably, the CEE alone arm had a negative impact on global cognitive function, however this negative impact was worsened when pooled with the data from the CEE + MPA arm [91]. Interestingly, short-term HT treatment in women with existing AD was associated with some benefits on psychiatric symptoms in the CEE group but not in the CEE + MPA group [162]. These and related issues suggest that the inclusion of a progestogens may influence the effects of CEE alone on cognitive outcomes and risk of dementia in post-menopausal women [75].

Despite the common use of the progestogen MPA in current HT paradigms, researchers have only relatively recently begun to investigate the effects of progesterone on the CNS in regards to aging and neurodegenerative diseases. Although compelling experimental evidence indicates numerous protective actions of estrogen and progesterone when delivered independently [44,295], comparatively less is known about interactions between estrogen and progesterone when they are administered together. Interestingly, accumulating observations indicate that progesterone often antagonizes rather than synergizes with estrogen-mediated neuroprotective actions. This incomplete understanding highlights the need to determine the interactive effects of these hormones in the brain.

Findings from an increasing body of research have begun to provide insight into how beneficial neural actions of estrogen are affected by interactions with progesterone. Findings from both *in vitro* and *in vivo* paradigms suggest that progesterone treatment can antagonize estrogen neuroprotection. For example, long-term progesterone treatment in aged (23–24 mo) OVX female rats blocked estrogen upregulation of brain derived neurotrophic factor, nerve growth factor, and neurotrophin 3 [32]. In a similar paradigm of hormone treatment in middle-aged OVX rats, estrogen-induced improvement in spatial memory performance was blocked by co-administration of progesterone [33]. More specific to neuron viability though are recent studies from our laboratory demonstrating that progesterone blocks estrogen neuroprotection from excitotoxic injury in female rats. In both young adult (3 mo) [286] and middle-aged (14 mo) [55] OVX

rats, continuous E₂ treatment reduced kainate-induced neuron loss in hippocampus CA2/3 whereas continuous progesterone did not significantly affect neuron viability. Importantly, when progesterone was included with E₂, estrogen neuroprotection was no longer observed [55,286]. Similarly, Brinton and colleagues recently reported that E₂ and progesterone administered independently to wild type rats enhanced several markers of brain mitochondrial function but, when replaced in combination, the hormones showed attenuated rather than enhanced responses [167].

While the mechanisms behind this antagonistic property remain unknown, our laboratory has begun to investigate the possibility that progesterone modulates estrogen function in part by regulating ER expression. We have observed in primary neuron culture that low physiological concentrations of progesterone rapidly downregulate mRNA levels of both ER α and ER β [174]. Functionally, this progesterone-mediated decrease in ER expression was associated with inhibition of both ERE-mediated transcriptional activity and estrogen neuroprotection against apoptosis [174]. Although progesterone treatment by itself did not significantly affect apoptosis in this paradigm, abundant evidence demonstrates that progesterone can activate several neuroprotective cell signaling pathways, including Akt [318] and ERK [233,232] signaling and upregulation of the anti-apoptotic protein Bcl-2 [232]. Further, as reviewed in an accompanying article, progesterone can significantly protect neurons against numerous insults [44,295]. Thus, independently estrogen and progesterone can exert protective actions, but in combination they can inhibit each other and thus fail to protect. Perhaps not unexpectedly, the interactive neuroprotective effects of the two female sex steroid hormones are not quite so straightforward. Besides antagonistic effects, progesterone can also synergistically interact with estrogen to promote beneficial neural effects including increased spine density [100,313]. In OVX female rats, acute progesterone treatment (2–6 h) was observed to augment the estrogen-induced increase in spine density, whereas prolonged progesterone treatment (18 h) blocked the estrogen effect [362]. Thus, a key factor in understanding estrogen neuroprotection and perhaps its relevance to HT in post-menopausal women is elucidation of the interactions between estrogen and progesterone.

A similar progesterone regulatory relationship also appears to affect estrogen protection from indices of AD-like neuropathology. In recent studies, our laboratory has begun to investigate how progesterone interacts with estrogen in regulating A β accumulation in the 3xTg-AD transgenic mouse model of AD. As discussed above, we found that 3 months following OVX of young adult female 3xTg-AD mice, there were robust increases in A β accumulation and tau phosphorylation and impaired performance in spontaneous alternation behavior in comparison to sham OVX 3xTg-AD mice [54]. Continuous E₂ treatment during the 3 month OVX period largely prevented the worsening of AD-like neuropathology and behavioral performance, however continuous progesterone by itself did not affect OVX-induced changes in either A β accumulation or behavior. Consistent with an antagonistic role of progesterone, we observed that co-treatment with progesterone antagonized the beneficial effect of estrogen in lowering A β accumulation [54]. However, estrogen and progesterone co-treatment did show a beneficial effect in reducing levels of tau hyperphosphorylation, suggesting positive estrogen-progesterone interactions. Consistent with a beneficial role of progesterone, Frye and colleagues report that long-term progesterone treatment following OVX in another transgenic mouse model of AD was associated with some cognitive benefits [104]. Taken together, these studies provide the first information to date on the interactive effects of estrogen and progesterone on AD-like neuropathology and demonstrated the potential for both positive and negative outcomes in terms of protection from AD-related neuropathology.

Despite evidence of antagonistic neural effects of progesterone on estrogen neuroprotective actions, progestogens are still deemed a necessary component of HT in women with a uterus. Therefore, HT may need to be optimized to maximize the benefits and minimize the unwanted consequences associated with estrogen-progestogen interactions. One possible strategy is the use of cyclic hormone delivery rather than the continuous, combined treatment that is currently common to HT. Initial clinical evaluation of cyclic progestogen exposure has been completed and more is underway. Several clinical HT trials have incorporated a comparison between continuous versus cyclic progestogen in post-menopausal women on osteoporosis and cognitive function. For example, two completed studies have both demonstrated that long-term HT with a cyclic progestogen dose was able to increase bone mineral density in post-menopausal women [239,56]. Similarly, a continuous estrogen plus cyclic progestogen paradigm is currently employed in the KEEPERS (Kronos Early Estrogen Prevention Study) Cognitive and Affective Study, a randomized, placebo-controlled, double-blind study investigating the effects of HT in post-menopausal women who are within 36 months of their final menstrual period [357]. This and similar new trials promise to provide important insight on the efficacy of cyclic hormone delivery and the hypothesized importance of a critical window of hormone intervention.

Experimental studies in animal models lend support for the use of cyclic rather than continuous progesterone to optimize estrogen neuroprotection. For example, Gibbs have demonstrated that short-term treatment with E₂ and progesterone can improve cholinergic function [116], with maximal benefit resulting from cyclic administration of estradiol and progesterone and the least benefit from continuous combined treatment [115]. In our laboratory, we have begun investigating the potential utility of cyclic progesterone against AD neuropathology by comparing cyclic versus continuous progesterone in the presence and absence of continuous E₂ in OVX 3xTg-AD mice. Our results show that whereas continuous progesterone largely inhibits estrogen protection from AD-related neuropathology, cyclic progesterone appears to significantly increase estrogen protection against A β accumulation, tau phosphorylation, and working memory deficits (unpublished observations). These exciting new findings support the hypothesis that estrogen-progesterone interactions can yield additive neuroprotection and that cyclic hormone delivery may be a critical parameter.

7. Age-related androgen depletion and Alzheimer's disease

In parallel to the relationships between age-related estrogen loss in women and increased AD risk, testosterone is depleted as a normal consequence of aging in men and is linked with elevated risk of AD. As discussed above, a significant biological event in women that contributes to the role of aging in AD is menopause and the resultant loss of the sex steroid hormones estrogen and progesterone. Although men do not experience menopause *per se* (i.e., a cessation of reproductive ability, nearly complete loss of sex steroid hormones), men do experience a somewhat similar process termed androgen deficiency in aging males (ADAM). ADAM refers to normal, age-related depletion of testosterone and the corresponding constellation of symptoms that reflect dysfunction and vulnerability to disease in androgen-responsive tissues including brain [24,50,96,125,179,183,217,224,302]. The decline in testosterone levels begins in the 3rd decade and continues at an annual rate of 0.2–1% for total testosterone and 2–3% for bioavailable testosterone [94,131,227]. Unlike menopause, aging men do not experience comparable levels of andropause. That is, although all men exhibit significant age-related testosterone loss typically beginning in the third decade of life, men vary in the extent of testosterone loss and the corresponding severity of clinical manifestations [226,326]. It

is estimated that 30–70% of men aged 70 and older are hypogonadal, resulting in at least 5 million aging men in the US suffering the consequences of andropause and only a small minority of those receive hormone treatment [142,225]. ADAM is associated with increased risk of sarcopenia, osteoporosis, falls, frailty, and all cause mortality.

The brain is a highly androgen responsive tissue where androgens induce several beneficial actions. For example, androgens have been shown to improve mood and promote select aspects of cognition, including spatial abilities [127,172] and verbal fluency [4]. Men with a higher free testosterone index have been found to perform better on visual and verbal memory and exhibited better long-term memory [23], while those with a low free testosterone index can show decreased visual memory, visuomotor scanning, verbal memory, and visuospatial processing [219]. ADAM has been associated with impaired cognitive performance in some but not all studies [141,219].

One recently established consequence of ADAM is an increased risk for the development of AD. Several [161,160,159,274,352] but not all [255] studies have identified a relationship between low circulating levels of testosterone and a clinical diagnosis of AD. In these studies, the relationship between testosterone and AD appears to be strongest when circulating levels of free rather than total testosterone are examined, and when mean ages are under 80 years [161,160,159,249]. The relationship between testosterone and AD may be influenced by the presence of at least one apolipoprotein $\epsilon 4$ allele, a genetic risk factor for AD [322]. Specifically, men with at least one $\epsilon 4$ allele had lower levels of testosterone than men without an $\epsilon 4$ allele [160]. Animal studies support a link between apolipoprotein E, testosterone, and AD [269,270].

Although the majority of studies have identified a relationship between low testosterone and increased AD risk in men, most were unable to determine whether low testosterone contributes to the disease process or is merely a result of it. However, two complementary studies suggest low testosterone occurs prior to or in the early stages of AD pathogenesis, and thus likely acts a risk factor. The first study compared clinical diagnosis of dementia with blood levels of testosterone in the prospective Baltimore Longitudinal Study on Aging [220]. Male subjects were followed for 4–37 years with a mean of 19 years per subject and were diagnosed as clinically normal at the time of their first testosterone measurement. Subjects that eventually received a clinical diagnosis of AD showed lower circulating levels of free testosterone. Interestingly, in those men with AD, testosterone levels were reduced at check-ups 5–10 years prior to diagnosis [220], suggesting androgen loss occurred well before clinical manifestations of the disease. Consistent with this study are findings from a study by our laboratory in which we linked low brain levels of testosterone with increased risk of AD in men [284]. First, using human post-mortem brain tissue from neuropathologically normal men, we found that levels of testosterone but not E_2 show a significant age-related decline. When we examined changes in brain levels of hormones across cases stratified by neuropathological status, we found significantly decreased brain levels of testosterone in AD cases as compared with neuropathologically normal cases even after controlling for the age-related hormone loss [284]. We also measured brain levels of androgens in cases with mild neuropathological changes, consistent with the earliest stages of AD. These cases also exhibited low testosterone levels [284], again indicating that testosterone loss occurs prior to robust pathology and thus may contribute to the development of AD. Taken together, these results suggest age-related testosterone depletion in men is a risk factor for AD.

Unlike the numerous clinical studies that have evaluated the efficacy of HT use in treating and or preventing AD in post-menopausal women, comparatively few studies have examined testos-

terone therapy in men for protective roles against age-related cognitive decline and development of dementia. Androgen therapies have been approved and used for the treatment of hypogonadism in men and are typically associated with reduced fat mass and improved muscle mass and bone density as well as increased mood, libido, and overall quality of life [31,327,332]. However, clinical evaluation of beneficial cognitive effects of testosterone therapy have been mixed. For example, a study of hypogonadal and eugonadal men found that testosterone increased verbal fluency [4]. Others report improvements in spatial cognition and working memory following testosterone treatment [62,173,172]. In contrast, some studies did not find significant changes in cognition following testosterone therapy [30,90,141,210,339].

A few studies have evaluated the effects of testosterone therapy in subjects with AD. In a small clinical study of men recently diagnosed with AD, testosterone treatment for up to 1 year contributed to improvement in both overall cognitive ability and visual spatial skills [328]. In contrast, other studies have not reported significant benefits of testosterone therapy in men with mild cognitive impairment and AD [63,206]. As with the observed inconsistencies in the literature of HT use in women, there are likely several factors that contribute to the observed differences between testosterone studies, including cognitive domains, treatment type and duration, and the age and other characteristics of the subjects.

8. Testosterone neuroprotection and Alzheimer's disease insults

One beneficial action of androgens that is hypothesized to contribute to a role in reducing risk of AD is neuroprotection. Androgens are established promoters of neuron viability during neural development as well as in adult brain following mechanical injury and disease-related toxicity. One target of androgen neuroprotection is motoneurons following axotomy [178]. In this paradigm, testosterone treatment accelerates the rate of nerve regeneration and attenuates neuron loss [164,178,177,193,194,195,330,377,379]. Similarly, following facial nerve crush in male hamsters, testosterone increased the rate of axonal growth and functional recovery [193,192]. These effects are true not only for testosterone but also its potent androgen metabolite dihydrotestosterone (DHT) [378,377,379]. In addition, the anti-androgen flutamide was able to block testosterone's neuroprotective effects on motor neurons [195], corroborating the role of androgen versus estrogen pathways. The mechanism behind this neuroprotective action appears to be through androgen regulation of trophic factors [378,379]. Recently, studies have found that in addition to long-term treatment, short-term testosterone, DHT, and estrogen treatments are protective and suggest a more direct mechanism of hormone action [164].

In addition to neuroprotective effects on motor neurons, androgens have also been found to promote neuron survival in brain regions vulnerable to neurodegenerative diseases such as Alzheimer's disease. These areas include the hippocampus and cortical regions, which are both affected in AD and rich in androgen receptors [314]. In a study by Garcia Segura and colleagues, acute testosterone treatment attenuated neuron loss in the hilus of the dentate gyrus following excitotoxic lesion in ORX male mice [16]. Interestingly, acute treatment of E_2 was also protective while DHT treatment did not protect against neuron loss in androgen depleted mice. Furthermore, the protective effect of testosterone was blocked by an aromatase inhibitor, suggesting that in this model of acute hormone treatment, estrogen is responsible for testosterone neuroprotection [16]. A study from our laboratory investigated the effect of long-term hormone replacement on neuronal death induced by excitotoxic lesion. In this study, depletion of endogenous androgens as a consequence of ORX resulted in increased hippo-

campal neuron loss following kainate lesion in comparison with sham ORX rats. However, in ORX rats treated for two weeks with DHT, this increase in cell loss was blocked [272]. In contrast to the results of Garcia Segura and colleagues, we found that rats treated with E₂ did not exhibit decreases cell loss following kainate lesion. This suggests that androgen regulation of neuroprotection in this paradigm is a result of androgen rather than estrogen pathways. Behavioral responses to seizures were measured and no differences were observed between groups suggesting that the observed androgen neuroprotection was not a result of decreased seizure severity [272]. Although we did not observe an androgen-mediated effect on seizure severity, other studies have found a significant effect of androgens on seizure severity. In studies by Frye and colleagues, testosterone decreased neuron loss by inhibiting seizure activity [102,103]. Subsequent studies found that protection was due to DHT metabolism to 5 α -androstane-3 α , 17 α -diol, an androgen that acts on GABA_A receptors. GABA activation reduces excitatory signaling, which in turn attenuates seizure activity thereby minimizing lesion severity [87,88,277].

While *in vivo* models provide valuable insight into androgen neuroprotection, neuron culture models of toxicity have proven valuable in defining the underlying molecular mechanisms. Cell culture models of neural injury have demonstrated testosterone protection against serum deprivation [45,138], A β toxicity [229,260,384], and oxidative damage [2]. Testosterone neuroprotection against serum deprivation-induced apoptosis requires activation of an androgen receptor (AR) dependent mechanism [138]. Specifically, the anti-androgen flutamide attenuated protection while an aromatase inhibitor had no effect on neuron viability [138]. Consistent with this androgen-mediated mechanism of androgen neuroprotection is an early study from our laboratory, which found that testosterone neuroprotection against toxicity induced by extracellular A β results from DHT not E₂ [260]. DHT treatment in this paradigm was equally as protective as testosterone, but use of an anti-estrogen droloxifene failed to block protection, suggesting androgen pathways are responsible for neuroprotection [260]. Further, we observe androgen neuroprotection in PC12 cells transfected with AR but not in either untransfected PC12 cells or those transfected with empty vector [229].

There are several potential mediators of androgen neuroprotection downstream of AR. Some evidence suggests androgen neuroprotection may be mediated through attenuation of oxidative stress [2]. Another potential mechanism involves a classic genomic mechanism, increased expression heat shock proteins. Androgen attenuation of A β induced toxicity was associated with elevated levels of heat shock protein 70, which is known to participate in protective responses against cellular stress and neurodegeneration [384]. Recent work from our lab identified a non-genomic, AR-dependent mechanism involving activation of a mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase (ERK) pathway [229]. We observed that physiological levels of testosterone and DHT rapidly and transiently activated MAPK/ERK signaling in cultured hippocampal neurons. Downstream of ERK, we found that androgens activated p90 kDa ribosomal S6 kinase (Rsk), which in turn phosphorylates the pro-apoptotic protein Bad. Phosphorylation of Bad results in its inactivation of Bad, thereby tilting the balance of apoptosis towards increased cell viability. Pharmacological inhibition at any step of this pathway prevents both phosphorylation of Bad and androgen neuroprotection [229]. Confirming the non-genomic nature of this pathway, we found that in this neuron culture paradigm the classic anti-androgens flutamide and cyproterone acetate mimicked neuroprotection against apoptotic insults afforded by testosterone and DHT even though they also blocked classic genomic actions of androgens [231]. Further, protective actions of flutamide and cyproterone acetate were only observed in AR-containing cell lines. Whether activation of protective andro-

gen pathways requires membrane AR, intracellular AR, or both is unclear. We observed that testosterone conjugated to albumin – which is designed to prevent cell entry and thus permit only activation of membrane receptors – was ineffective in activating protective MAPK/ERK androgen signaling [229]. Similarly, Gatson and colleagues reported that while DHT phosphorylates both ERK and Akt, albumin-conjugated DHT resulted in dose-dependent suppression of ERK signaling in glioma cells expressing AR [113]. Pathways of androgen neuroprotection are summarized in Fig. 2.

In contrast to these observations of androgen neuroprotection, there appear to be circumstances in which androgens fail to protect against neural injury and can even exacerbate insults. For example, Dluzen and colleagues found that E₂ but not testosterone reduces methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) nigrostriatal dopaminergic toxicity [82]. Further, testosterone has been found to exacerbate neuron loss following middle cerebral artery occlusion (MCAO) [372,371]. In this model removal of testosterone 6 h prior to MCAO reduces lesion volume by as much as half [372,371]. It is not clear whether the absence of androgen neuroprotection in these paradigms reflects roles of brain region, insult, and or other factors. One important issue in at least some studies may be androgen concentration. That is, at physiological low nanomolar levels testosterone can protect against excitotoxicity in cultured neurons, but worsens cell death when present at supraphysiological micromolar levels [244]. Similarly, micromolar but not nanomolar concentrations of testosterone were associated with increased calcium signaling and neuronal apoptosis [92,112]. Thus, although there is ample evidence of androgen neuroprotection against AD-related insults, androgen effects on neuron viability may depend on a number of factors, including brain region, type of insult, and hormone concentration.

In addition to direct neuroprotection, androgens also protect against another form of neuropathology directly relevant to AD, hyperphosphorylation of tau. Abnormal, excessive phosphorylation of the cytoskeletal protein tau in the form of neuropil threads and neurofibrillary tangles is a defining neuropathological characteristic of AD and several other neurodegenerative disorders [166,355,358]. Although relatively little research has examined the relationship between androgens and tau hyperphosphorylation, available evidence does indicate that androgens are protective against this pathology. Papasozomenos and colleagues have examined the effects of testosterone and E₂ on tau hyperphosphorylation using a model of heat shock-induced phosphorylation. In this paradigm, testosterone but not E₂ prevents tau hyperphosphorylation [252,250,251]. In addition to affecting phosphorylation of tau, recent evidence suggests that androgens also regulate tau cleavage [253]. Specifically, testosterone prevented calpain-mediated tau cleavage preventing the generation of the 17-kDa tau fragment [253].

9. Testosterone regulation of β -amyloid accumulation

In addition to classic neuroprotective actions, androgens may also protect the brain from AD by regulating accumulation of A β . Initial work suggesting a relationship between androgens and A β came from a small study evaluating men treated with anti-androgen therapies for prostate cancer. Gandy and colleagues found that within several weeks following initiation of anti-androgen therapy (consisting of leuprolide and flutamide), circulating levels of testosterone and E₂ were largely depleted whereas plasma levels of A β were significantly elevated [107]. Martins and colleagues similarly reported an association between androgen depletion and elevated A β levels in males receiving anti-androgen therapy for the treatment of prostate cancer [6] and in older males suffering from memory loss or dementia [117]. To what extent these observations reflect effects of androgen versus estrogen pathways or perhaps re-

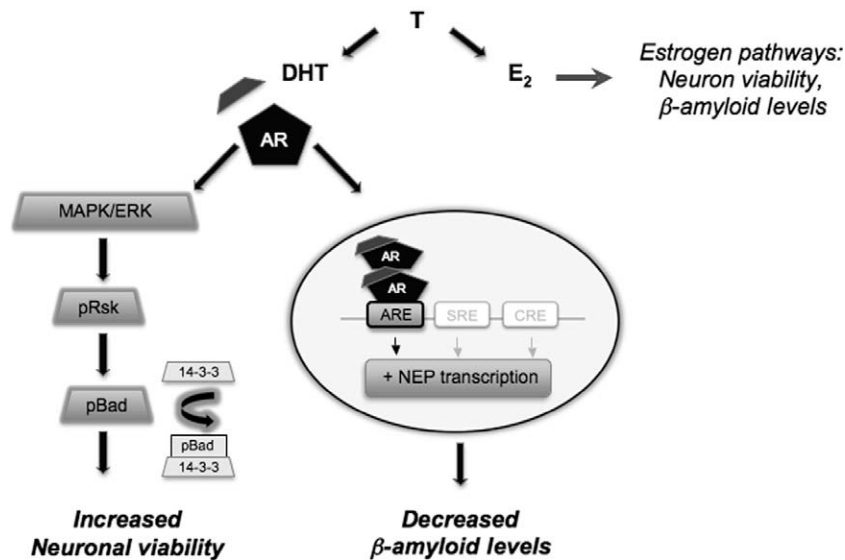


Fig. 2. Androgens activate neuroprotective pathways that may attenuate Alzheimer's disease. First, testosterone (T) is aromatized in brain to 17 β -estradiol (E₂), which activates estrogen-mediated neuroprotective pathways (summarized in Fig. 1). Second, testosterone and its metabolite dihydrotestosterone (DHT) activate AR-dependent protective pathways. T and DHT reduce neuronal apoptosis by a non-genomic signaling cascade involving activation of MAPK/ERK, followed by activating phosphorylation (p) of Rsk, and inactivating phosphorylation of the pro-apoptotic protein Bad. Also, androgens decrease levels of the AD-related protein A β by a classic genomic mechanism involving activated AR interaction with androgen response elements (ARE) on the neprilysin gene, which results in increased expression of this A β -catabolizing enzyme.

flect associated changes in gonadotropins remains incompletely resolved [13,283].

Consistent with the observations in aging men, experimental work in rodents also indicates that androgens function as endogenous negative regulators of A β . Early studies in our laboratory demonstrated that androgens but not estrogens reduce brain levels of soluble A β in male rats [271]. Specifically, we found that ORX-induced depletion of endogenous androgens was associated with a modest but significant increase in soluble A β from hemi-brain lysates. Further, DHT treatment in ORX rats resulted in a significant reduction in brain A β levels, although E₂ treatment had no effect [271]. We observed similar findings on the relationship between androgen levels and A β accumulation in the 3xTg-AD mouse model of AD. Male 3xTg-AD mice were depleted of androgens by ORX at age 3 mo, a time prior to the development of significant AD-like pathology [238]. Mice were exposed immediately to either DHT or vehicle, treatments that were maintained continuously for the next 4 months. After the treatment period, we observed significant intracellular accumulation of presumably insoluble A β in gonadally intact, sham ORX 3xTg-AD mice (age 7 mo) in the CA1 hippocampus, subiculum, and amygdala [285]. In comparison to the sham ORX animals, the ORX mice showed significantly higher levels of A β in all three brain regions as well as significantly poorer behavioral performance on a spontaneous alternation task [285]. The elevated pathology and exacerbated behavioral impairments in the ORX group were blocked in ORX mice treated with DHT, suggesting a preventive effect of androgens in regulation of AD-related pathology. Confirming our findings in animal models, a recent study reported that levels of A β in plasma and cerebrospinal fluid were significantly elevated following ORX in guinea pigs, an effect prevented by testosterone replacement 1 week following ORX [346].

There are likely several mechanisms that contribute to androgen regulation of A β (Fig. 2). One obvious possibility is that aromatase-mediated conversion of testosterone to E₂ in brain allows activation of the several estrogen pathways of A β regulation discussed above. In fact, cell culture studies are consistent with indirect testosterone activation of estrogen-mediated regulation of APP processing. The first study to examine testosterone regulation of APP and A β in culture found that prolonged testosterone treatment was associated with increased α -secretase cleavage of APP and

reduced A β [128]. Unclear was whether these findings involved direct androgen pathways, indirect activation of estrogen pathways, or both. In a subsequent culture study, testosterone was also observed to promote proteolysis of APP by α -secretase, however this effect was blocked in the presence of aromatase inhibitors suggesting estrogen dependence [121]. In our study of male rats in which androgens were found to regulate brain levels of soluble A β , we did not observe detectable differences in either full-length APP or APP α across androgen treatment groups [271], perhaps indicating that alterations in APP processing are not the only mechanism by which androgens affect A β levels.

In addition to regulating A β generation via effects on APP proteolysis, androgens may also decrease A β levels by promoting endogenous clearance pathways. Recent evidence from our group demonstrates that androgens reduce A β levels as a consequence of regulating expression of the A β -catabolizing enzyme neprilysin [376], a critical enzyme in homeostasis of brain A β [170]. In neural cell cultures, we found that androgens robustly increase protein levels of neprilysin. A classic, AR-dependent genomic mechanism is implicated since (i) the neprilysin gene contains androgen response elements [304], (ii) neprilysin regulation was blocked by the anti-androgens flutamide and cyproterone acetate, and (iii) androgens only increased neprilysin in AR-containing cells [376]. Over-expression of human APP in cultured cells resulted in elevated levels of soluble A β that were reduced by testosterone and DHT. Further, we found that pharmacological inhibition of either AR or neprilysin blocked the ability of androgens to reduce A β levels, suggesting that the A β -lowering actions of androgens is mediated by AR-dependent regulation of neprilysin expression [376]. Importantly, these observations were replicated in male rats. We found that ORX-induced androgen depletion resulted in decreased levels of NEP and elevated A β , and DHT replacement restored NEP and A β to levels observed in sham GDX animals [376].

10. Emerging strategies of hormone-related therapies in Alzheimer's disease

As reviewed in this article, there are numerous neuroprotective actions of estrogens and androgens that have direct relevance to

AD pathogenesis and compelling potential to prevent and possibly treat the disease. However, the promise of estrogen-based and androgen based HTs in reducing AD risk have yet to be realized. As findings and directions from clinical and basic science research become increasingly integrated, it is anticipated that critical parameters affecting HT efficacy will be optimized, including age of HT initiation as well as the formulation, regimen, and delivery of HT. As ongoing research continues to address these crucial and immediate concerns, an emerging area of investigation is the development of natural and synthetic hormone mimetics that will preferentially activate estrogen and androgen neuroprotective mechanisms while minimizing deleterious consequences in other tissues.

Estrogen compounds that show tissue-selective agonist actions are termed selective estrogen receptor modulators (SERMs). Currently the most studied and clinically relevant SERMs are tamoxifen and raloxifene, synthetic compounds that exhibit tissue-dependent ER agonist and antagonist actions. As a potent antagonist of estrogen action in breast tissue, tamoxifen is best recognized as an antiestrogen used to treat breast cancer although it can exert agonist ER effects on bone and lipids [48,300]. Interestingly, low concentrations of tamoxifen can protect cultured neurons from toxicity due to A β and glutamate [243], suggesting the potential for a protective role against AD. However, tamoxifen has also been observed to block E $_2$ -mediated protection in cultured neurons [57,383]. Potential benefits of tamoxifen use in post-menopausal women for prevention or treatment of AD has not been well studied. Some studies indicate increased risk of cognitive deficits in tamoxifen users [246,308], whereas another study suggested tamoxifen may reduce AD risk [41]. Like tamoxifen, raloxifene antagonizes estrogen actions in breast but has agonist actions on bone [48,81]. In brain, raloxifene mimics some but not all protective estrogen actions. Raloxifene increases choline acetyltransferase in hippocampus of OVX rats [363] and in cultured neurons it increases neurite outgrowth [235] and can reduce A β toxicity [243]. Conversely, E $_2$ but not raloxifene was effective in attenuating A β -induced inflammatory reaction in OVX rats [334]. In post-menopausal women, raloxifene use has been linked with reduced risk of cognitive impairment and development of AD [370].

Currently, effort is being focused on next generation SERMs that exhibit more robust and specific neuroprotective actions [42,303]. For example, Brinton and colleagues recently developed a synthetic SERM with both estrogenic and antioxidant potential that protects cultured neurons from cell death [389]. Evaluation of such compounds in animal models of AD is only beginning. Towards this end, our laboratory has begun to investigate two particular SERMs, propylpyrazole triol (PPT) and diarylpropionitrile (DPN), which show relative specificity for ER α and ER β , respectively. Although we observe that both compounds protect cultured neurons from A β toxicity [67], PPT but not DPN treatments effectively mimicked E $_2$ in reducing A β accumulation and improving behavioral deficits in OVX 3xTg-AD mice [53].

In parallel to the ongoing research on SERMs, there has been a recent growth in the interest and development of tissue-specific selective androgen receptor modulators (SARMs) [108,147,186]. Given the prevalence of ADAM and its widespread deleterious consequences, androgen based therapy is of considerable interest. However, prostate cancer, which is the second leading cancer among aging men in terms of both prevalence and cause of death [99], is androgen-dependent and typically treated by androgen deprivation therapy. Consequently, the use of testosterone therapy with its potential to increase risk and or progression of prostate tumorigenesis has been controversial [183] and promoted the development of SARMs that lack significant androgen action in prostate but exert agonist effects in se-

lect androgen-responsive tissues of interest, including brain, muscle, and bone.

Several strategies of SARM design are currently being pursued [46,108,359]. One strategy is to develop novel steroidal compounds that are not substrates for the enzyme 5 α -reductase or yield reduced metabolites with minimal androgenicity. Testosterone is converted to DHT by the actions of 5 α -reductase, an enzyme localized in specific target tissues such as prostate. Prostate growth depends largely on the actions of DHT rather than T because DHT exhibits ~10-fold greater net potency, which reflects both a higher binding affinity for AR and a slower dissociation rate from AR [359]. SARMs that are not 5 α -reductase substrates or form DHT-like derivatives with weak androgenic activity have low androgen action in prostate [108,188,201,211,245,301,342]. A promising SARM in this category is 7 α -methyl-19-nortestosterone, commonly called MENT [223,301,342], which was developed by the Population Council and is currently in clinical trials as an androgen therapy for hypogonadal men [10,345]. MENT shows low androgen activity in prostate but is more potent than T in other peripheral androgen-responsive tissues including bone [76,301,342] and muscle [76,301,342]. The effects of MENT on neural function are virtually unknown, but it has been shown to mimic the ability of testosterone to induce sexual behavior in castrated rats [223] and is a robust regulator of the hypothalamic–pituitary–gonadal axis, suggesting neural efficacy.

Another SARM design strategy is the development of non-steroidal synthetic AR ligands. One such SARM is flutamide, which mimics the abilities of T and DHT to increase hippocampal spine density in both male and female rats [207,208]. In cultured neurons, we have found that flutamide antagonizes classic genomic actions of T and DHT but mimics rather than blocks the nongenomic neuroprotective actions of these androgens [230]. Of particular interest are novel compounds that bind AR but have altered interactions with AR binding pocket side chains that underlie tissue specificity. Recent research has determined that although synthetic SARMs must closely mimic the rigid backbone core structure of the AR ligand binding domain, there can be extensive variation in how they interact with amino side chains in the binding pocket [359]. Thus, SARMs are predicted to exert tissue-specific effects dependent in part upon how they interact with amino acid sidechains in the AR binding pocket [36,46,201]. Recent research indicates success in developing SARMs with desired tissue specificity [245]. As with SERMs, the development of brain-specific SARMs that exert neuroprotective actions associated with reduction of AD pathogenesis is a key topic of ongoing research.

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