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Interactions between inflammation, sex steroids, and Alzheimer's disease risk factors

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Abstract

Alzheimer's disease (AD) is an age-related neurodegenerative disorder for which there are no effective strategies to prevent or slow its progression. Because AD is multifactorial, recent research has focused on understanding interactions among the numerous risk factors and mechanisms underlying the disease. One mechanism through which several risk factors may be acting is inflammation. AD is characterized by chronic inflammation that is observed before clinical onset of dementia. Several genetic and environmental risk factors for AD increase inflammation, including apolipoprotein E4, obesity, and air pollution. Additionally, sex steroid hormones appear to contribute to AD risk, with age-related losses of estrogens in women and androgens in men associated with increased risk. Importantly, sex steroid hormones have anti-inflammatory actions and can interact with several other AD risk factors. This review examines the individual and interactive roles of inflammation and sex steroid hormones in AD, as well as their relationships with the AD risk factors apolipoprotein E4, obesity, and air pollution.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that currently affects 5 million people in the United States alone. AD is characterized by several neuropathological features, including the accumulation of amyloid β ($A\beta$) and hyperphosphorylated tau, gliosis, and synaptic and neuron loss (Cherry et al., 2014; Glass et al., 2010; LaFerla, 2010; Morris et al., 2014). As there is currently no successful therapeutic intervention to stop or slow the progression of AD, much research has focused on identifying risk factors for, as well as mechanisms underlying, the disease.

AD is a multifactorial disease with a number of well established genetic and environmental risk factors. The single greatest risk factor is aging, with prevalence of AD approximately doubling every 5 years after the age of 65 (Hebert et al., 2013; LaFerla, 2010). In terms of genetic risk, only a small number of cases are the result of autosomal dominant mutations,

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all of which are associated with increased accumulation of A β (LaFerla, 2010; Tanzi, 2012). The most significant genetic risk factor for AD is the ϵ 4 allele of the cholesterol transporter apolipoprotein E (*APOE4*). Among other effects, *APOE4* increases risk in part by facilitating A β accumulation (Saunders et al., 1993; Strittmatter et al., 1993). Additionally, a number of single nucleotide polymorphisms in genes important in innate immunity have also been associated with increased risk for AD (Tanzi, 2012), pointing to the role of inflammation in AD.

In addition to genetic risk factors, there are a number of environmental or lifestyle factors that affect AD risk. For example, the following factors have been shown to have a positive correlation with AD risk: lower education (Ferrari et al., 2014; Sharp and Gatz, 2011), head injury (Breunig et al., 2013), obesity (Emmerzaal et al., 2015), and air pollution (Calderon-Garciduenas et al., 2012). On the other hand, higher education (Sharp and Gatz, 2011) and greater physical exercise (Brown et al., 2013; Tolppanen et al., 2015) are negatively correlated with AD risk. Interestingly, many of these environmental factors also affect inflammation, possibly providing a shared mechanism through which they modulate AD risk.

Sex differences also impact AD risk, with women accounting for approximately two-thirds of AD patients (Hebert et al., 2013). Moreover, the progression of the disease differs between sexes, with men showing a more rapid progression (Lapane et al., 2001; Stern et al., 1997), but women showing greater severity for clinical dementia (Barnes et al., 2005; Corder et al., 2004; Irvine et al., 2012). These sex differences are likely to be due to differences in neurophysiological substrates between men and women as well as differential actions of sex steroid hormones. Both estrogens and androgens have neuroprotective effects and age-related loss of these sex steroid hormones increases risk for AD in both sexes.

No single factor genetic or environmental entirely drives AD risk. Rather, there are multiple risk factors that interact to determine AD risk. Importantly, genetic and environmental risk factors have been shown to differentially affect men and women, and to interact with sex steroid hormones. Though there are multiple pathways through which these factors may interact to drive AD pathogenesis, the current review will focus on inflammation. Neuroinflammation is increasingly regarded as an essential component of AD pathogenesis and many AD risk factors impact inflammatory pathways. Thus, we begin by discussing the importance of inflammation in AD, and the role of sex differences and sex steroid hormones. We then focus on the genetic risk factor *APOE4* and the environmental risk factors obesity and air pollution, including discussion of how these factors affect inflammation and interact with sex steroid hormones.

Inflammation and Alzheimer's disease

Inflammation is a key pathological component in AD that has been proposed as a major mechanism both in the initiation and progression of the disease (Wyss-Coray and Rogers, 2012). Normal aging is associated with an increase in chronic inflammation (Singh and Newman, 2011), suggesting that inflammation is one of several age-related changes that may cooperatively increase AD risk. Several pathways through which inflammation can

drive AD pathogenesis have been identified. For example, increased levels of pro-inflammatory cytokines can stimulate amyloid precursor protein (APP) processing to generate more A β , which not only directly impairs neural health, but also acts on microglia and astrocytes to further increase inflammation (Blasko et al., 2004). In this way, inflammation has been proposed to be both a driving force and a consequence of AD pathology (Heneka et al., 2015). Interestingly, levels of pro-inflammatory cytokines are elevated in serum even before there is detectable A β pathology (Avila-Muñoz and Arias, 2014; Eikelenboom et al., 2011), pointing to a role for inflammation in the initiation of disease. Indeed, several conditions associated with neural and systemic inflammation increase AD risk (Andersen et al., 2005; Brayne et al., 1998; Fleminger et al., 2003; Kamer et al., 2008; Xu et al., 2011).

Involvement of the immune system in AD pathogenesis is supported by genome wide association studies, which identified several alleles related to microglial function and/or innate immunity as AD risk factors. These immune-related genes include complement receptor 1 (CR1) (Lambert et al., 2013; Naj et al., 2011), triggering receptor expressed on myeloid cells 2 protein (TREM2) (Guerreiro et al., 2013), and CD33 (Hollingworth et al., 2011; Naj et al., 2011). CR1 in immune cells interacts with activated complement components and triggers the clearance of bound factors (Fonseca et al., 2016). Components of the complement signaling pathway can bind to fibrillar A β (Afagh et al., 1996) as well as to neuronal synapses (Hong et al., 2016). These actions can stimulate microglia to phagocytose both A β and synapses, which could be either beneficial or detrimental in the context of AD (Fonseca et al., 2004). TREM2 is enriched in white matter and in microglia surrounding A β plaques, and has functions associated with promoting phagocytosis while suppressing cytokine signaling. Heterozygous loss-of-function mutation in TREM2 predisposes to AD (Guerreiro et al., 2013). CD33 is found in monocytes and contains an immunoreceptor that is typically an inhibitor of cellular activity (Bradshaw et al., 2013). CD33 expression is increased in the microglia of AD brains and it inhibits uptake and clearance of A β 42 (Griciuc et al., 2013). Collectively, these findings strongly support the position that AD pathogenesis is promoted by neuroinflammation, a process that involves both glial cells and the cytokines they produce.

Soluble mediators of immunity

Cytokines are key mediators of neuroinflammation. Cytokines are a soluble, multifunctional, heterogeneous group of proteins that usually act locally, in a paracrine or autocrine way, although they can travel through the bloodstream to mediate effects on numerous tissues. Interleukins (IL), tumor necrosis factors (TNF), interferons (IF), transforming growth factors (TGF), and chemokines comprise the major cytokines that can activate cells, cause apoptosis, and attract cells to a site of injury (Zheng et al., 2016). Cytokines can typically be classified as pro-inflammatory and anti-inflammatory, and the balance between them enables an immediate and tightly controlled response against pathogens. However, in AD, the resolution of the inflammatory process is impaired and, consequently, the balance between pro-inflammatory and anti-inflammatory cytokines is altered.

Aging is characterized by a net increase in the expression of inflammatory genes, which are further increased in the context of AD (Blalock et al., 2005; Colangelo et al., 2002). In brains of AD patients, cytokines including IL-6, IL-1 β , and TGF β accumulate preferentially around amyloid plaques (Hull et al., 2006; van der Wal et al., 1993). Interestingly, in the cerebrospinal fluid (CSF) of AD patients, both pro- and anti-inflammatory cytokines are elevated (Brosseron et al., 2014), suggesting a disruption of immune system homeostasis rather than a biased upregulation of only pro-inflammatory genes. Levels of some cytokines like IL-1 β , correlate with cognitive deterioration (Cacabelos et al., 1991). Cytokine polymorphisms have been found to interact with other AD risk factors (Di Bona et al., 2008; Lee et al., 2015), including *APOE4* (Chapuis et al., 2009; Liu et al., 2014; Wang and Jia, 2010; Yu et al., 2009). Thus, cytokines are poised to play a central role in the inflammatory processes associated with AD.

Several studies have successfully reduced AD-like pathology in transgenic mouse models using anti-inflammatory strategies. For example, targeting TNF α synthesis (Gabbita et al., 2015; Tweedie et al., 2012) or the TNF receptor (Detrait et al., 2014) reduced A β and tau pathology and restored memory deficits in AD transgenic mice. However, some studies have found the opposite, instead showing attenuation of A β deposition in the hippocampus of transgenic AD mice that overexpress TNF α (Chakrabarty et al., 2011). One important aspect to account for divergent findings may be the timing of the intervention. That is, cytokine overexpression prior to significant pathology may be beneficial, as has been observed with TNF α (Chakrabarty et al., 2011) and IL-6 (Chakrabarty et al., 2010). However, chronic TNF- α overexpression leads to an increase in inflammation and ultimately to neuronal cell death in 3xTg-AD mice (Janelins et al., 2008). Thus, a heightened inflammatory response may be beneficial at early stages of AD pathogenesis, but detrimental once pathology has progressed.

In addition to their role in inflammation, cytokines also play important roles in other aspects of AD, including memory, cell death, tau hyperphosphorylation and amyloidogenesis. For instance, elevated levels of TNF α can cause memory impairment in the hippocampus through TNFR1 activation in astrocytes (Habbas et al., 2015). Other studies confirm TNFR1 participation by showing that TNF α mediates memory impairment induced by A β in mice and monkeys through this receptor (Lourenco et al., 2013). Similarly, IL-1 β production promotes APP processing and tau pathology, contributing to impaired synaptic plasticity and memory formation (Pickering and O'Connor, 2007; Sheng et al., 2000), and neutralizing antibodies against IL-1 β improve cognitive deficits in an AD mouse model (Kitazawa et al., 2011). IL-6 also contributes to APP processing and neurofibrillary tangle formation (Spooren et al., 2011), and its levels are correlated with cognitive decline in humans (Weaver et al., 2002). Hence, soluble inflammatory factors can influence AD pathology through multiple fronts.

Although inhibition of cytokines would seem to be a reasonable therapeutic strategy, the role of cytokines in AD pathogenesis is multifactorial and benefits also arise from cytokine signaling. Immune responses can be broadly classified as pro-inflammatory or anti-inflammatory, but their roles are pleiotropic and complex. Indeed, several studies have shown that inhibition of anti-inflammatory pathways is beneficial in AD models. For

example, IL-10 and TGF β are considered anti-inflammatory cytokines. Blocking TGF β in peripheral macrophages results in their infiltration into the brain and increases clearance of A β plaques (Town et al., 2008). Likewise, IL-10 deficiency increases microglial A β phagocytosis, preserves synaptic integrity, and attenuates cognitive decline in AD transgenic mice (Guillot-Sestier et al., 2015). Collectively, findings indicate that inhibition of AD pathogenesis will likely require modulation rather than broad inhibition of glial activities.

Cellular mediators of immunity

Microglia and astrocytes are glial cell types that are essential mediators of neuroinflammation. Both cell types are activated in AD, a response characterized in part by increased production and secretion of cytokines, chemokines, complement proteins, and acute-phase proteins (Morgan et al., 2005). Chronic activation of microglia and astrocytes has been implicated in the pathophysiology of AD in humans and in mouse models.

Microglia are tissue-resident macrophages in the brain. They are immune cells that are responsible for tissue surveillance and represent the first line of defense in the CNS. Microglia are able to phagocytose foreign particles and are important participants in the elimination of pathogens from the brain (Prinz and Priller, 2014). Although they are macrophages, they differ to some extent from the macrophages that reside in other tissues: microglia originate from hematopoietic stem cells of the yolk cell during development and not from the bone-marrow, and they are long-lived cells that are able to self-renew (Ginhoux et al., 2010; Yona et al., 2013).

In addition to screening the brain parenchyma for abnormalities (Sierra et al., 2015), under normal conditions microglia participate in many functions that promote neural health including synaptic pruning and remodeling (Paolicelli et al., 2011; Schafer et al., 2012) and synaptic plasticity (Parkhurst et al., 2013). Upon encountering pathogens or injuries, microglia adopt activated phenotype(s). Activated states differ from the resting state by alterations in morphology (the cytoplasmatic projections retract and cell bodies become more amoeboid), as well as changes in surface protein expression, phagocytic ability, mobility, and proliferative capacity. Macrophage responses to pathogens are typically categorized into M1 or M2 polarization. The M1 state is pro-inflammatory, cytotoxic and phagocytic, whereas the M2 state supports tissue remodeling, promotes fibrosis and is anti-inflammatory (Durafour et al., 2012). This classification system has been extended to microglia as well, but it cannot account for the entire range of phenotypes that can be found in the brain, especially under chronic inflammatory conditions (David and Kroner, 2011; Holtman et al., 2015). A range of activated microglial phenotypes can be generated depending on the insults and modulators encountered (Hanisch and Kettenmann, 2007). For example, microglia isolated from mouse models of neurodegeneration and aging express genes related to antigen presentation, lysosome function, phagocytosis, A β phagocytosis, and apoptosis, whereas microglia isolated from models of acute inflammation mainly express genes related to NF κ B signaling (Holtman et al., 2015). Because AD is a multifactorial disease in which both lifestyle factors and genetic variants impact the outcome of the disease, microglial phenotypes will also vary significantly based on these factors.

One important role for microglia in AD is their participation in A β clearance (Prinz and Priller, 2014). Importantly, the ability of microglia to effectively clear A β appears to be impaired in AD. Interestingly, two interactive regulators of microglial phagocytosis, CD33 and TREM2, have polymorphisms linked to increased risk for AD (Ma et al., 2014; Walker et al., 2015). Although the relationships between A β clearance, CD33, and TREM2 remain to be fully resolved, their association suggests an imbalance in this pathway (Malik et al., 2013). Microglia are recruited to A β plaques during the progression of AD, but studies have suggested that microglia are not able to degrade A β (Paresce et al., 1997). This failure in clearance may exacerbate the inflammatory response (Sokolowski and Mandell, 2011). Both decreased A β phagocytosis and increased cytokine production are associated with cognitive decline in AD (Mawuenyega et al., 2010; Orre et al., 2014).

Microglia can sense A β via cell-surface receptors including the toll-like family of receptors (TLR) (Fassbender et al., 2003; Salminen et al., 2009; Tahara et al., 2006). TLR activation leads to a signaling cascade that culminates in activation of immunomodulatory transcription factors (Israel, 2010). Polymorphisms in one member of this family, the TLR4 receptor, have been associated with increased AD risk (Balistreri et al., 2008). Importantly, TLR4 interacts with other modulators of AD, including apoE4 (Tai et al., 2015), saturated fatty acids (Lee et al., 2001), and pollution particulate matter (Bauer et al., 2012). TLR4 can bind to A β , leading to activation of the transcription factor NF κ B and increased expression of inflammation-related genes (Landreth and Reed-Geaghan, 2009; Stewart et al., 2009). NF κ B is a key transcription factor involved in inflammation, cell division, and apoptosis (O'Neill and Kaltschmidt, 1997). Interestingly NF κ B upregulation is observed in the brain of AD patients (Ferrer et al., 1998), and blocking NF κ B decreases A β in cell culture and animal models of AD (Collister and Albeni, 2005; Jiang et al., 2014; Solberg et al., 2015; Yoon et al., 2014). Thus, in order to clear A β , microglia must be able to sense and recognize its presence, trigger an inflammatory response, and phagocytose and degrade A β . Disruption in any of these important microglial functions can contribute to the A β accumulation associated with AD pathology.

A number of studies have examined the effects of inhibiting microglial activity on AD outcomes. Inhibiting microglial proliferation via pharmacological blockade of the colony-stimulating factor 1 receptor (CSF1R) improves memory and prevents synaptic degeneration in a mouse model of AD, without affecting A β plaques (Olmos-Alonso et al., 2016). Likewise, eliminating microglia prevents neuronal loss and neuroinflammation, and improves memory, without altering levels of A β (Spangenberg et al., 2016). Furthermore, administration of minocycline, a tetracyclic antibiotic that inhibits microglial activation, ameliorates AD-like pathology in transgenic mice and downregulates inflammatory markers, partially through inhibition of NF κ B, and BACE-1 (Ferretti et al., 2012; Zemke and Majid, 2004). Shifting microglial activation states from the pro-inflammatory M1 to a more anti-inflammatory M2 phenotype has also proven to be effective. Deficiency of the NLRP3 inflammasome skews activated microglia towards an M2-like state in AD transgenic mice, resulting in increased A β clearance and enhanced tissue remodeling (Heneka et al., 2013).

Astrocytes also play an important role in AD. Activated astrocytes are characterized by increased expression of glial fibrillary acidic protein (GFAP) and functional impairment.

Like microglia, astrocytes release cytokines, nitric oxide, and other cytotoxic molecules after exposure to A β , thus exacerbating neuroinflammation (Johnstone et al., 1999). Astrocyte activation may occur even before A β deposition and thus contribute to both early and late phases of AD pathogenesis (Kummer et al., 2014). Furthermore, astrocytes are able to migrate and accumulate around plaques (Funato et al., 1998), participating in A β degradation (Wyss-Coray et al., 2003; Yin et al., 2006). ApoE is needed for astrocyte-mediated A β clearance (Kolstinaho et al., 2004) and astrocyte-dependent lipidation of apoE increases the ability of microglia to clear A β (Terwel et al., 2011). However, in addition to their beneficial effects on A β clearance, astrocytes also contribute to a feedback process that exacerbates A β pathology. For example, A β decreases glutamate uptake by astrocytes, which can increase excitotoxicity and decrease neuron viability (Antuono et al., 2001; Matos et al., 2008; Verkhratsky et al., 2010). Moreover, astrocytes increase APP expression upon neuronal injury, which may contribute to increased A β accumulation after injury (Siman et al., 1989). Human astrocytes synthesize A β -40 and -42 when stimulated by IF γ , TNF α or IL-1 β , events that can occur early in AD development (Blasko et al., 2000; Monson et al., 2014). Thus, astrocytes can have both beneficial and harmful roles in the context of AD.

Other cells of the immune system also may play important roles in AD, although their contributions to pathology are still poorly understood. Recently, increased attention has been given to the adaptive immune system, which is able to coordinate and control the innate immune system. B cells and T cells have been suggested to modulate AD pathogenesis in that they can modulate microglial function by stimulating phagocytic ability with antibodies and controlling release of inflammatory cytokines (Marsh et al., 2016). A β immunization aims to modulate CNS immune cells by increasing the amount of antibodies directed against A β in the serum. A β -42 immunization prevents deposition and enhances clearance of amyloid plaques, and decreases gliosis in animal models of AD (Schenk et al., 1999). In humans, A β immunotherapy enhances plaque clearance, and reduces microglia and astrocyte activation (Nicoll et al., 2003; Zotova et al., 2013).

Sex steroid hormones and Alzheimer's disease

Significant sex differences exist in AD, with women being at heightened risk, even after controlling for the fact that women live longer than men (Li and Singh, 2014). Sex differences in genetic and environmental risk factors for AD have not been well studied, though there is evidence women are disproportionately affected by some factors. For example, *APOE4* is regarded as the single greatest genetic risk factor for AD, however, this risk is modified by sex, as a single copy of *APOE4* increases risk approximately four-fold in women, but has a comparatively modest on AD risk in men (Farrer et al., 1997; Payami et al., 1994). A more recent study found that presence of *APOE4* increases rates of conversion from cognitively normal to mild cognitive impairment (MCI) and from MCI to AD significantly more strongly in women than in men (Altmann et al., 2014).

Interestingly, there is often a female sex bias in rodent models of AD. Our lab and others have demonstrated that female AD transgenic mice have significantly greater AD-like neuropathology than males (Carroll et al., 2010; Hirata-Fukae et al., 2008; Schafer et al., 2007). Intriguingly, even the sex bias associated with *APOE4* is replicated in transgenic

mice, as we have recently shown that presence of human *APOE4*, compared to human *APOE3*, increases AD-like pathology more strongly in female than in male AD-transgenic mice (Cacciottolo et al., 2016). Though these sex differences may involve inherent neural differences between men and women, there is a wealth of data demonstrating the importance of sex steroid hormones in modulating AD risk.

Estrogen and AD

The primary female sex steroid hormone, 17 β -estradiol, is protective against AD, and its age-associated decline increases risk of developing the disease (Manly et al., 2000; Pike et al., 2009). Low circulating levels of 17 β -estradiol (E2) are associated with AD (Rosario et al., 2011; Yue et al., 2005), and women with AD have lower brain levels of estrogens than age-matched cognitively normal controls (Rosario et al., 2011; Yue et al., 2005). Moreover, surgically induced menopause performed prior to natural menopause, results in prematurely low E2 levels and increased risk of AD (Phung et al., 2010; Rocca et al., 2007).

Experimental findings in rodent models support the idea that E2 is protective and loss of this sex steroid hormone can accelerate AD-like pathology. For example, depleting sex steroid hormones in female AD-transgenic mice via ovariectomy increases A β and worsens behavior (Carroll et al., 2007; Levin-Allerhand et al., 2002; Xu et al., 1998; Zheng et al., 2002). Additionally, in these same studies, treatment with E2 in ovariectomized female AD-transgenic mice reverses the adverse effects of ovariectomy, suggesting protective roles of E2 in AD.

Though studies in both humans and rodents have demonstrated the adverse effects of E2 loss, the benefits of estrogen-based hormone therapy are not yet clear. A number of studies found decreased rates of dementia in women using hormone therapy (Kawas et al., 1997; Paganini-Hill and Henderson, 1994; Tang et al., 1996; Zandi et al., 2002). However, a large double-blinded, placebo-controlled clinical trial, the Women's Health Initiative, found that hormone therapy actually increased rates of cognitive decline and risk of dementia (Shumaker et al., 2004; 2003). However, there is evidence that initiation of hormone therapy near the onset of menopause may be necessary to realize protection from AD (Shao et al., 2012; Whitmer et al., 2011). Recent clinical trials that included early initiation of hormone treatment found that it was associated with reduced A β accumulation (Kantarci et al., 2016), but without cognitive benefits (Gleason et al., 2015; Henderson et al., 2016). Thus, though the loss of E2 is clearly a risk factor for AD and E2 does have several neuroprotective roles, its therapeutic applicability is not straightforward and requires further research.

Testosterone and AD

As appears to be the case for estrogens in women, testosterone may protect against AD in men. Indeed, most (Hogervorst et al., 2001; Moffat et al., 2004; Paoletti et al., 2004) but not all (Pennanen et al., 2004) studies report that age-related loss of testosterone in men is associated with increased risk of AD. The relationship between testosterone and AD is apparent at least ten years prior to clinical diagnosis (Moffat et al., 2004), suggesting that low testosterone contributes to, rather than results from, the disease process. Consistent with this possibility, low brain levels of testosterone are linked with AD diagnosis and are

inversely correlated with A β levels in men with evidence of early AD pathology (Rosario et al., 2011; 2004). Parallel to surgical menopause in women, prostate cancer patients treated with androgen-deprivation therapy have increased plasma A β levels (Gandy et al., 2001), and an increased risk of developing AD (Nead et al., 2016).

Research on the effects of testosterone in male rodents is consistent with findings in humans. For example, age-related loss of testosterone in male rats correlates with increased brain levels of soluble A β (Rosario et al., 2009). Moreover, gonadectomizing male mice, which depletes ~95% of endogenous testosterone, increases A β levels while treating with non-aromatizable androgens blocks the effects of gonadectomy, both in non-transgenic mice (Ramsden et al., 2003) and AD transgenic mice (Rosario et al., 2010; 2006). Further, genetic modifications that yield increased testosterone are associated with decreased neuropathology in AD transgenic mice (McAllister et al., 2010).

Research on androgen replacement therapy is very limited. However, one study found improvements in spatial and verbal memory in cognitively normal older men given weekly injections of testosterone (Cherrier et al., 2005a). Moreover, weekly testosterone treatments improved spatial and verbal memory in men with mild cognitive impairment or AD (Cherrier et al., 2005b), and improved reported quality of life in AD patients (Lu et al., 2006). However, long-term effects of androgen-replacement therapy on AD outcomes have thus far not been studied.

In summary, age-related losses in sex steroid hormones are associated with increased levels of A β and increased risk of AD in both men and women. Importantly, these relationships are observed in rodent models as well. The sex-specific associations of AD with estrogens in women, and with androgens in men, may contribute to observed sex differences in AD, although early developmental effects of sex steroid hormones may also be relevant (Pike, in press). A number of pathways through which sex steroid hormones may exert their protective effects against AD have been proposed (Pike et al., 2009; Singh and Su, 2013). For the purposes of this review, we will focus mainly on the effects of estrogens and androgens on inflammatory pathways, as discussed below.

Sex steroid hormones and inflammation

One important factor regulating inflammation is sex, as there are innate sex differences in susceptibility to inflammation. Several lines of evidence point to the role of sex steroid hormones in contributing to sex differences in inflammation (Angele et al., 2006; Kalaitzidis and Gilmore, 2005; Pike et al., 2009). One of the most compelling pieces of evidence is the finding that females are protected against several inflammation-related diseases during adulthood, but become susceptible to them during aging after sex steroid hormones levels decline (Greendale et al., 2011; Manly et al., 2000; Zandi et al., 2002). In adulthood, prior to the middle age onset of menopause in women, men tend to exhibit a higher inflammatory predisposition than women (Albertsmeier et al., 2014). Interestingly, mirroring the effects of age-dependent hormonal decline, girls of age 10 hospitalized with respiratory/inflammatory conditions showed an increased response in all inflammatory parameters analyzed when compared to a matched boy, suggesting that females may be more susceptible to

inflammation in the absence of sex steroid hormones (Casimir et al., 2010). In fact, decreased levels of sex steroid hormones in women as well as in men are associated with increased inflammation (Straub, 2007; Tang et al., 2014). This phenomenon is seen in hypogonadal men (Kalinchenko et al., 2010), in aged men (Nakhai-Pour et al., 2007) and in post-menopausal women (Pfeilschifter et al., 2002).

Physiological levels of E2 are generally protective, therefore the decrease in E2 levels during menopause and perimenopause offers an explanation to the pro-inflammatory profile seen in aged female brains (Rocca et al., 2011; M. X. Tang et al., 1996). Moreover, decreased sex-hormone levels are associated with onset of some neurological disorders (Vegeto et al., 2008). In women, diminished E2 production and the consequent decrease in estrogen receptor (ER)-mediated anti-inflammatory activity may represent a trigger for postmenopausal associated brain dysfunction (Benedusi et al., 2012). In fact, E2 availability and regulation of inflammation appear to interact in regulating AD risk in women. Specifically, polymorphisms in aromatase, the rate-limiting enzyme in E2 synthesis, increase risk and/or decrease age of onset of AD (Corbo et al., 2009), an effect that appears strongest in women (Chace et al., 2012; Medway et al., 2014). Interestingly, the AD risk associated with aromatase polymorphisms interacts with a polymorphism in the anti-inflammatory cytokine IL-10 (Medway et al., 2014). Given that E2 is able to increase IL-10 expression (de Medeiros and Maitelli, 2011; Dimayuga et al., 2005; Velders et al., 2012; Yates et al., 2010), the age-dependent decrease in E2 coupled with alterations in E2 production associated with aromatase polymorphisms may contribute to the inflammatory pathways implicated in AD pathogenesis.

Male sex steroid hormones also have anti-inflammatory effects. Blood levels of testosterone begin to drop around age 30 in males, which leads to functional changes in androgen receptor (AR)-regulated tissues, altering metabolic processes and inflammatory responses (Harman et al., 2001; Maggio et al., 2005). Estradiol can exert its protective effects through its antioxidant capacity (Wang et al., 2006), by binding to ERs and altering gene expression or kinase pathways (Pike et al., 2009). Testosterone inhibits expression and release of cytokines and chemokines by acting through AR as well as through non-classical surface receptors (Maggio et al., 2005; Malkin et al., 2004; Rettew et al., 2008). Furthermore, glial cells express receptors for sex steroid hormones (Jung-Testas and Baulieu, 1994) and regulate glial functions, suggesting that sex steroid hormones can modulate neurodegenerative disease progression in part by regulating neuroinflammation (Vegeto et al., 2008).

Sex steroid hormones modulate glia

Microglia and astrocytes express ER α , ER β (Azcoitia et al., 2001; Vegeto et al., 2001) and AR in the nervous system (Puy et al., 1995). These receptors are upregulated during injury and neurodegeneration (García-Ovejero et al., 2002; Savaskan et al., 2001). Sex steroids have effects on various cell processes involved in injury and cell death, including effects on myelination (Curry and Heim, 1966), vasculature (Mendelsohn, 2002), apoptosis (Garcia-Segura et al., 1998), cell survival (Doncarlos et al., 2009) and inflammation (Straub, 2007).

Estradiol has been shown to reduce both acute and chronic inflammation. For example, pretreatment with E2 reduces acute inflammation after lipopolysaccharide injection in both male and female mice (Tapia-Gonzalez et al., 2008). Under conditions of chronic inflammation associated with AD, E2 attenuates microglial activation and decreases the number of microglia surrounding plaques in animal models of AD (Vegeto et al., 2006). Moreover, E2 increases A β uptake by microglia derived from human cortex (Li et al., 2000). Sex steroid hormones have significant effects on several functions of microglia (Nalbandian and Kovats, 2005). For example, E2 can modulate microglia's antigen-presenting function by changing expression of the major histocompatibility complex (MHC) and co-stimulatory molecules, which alters the way microglia and dendritic cells interact with lymphocytes (Tzortzakaki et al., 2003). Moreover, E2 modulates pathogen-sensing by altering how microglia perceive the environment (Hirata et al., 2007). There is still no consensus on whether ER α or ER β is more important in mediating the effects of E2 on microglial responsiveness to insults (Baker et al., 2004; Saijo et al., 2011; Sierra et al., 2008; Vegeto et al., 2006; 2003; Wu et al., 2013), although the activation of both receptors by ER ligands appear to induce anti-inflammatory responses (Chadwick et al., 2005; Ghisletti et al., 2005).

Androgens also suppress inflammation as a consequence of activating ARs and/or non-classical surface receptors (Liu et al., 2005), which are associated with decreasing both humoral and cell-mediated immune responses (Koçar et al., 2000). AR expression is upregulated on microglia and astrocytes in response to injury. In a model of brain injury, either pre- or post-treatment with testosterone and its metabolites, E2 and dihydrotestosterone, decreased reactive gliosis (Barreto et al., 2007). Testosterone binding to AR after injury also activates genes related to repair (Garcia-Segura et al., 1999; García-Ovejero et al., 2002). Furthermore, testosterone modulates the innate immune system by downregulating TLR4 expression through non-classical surface receptors (Rettew et al., 2008).

In addition to their effects on microglia, sex steroid hormones also modulate astrocytes. For example, E2 can regulate morphology (Luquin et al., 1993), transcriptome machinery (Mydlarski et al., 1995; Tomás-Camardiel et al., 2005), and the secretome (Garcia-Segura et al., 1996; Stone et al., 1997) of astrocytes. Moreover, E2 acts on mitochondrial respiratory complexes (Araújo et al., 2008) and upregulates synthesis of other steroids, like progesterone (Sinchak et al., 2003). Sex steroid hormones are able to modulate astrocyte communication with other astrocytes, endothelial cells, neurons, and microglia. Therefore, regulation by sex steroid hormones influences several processes including synaptic plasticity (McCarthy et al., 2002), blood flow (García-Ovejero et al., 2005) and inflammation (Cerciat et al., 2010). For example, in hypothalamic astrocytes, synaptic connectivity is regulated by E2 (Garcia-Segura et al., 1994). Astrocytes exhibit decreased secretion of the cytokines and chemokines IL-6, IL-1 β , TNF α , IFN- γ -inducible protein 10, and MPP9 following treatment with E2 (Cerciat et al., 2010; Lewis et al., 2008). Consistent with an anti-inflammatory role, ovariectomy-induced E2 depletion results in increased IL-1 β levels in the hippocampus via NLRP3 inflammasome, which interacts with the TLR4/NF κ B pathway to sustain and further increase inflammation (Xu et al., 2016). On the other hand, E2 administration to astrocytes decreases inflammasome activation as well as NF κ B activation, likely by impairing its ability to translocate to the nucleus (Cerciat et al., 2010; Xu et al., 2016). Furthermore, E2

decreases cell body enlargement of astrocytes, often called astrogliosis, that is associated with age-related increases in inflammation (Lei et al., 2003).

Estradiol does not always decrease activation of astrocytes. In models of excitotoxicity in the olfactory bulb and in spinal cord injury, E2 increases expression of GFAP, a marker of astrocyte activation (Lewis et al., 2008; Ritz and Hausmann, 2008). Likewise, testosterone injection in the hippocampus can promote astrogliosis and memory impairment in male rats (Emamian et al., 2010). The regional differences in astrocytic responsiveness to hormones can partially be explained by the existence of subpopulations of astrocytes with different properties within each region, as well as by the interaction with other cells that can modulate astrocytic function (Ma et al., 1994; Torres-Aleman et al., 1992). Additional research is needed in order to establish under what conditions sex steroid hormones either reduce or exacerbate astrocyte activation.

Glial cells can produce neurosteroids

One important function of glial cells is synthesis of neurosteroids from cholesterol in the brain (Papadopoulos et al., 1992). Neurosteroids can modulate neuronal excitability, as well as glial function (Papadopoulos et al., 2006). In order to form active neurosteroids, cholesterol molecules bind to steroidogenic acute regulatory protein (StAR) and to the translocator protein (TSPO) on the mitochondrial surface, and are then translocated to the inner mitochondrial membrane and cleaved by CYP11A1 to form pregnenolone (Papadopoulos and Walter, 2012; Rone et al., 2009; Selvaraj and Stocco, 2015), which is a precursor for testosterone and E2 (Reddy, 2010).

Though controversial, several lines of evidence indicate that TSPO may be a key regulator of steroidogenesis and inflammation. For instance, when TSPO is knocked down, steroidogenesis is impaired (Kelly-Herskovitz et al., 1998; Hauet et al., 2005) and levels of pro-inflammatory cytokines are increased (Bae et al., 2014). However, a new TSPO knockout mouse model has challenged previous findings (Papadopoulos et al., 1997), as it was demonstrated that steroid levels and fertility were not affected by the absence of this protein (Morohaku et al., 2014; Tu et al., 2014). Regardless of its role in neurosteroidogenesis, TSPO has important roles in glial function and inflammation.

TSPO expression is upregulated by glial cells under conditions of neuronal injury and inflammation (Papadopoulos, 1993; Vowinckel et al., 1997). In line with this evidence, TSPO is upregulated in many neurological disorders such as glioma (Cornu et al., 1992), multiple sclerosis (Vowinckel et al., 1997), Parkinson's disease (Gerhard et al., 2006), Huntington's disease (Schoemaker et al., 1982), epilepsy (Nadler, 1981), schizophrenia (van Kammer et al., 1993) and AD (McGeer et al., 1988). Interestingly, treatment with TSPO ligands in animal models decreases inflammation, suggesting therapeutic potential of TSPO ligands. Indeed, microglia exhibit reduced activation when exposed to TSPO ligands (Barron et al., 2013; Karlstetter et al., 2014), and have decreased expression of cytokines, chemokines, and reactive oxygen species (Bae et al., 2014; Karlstetter et al., 2014; Lin et al., 2015; Wang et al., 2014). TSPO ligands also improve the proliferative capacity and increase the phagocytic ability of microglia, thereby increasing their ability to clear debris after injury or neurodegeneration (Choi et al., 2011; Karlstetter et al., 2014). Research suggests

that these outcomes may be partially mediated by TSPO reducing expression of NF κ B and/or AP-1 transcription factors (Bae et al., 2014; Zhao et al., 2012). Moreover, TSPO overexpression decreases inflammation whereas knocking down TSPO increases inflammation (Bae et al., 2014). However, it is not clear whether the protective effects of TSPO are solely dependent upon its role in neurosteroidogenesis. The effects of TSPO ligands on glial modulation could be independent of the steroidogenic machinery, and instead be mediated by other cellular processes including calcium influx, mitochondrial function, and apoptosis (Casellas et al., 2002; Hong et al., 2006; Lin et al., 2015; Yiangou et al., 2006).

Therapeutic usage of TSPO ligands to treat AD has been previously proposed (Papadopoulos et al., 2006; Veenman and Gavish, 2000). This possibility is supported by the abilities of TSPO to modulate microglial phenotype and decrease inflammation, while in turn could promote plaque clearance. In fact, previous work in our lab demonstrated that treatment of male 3xTg-AD mice with TSPO ligands significantly attenuated glial activation, reduced A β accumulation, and improved behavioral performance (Barron et al., 2013). The potential role of sex steroid hormones in these actions has yet to be determined. It is worth noting that TSPO ligands increase levels of several neurosteroids, including allopregnanolone which may have a therapeutic role in AD (Irwin et al., 2014).

As described above, TSPO appears to play an important role in the synthesis of sex steroid hormones in brain, and treatment with sex steroid hormones has been shown to decrease inflammation. Since glial cells are particularly sensitive to the effects of sex steroid hormones and also participate in their metabolism, another approach to modulate inflammation is through manipulation of the steroidogenic pathway. TSPO is a unique target in this regard, as its function in modulating inflammation has been shown to be via both steroid-dependent and independent pathways. Because inflammation is an essential component of AD, increasing levels of sex steroid hormone in the brain may present a viable therapeutic approach.

Modifiers of Alzheimer's disease risk and their interaction with inflammation and sex steroid hormones

The degree of heritability and development of AD varies greatly in the human population (Coon et al., 2007; Gatz et al., 2006). This implies that several genetic and environmental factors modify risk for AD (Rosenthal et al., 2012; Ryman and Lamb, 2006). Identifying and determining the relative contribution of the many environmental and genetic risk factors for AD is presumed to increase understanding of the mechanisms driving AD pathogenesis. Moreover, identification of modifiable risk factors may also reveal potential therapeutic targets. In this review, we focus on apolipoprotein E ϵ 4 allele (*APOE4*), obesity, and air pollution, AD risk factors that both involve inflammatory pathways and are modulated by sex steroid hormones.

1. Apolipoprotein E

The *APOE4* allele is the greatest genetic risk factor for late onset AD (Corder et al., 1993). Three isoforms of *APOE* exist in humans: $\epsilon 2$ (*APOE2*), $\epsilon 3$ (*APOE3*), $\epsilon 4$ (*APOE4*). *APOE3* is the most common allele (77% frequency) and *APOE2* is the least common (8%) (Mahley, 1988). The presence of one *APOE4* allele can confer up to a 3 – 4 fold increased risk of developing AD (Corder et al., 1993). However, *APOE4* is neither necessary nor sufficient to cause AD, suggesting that *APOE4* likely interacts with other risk factors to modulate vulnerability to AD. Importantly, *APOE4* increases risk of AD significantly more strongly in women than it does in men (Altmann et al., 2014; Farrer et al., 1997; Payami et al., 1994), but how *APOE4* and sex interact is still unclear.

In animal models, *APOE4* is also linked to greater AD-like pathology, where it has been shown to potentiate oligomerization of A β (Belinson and Michaelson, 2009) and accelerate A β plaque formation (Youmans et al., 2012). ApoE is mainly synthesized by astrocytes, to a lesser extent by microglia, and very little is made by neurons. ApoE has several important biological roles in brain, the efficacy of which is significantly affected by *APOE* genotype. For example, a key function of apoE in brain is to transport cholesterol from astrocytes to neurons (Bu, 2009), and apoE4 is less efficient in doing so than apoE3 (Gong et al., 2002; Rapp et al., 2006). Moreover, the lipidation state of apoE determines its half-life in brain, its ability to inhibit neuroinflammation, and its ability to bind and clear A β through receptors in the blood-brain barrier (Castellano et al., 2011; Hirsch-Reinshagen et al., 2004; Holtzman et al., 2000; Tai et al., 2015). Lipidation of apoE by ABCA1, which is produced by microglia and astrocytes, is also isoform-dependent with the following rank order of efficacy: apoE2 > apoE3 > apoE4 (Boehm-Cagan and Michaelson, 2014; Tai et al., 2013; Wahrle et al., 2004).

The result is that apoE4 carriers have lower brain levels of apoE, enhanced neuroinflammation, and greater A β accumulation (Licastro et al., 2007; Tai et al., 2015). These differences between apoE3 and apoE4 have important effects on biological functions including synaptogenesis, mitochondrial function, brain volume, and A β clearance (Cedazo-Mínguez, 2007; Huang, 2010; Kim et al., 2009), as well as on risk of cardiovascular disease and atherosclerosis (Hixson, 1991; Stengard et al., 1998). Importantly, the three *APOE* isoforms are known to have significantly different effects on inflammation, which may be one mechanism underlying their divergent effects on AD risk.

ApoE modulates inflammation—ApoE4 has been shown to increase susceptibility to inflammation (LaDu et al., 2000), in both animal models and in humans. For example, following a systemic lipopolysaccharide (LPS) injection, targeted-replacement (TR) mice expressing human *APOE4* have a greater increase in pro-inflammatory cytokines, both in brain and peripherally, than do *APOE3*-TR mice (Lynch et al., 2003). Microarray analysis has shown that the greatest differences between apoE3 and apoE4 in response to LPS are in genes involved in the NF κ B signaling pathway (Ophir et al., 2005).

As in animal models, apoE4 is associated with greater baseline as well as LPS-stimulated levels of inflammatory cytokines among non-AD (Gale et al., 2014) and AD patients (Olgiati et al., 2010). Interestingly, non-steroidal anti-inflammatory drugs have been found to reduce risk for AD only in apoE4 carriers (Barger and Harmon, 1997; Schram et al.,

2007), reinforcing the idea that there are important interactions between apoE4 and inflammation in AD.

The role of apoE in inflammation appears to be partly mediated via its modulation of macrophages, microglia, and astrocytes (Vitek et al., 2009). For instance, apoE binds to the LRP1 receptor on glial cells, suppressing JNK activation, and thereby reducing inflammation (Pocivavsek et al., 2009). JNK belongs to the mitogen-activated protein kinase family and coordinates responses to harmful stimuli (Arthur and Ley, 2013). Interestingly, apoE4 has less affinity for LRP1 than do apoE2 and apoE3 (Bell et al., 2012). Thus, *APOE4* carriers have lower overall circulating apoE levels, due to decreased lipidation of apoE4, as well as reduced binding of apoE to its receptor, contributing to higher neuroinflammation in this population (Licastro et al., 2007). A similar outcome is observed in mice, in which there is a faster turnover and lower steady state concentration of apoE, as well as greater inflammation, in *APOE4*-TR mice (Riddell et al., 2008).

The effects of apoE4 on AD risk appear to be closely tied to its role in regulating microglial function. For example, among AD patients, *APOE4* carriers have an increase in the number of microglia, as well as in microglial activation (Egensperger et al., 1998). Two important functions of microglia are the release of cytokines and chemokines, and the clearing of debris and pathogens via phagocytosis, and these processes are usually tightly correlated (Fiala et al., 2007; Zhu et al., 2011). Under normal conditions, when microglia encounter an insult, they switch from a resting surveillance state to an active state, and both pro-inflammatory genes and phagocytosis-related genes are upregulated (Fu et al., 2014). However, in mice with AD-like pathology, microglial motility and A β phagocytosis are impaired even though cytokine production is increased (Krabbe et al., 2013). Additionally, macrophages and microglia expressing apoE4 show deficits in A β phagocytosis compared to apoE2-expressing cells (Guillot-Sestier et al., 2015; Zhao et al., 2009). Thus, normal microglial functions are impaired both in the presence of AD pathology and apoE4, and these may interact to exacerbate AD risk. The reasons why microglia exhibit impaired ability to clear debris in chronic diseases is uncertain. In a state of chronic disease, even when microglia are able to perform phagocytosis of A β , not all of it is successfully degraded by the lysosomes (Guillot-Sestier and Town, 2013). Intracellular A β degradation can be promoted via cholesterol efflux by accelerating trafficking of A β to the endocytic system (Lee et al., 2012). Cholesterol efflux activity is apoE isoform-dependent and *APOE4* carriers have poorer efficiency of cholesterol efflux, which possibly contributes to the higher risk of AD in *APOE4* carriers (Hara, 2002; Jiang et al., 2008a; 2008b; Michikawa et al., 2000). In line with this, co-localization of A β and late endosomes/lysosomes is significantly reduced when microglia are pretreated with apoE4 compared to apoE2 (Mahley and Rall, 2000). Thus, counteracting apoE4 effects by increasing apoE levels or lipidation status has been shown to ameliorate AD pathology in several mouse models of AD (Cramer et al., 2012; Jiang et al., 2008a; Wahrle et al., 2008).

Recent findings suggest that apoE4 also may increase inflammation by acting as a transcription factor for numerous genes, including several associated with immunoregulation. In an *in vitro* model, apoE was found to bind DNA and alter gene expression. Interestingly, apoE4 binding both decreased Sirt 1 levels and induced NF κ B

translocation to the nucleus to a greater extent than either apoE2 or apoE3 (Theendakara et al., 2016). Sirt 1 is a histone deacetylase involved in neuroprotection, cell survival, and metabolism (Zschoernig and Mahlnecht, 2008). Thus, the ability of apoE4 to suppress Sirt 1 and stimulate NF κ B signaling negatively affects neuronal health while simultaneously increasing inflammation.

To summarize, apoE is an important regulator of a number of inflammatory processes and modulates the functions of microglia and macrophages in brain. Importantly, the strength of apoE actions are often isoform-dependent, with apoE4 generally increasing inflammation while impairing the ability of immune cells to clear debris.

ApoE interacts with sex steroid hormones—In addition to its role in immunity, *APOE* status also interacts with sex steroid hormones. For example, the effects of hormone replacement therapy in menopausal women appear to vary between *APOE3* and *APOE4* carriers. More specifically, estrogen-based hormone therapy is associated with memory improvement and slower cognitive decline in non-*APOE4* carriers, but not in *APOE4* carriers (Burkhardt et al., 2004). Similar effects have been reported in mice, where E2 treatment in EFAD mice (contain both human *APOE* genotypes and AD transgenes) reduces A β pathology in ovariectomized *APOE2* and *APOE3* mice, but increases pathology in ovariectomized *APOE4* EFAD mice (Kunzler et al., 2014). The association between *APOE4* and E2 remains to be fully resolved as other reports show that estrogen-based hormone therapy exerts cognitive benefits (Ryan et al., 2009), reduces risk of AD (Rippon et al., 2006) and slows cellular aging (Jacobs et al., 2013), even in female *APOE4* carriers.

Interactive effects between sex and *APOE* are especially prevalent in the innate immune system. Adult macrophages from *APOE4*-TR male mice produce significantly higher levels of nitric oxide (NO) than those from *APOE3*-TR male mice, but female macrophages show no difference between *APOE3* and *APOE4* (Brown et al., 2002). The protective effect of sex-steroid hormones also varies with *APOE* status. Microglia cultures from *APOE3*-TR have suppressed LPS/IF- γ mediated NO production upon E2 treatment, whereas microglia cultures from *APOE4*-TR show only a very modest reduction in NO (Brown et al., 2008).

Interactions between *APOE* status and testosterone have also been demonstrated. For example, male *APOE4*-TR mice have greater baseline levels of nitrite and inflammatory cytokines than do *APOE3*-TR males (Colton et al., 2005). However, removal of circulating testosterone via castration results in a significant increase in levels of nitrite and cytokines in *APOE3*-TR but not *APOE4*-TR males (Colton et al., 2005). Interestingly, *APOE4*-TR male mice have greater cognitive impairments after castration, than do *APOE3*-TR males (Pfankuch et al., 2005; Raber et al., 2002). One suggested mechanism by which apoE interacts with testosterone is that apoE4 decreases tissue sensitivity to the hormone. Androgen receptor levels are downregulated (Raber, 2008), and androgens have reduced binding to AR in the presence of apoE4 (Raber et al., 2002). The apoE – testosterone interaction also is seen in hippocampal size, with volume being smallest in *APOE4* men who have low testosterone (Panizzon et al., 2010). Additionally, cognitively normal older men with *APOE4* exhibit significantly lower levels of testosterone than non-carriers, suggesting that *APOE* status may affect testosterone levels (Hogervorst et al., 2002). The apoE –

testosterone interaction may also extrapolate to females, as suggested by the finding that spatial learning and memory were improved with testosterone treatment only in *APOE4*-TR but not *APOE3*-TR female mice (Raber et al., 2002).

In summary, *APOE4* is associated with exaggerated pro-inflammatory immune responses. Though both E2 and testosterone exert largely anti-inflammatory actions, their effects differ depending upon *APOE* isoform. Additional research is needed to further elucidate *APOE* and sex interactions, and the mechanisms underlying them.

2. Obesity

Accumulating evidence points to a positive correlation between AD and obesity (Fitzpatrick et al., 2009; Gustafson et al., 2009; Jayaraman and Pike, 2014; Moser and Pike, 2016), although this is not always the case (Qizilbash et al., 2015). Parallel relationships have been observed in animal models. AD transgenic mice maintained on high-fat diet (HFD) and other obesogenic diets exhibit increased levels of A β accumulation and/or tau phosphorylation (Barron et al., 2013; Ho et al., 2004; Julien et al., 2010; Kohjima et al., 2010). In non-transgenic models, rodents show cognitive impairment and changes in behavior after HFD without presenting AD-like pathology, which may indicate a role of obesity in exacerbating rather than initiating AD (Hsu et al., 2014; Kanoski et al., 2010).

Interestingly, there may be a window during which obesity increases risk of AD, which could explain some of the discordant results in the human literature (Whitmer et al., 2005). That is, obesity in midlife seems to be an especially strong risk factor for AD (Emmerzaal et al., 2015; Fitzpatrick et al., 2009). During this period, adiposity is correlated with obesity-related vascular diseases, increased inflammation, and changes in blood-brain barrier integrity and brain morphology (Emmerzaal et al., 2015; Gustafson et al., 2007; Pannacciulli et al., 2006; Yaffe et al., 2004). Additionally, the deleterious effects of obesity may be further potentiated by a decrease in sex steroid hormones at midlife, which could be prevented by hormone therapy (Whitmer et al., 2011).

Obesity interactions with sex steroid hormones—Rates of obesity are similar between sexes, however the consequences of increased adiposity exhibit significant sex differences (Ogden et al., 2014). For example, middle-aged women are more susceptible to obesity-associated inflammation (Ahonen et al., 2012), whereas men have higher rates of metabolic syndrome (Pradhan, 2013). Animal studies corroborate these links, showing that male mice maintained on HFD have higher relative increases in weight and adiposity than females, and these are associated with greater impairments in glucose tolerance and insulin sensitivity (Estrany et al., 2013; Garg et al., 2011). In contrast, when exposed to HFD, female mice have less fat deposition and infiltrating macrophages, stronger insulin sensitivity and lipid production, and better synaptic plasticity than male mice (Hwang et al., 2010; Medrikova et al., 2012; Petterson et al., 2012). Interestingly, some of the protection against obesity observed in women is lost at menopause, suggesting a role for sex steroid hormones (Bloor and Symonds, 2014; Meyer et al., 2011).

Estrogens are generally protective against weight gain and adiposity. In response to HFD, E2 upregulates the heat shock protein HSP72, which decreases inflammation, thereby

protecting against the development of insulin resistance (Chung et al., 2008). Interestingly, female rats fed HFD show a downregulation of ER α , decreasing their sensitivity to E2, and making them more susceptible to glucose intolerance (Gorres et al., 2011). Likewise, male and female ER α knockout mice have increased adiposity, as well as insulin resistance and impaired glucose tolerance (Heine et al., 2000; Ribas et al., 2010).

As is the case with E2, testosterone is also largely protective against excess adiposity. There are reciprocal relationships between testosterone, adiposity, and its health consequences in aging men (Zitzmann, 2009). Increasing adiposity is associated with decreased levels of testosterone (Tang Fui et al., 2014). This is a bidirectional relationship as low testosterone is a risk factor for obesity (De Maddalena et al., 2012; Tang Fui et al., 2014). Testosterone replacement therapy may be a viable option, as it has been shown to reduce body weight and lower the risks of obesity and metabolic syndrome (Yassin et al., 2014). A recent meta-analysis of observational studies confirms the potential benefits of testosterone therapy in aging men (Corona et al., 2016). However, the effects of sex steroid hormones may be sex-dependent, as androgens have been reported to decrease insulin sensitivity in women's adipose tissue (Corbould, 2007). The animal literature is also consistent with beneficial effects of testosterone on obesity. In the obese Zucker rat, testosterone supplementation reduced body weight and significantly improved metabolic outcomes, including plasma insulin levels and glucose tolerance (Davis et al., 2012). Conversely, depletion of endogenous testosterone by gonadectomy worsens the effects of HFD in male mice. Our lab previously reported that gonadectomized male mice on HFD have a greater increase in blood glucose levels, insulin insensitivity, and pro-inflammatory cytokine expression than do gonadally intact males maintained on HFD (Jayaraman et al., 2014). Moreover, the effects appear to extend to brain as conditioned media collected from cultured glial cells generated from obese mice reduced neuron survival and neurite outgrowth in primary neurons (Jayaraman et al., 2014).

Obesity interacts with inflammation—Obesity is characterized by a chronic state of low-grade inflammation (Hotamisligil, 2006; Kratz et al., 2014). Macrophages residing in metabolically active tissues modulate cytokine production and lipid metabolism, actions that are modulated by adoption of an activated state in response to circulating saturated fatty acids (Kratz et al., 2014). Adipose tissue, liver, and gut have been reported to contribute to overall systemic inflammation, although their relative and temporal influences are still incompletely defined. It appears that adipose inflammation occurs prior to liver inflammation in a C57BL/6J mice model of diet-induced obesity (van der Heijden et al., 2015). Additionally, in the same model, it was shown that an imbalance in the gut microbiome triggers systemic inflammation and brain inflammation prior to weight gain (Bruce-Keller et al., 2015). Much work has been done on the effects of obesity on inflammation in various tissues, which are briefly addressed below.

The adipose tissue: Adipose tissue plays an important role regulating healthy metabolism. Indeed, mice lacking white adipose tissue exhibit insulin resistance, hyperglycemia, hyperlipidemia, and liver steatosis, all of which can be reversed via adipose tissue transplants (Gavrilova et al., 2000). In obesity, adipose tissue is characterized by

hypertrophic adipocytes and infiltration of macrophages, which are an important source of inflammation (Wellen and Hotamisligil, 2003). Additionally, adipocytes also can secrete pro-inflammatory cytokines and adipokines, further increasing inflammation and attracting macrophages (Greenberg and Obin, 2006). It is thought that pro-inflammatory cytokines contribute to the disruption in glucose homeostasis and insulin resistance often linked with obesity (Xu et al., 2003). In support of this position, deletion of macrophages can restore insulin and glucose homeostasis associated with obesity (Patsouris et al., 2008).

Central or visceral adipose tissue appears to be especially problematic because it preferentially accumulates triglycerides and is less sensitive to insulin than other fat depots (Märin et al., 1992; Wajchenberg, 2000). In the case of AD, central adiposity may be the best metabolic predictor of disease risk (Luchsinger et al., 2012; Whitmer et al., 2008). The distribution of fat differs between sexes, with abdominal visceral fat being more prevalent in men than in women (Bouchard et al., 1993; Enzi et al., 1986). Interestingly, visceral fat increases with aging, particularly in obese women, which may be attributed to depletion of estrogens at menopause (Matsuzawa et al., 1995). The gene profile in fat tissue also changes in a sex-specific manner. In response to obesity, males have a greater increase in expression of genes involved in inflammatory pathways, whereas females have a greater increase in expression of genes involved in insulin signaling and lipid metabolism. This may contribute to the observation that females have less central adiposity than men and are relatively protected against glucose and insulin resistance. These effects cannot be entirely explained by the presence of sex steroid hormones, since prepubertal ovariectomy only partially shifts the genetic profile to a more “male-like” expression (Grove et al., 2010).

The liver: The liver is also significantly affected by obesity-induced inflammation. Both diet- and genetically-induced obesity in animal models results in non-alcoholic fatty liver disease (NAFLD), which is characterized by the presence of steatosis, insulin resistance, systemic inflammation, and increased NF κ B activity (Cai et al., 2005; Fabbrini et al., 2009). NF κ B activation alone can cause insulin resistance without steatosis, which suggests that inflammation interferes with insulin signaling (Cai et al., 2005). Moreover, neutralizing antibodies against the pro-inflammatory cytokines IL-6 and TNF α are sufficient to partly reverse liver pathology associated with obesity (Fabbrini et al., 2009; Li et al., 2003).

The toll-like receptors, which recognize pathogen-associated molecular patterns, appear to be especially important in obesity-induced liver inflammation. Activation of TLRs culminates in NF κ B signaling cascade activation, which controls the expression of inflammatory genes including IL-6, pro-IL-1 β , TNF α and COX2 (Kawai and Akira, 2007). TLR4 is of special interest because of the ability of saturated fatty acids to activate this receptor (Lee et al., 2001; Shi et al., 2006), although this effect is still controversial (Erridge and Samani, 2009). Most findings suggest that TLR4 is involved in a number of inflammatory pathways associated with various neuropathologies as well as obesity, metabolic syndrome, and insulin resistance (Ahmad et al., 2012; Crack and Bray, 2007; Jia et al., 2014; Jialal et al., 2012; Pascual et al., 2011; Reyna et al., 2008; Wang et al., 2013). TLR4 is particularly important in the liver, where it was demonstrated that hepatocyte-specific TLR4 knockout mice maintained on HFD exhibited improved metabolic and inflammatory parameters, including ameliorated steatosis, glucose tolerance, insulin

sensitivity, and reduced expression of pro-inflammatory cytokines in plasma, fat and liver, in comparison to wild-type mice fed HFD (Jia et al., 2014).

The association between obesity and systemic inflammation has raised the question of whether this relationship could influence AD outcomes. Indeed, an acute model of NAFLD increases inflammation in the brain of non-transgenic and AD transgenic mice. Chronic NAFLD accelerates cerebral amyloid angiopathy, tauopathy and neuron loss, suggesting that aging and NAFLD are sufficient to trigger AD-like pathology (Kim et al., 2016).

The microbiome: Recently, the role of the gut and microbiome in obesity and inflammation has received increased attention. The human gut microbiome is the largest reservoir of microbes in the body, containing about 10^{14} microorganisms (Bhattacharjee and Lukiw, 2013). It is becoming evident that the intestinal microbiome influences the host's function well beyond the gut. Indeed, the microbiome has been implicated in a variety of diseases, including obesity, diabetes, non-alcoholic fatty liver disease, autism, multiple sclerosis, and cardiovascular disease (Caracciolo et al., 2014). Further, recent reviews have suggested a link between AD and the microbiome (Bhattacharjee and Lukiw, 2013; Hill et al., 2014a; 2014b; Shoemark and Allen, 2015), an idea supported by evidence of relationships between the microbiome, systemic inflammation, brain inflammation, and cognitive impairment (Bruce-Keller et al., 2015; Daulatzai, 2014).

One of the main factors affecting microbiome composition is diet (Caracciolo et al., 2014). Microbiome imbalance and disruptions in gut homeostasis have been observed in diet-induced as well as in genetic models of obesity (Ley et al., 2005; Turnbaugh et al., 2008). Microbiome imbalance leads to increased intestinal permeability, translocation of bacteria to the bloodstream, and systemic inflammation (Cani et al., 2008). In turn, systemic inflammation and consumption of high-energy diet can disrupt the blood brain barrier and cause cognitive impairments (Kanoski et al., 2010; Zlokovic, 2008). It is thought that these processes may facilitate the entrance of activated immune cells and bacterial components into the brain, and contribute to cognitive impairment (Pistell et al., 2010). An interesting development in support of this hypothesis is the recent finding that A β can act as a pore-forming antimicrobial peptide, suggesting that A β accumulation could occur in response to infection (Kumar et al., 2016). Perhaps consistent with this idea is the finding that the endotoxin LPS can potentiate A β fibrillogenesis, which suggests that elevated endotoxin levels during infections and gut leakage may drive pathogenesis AD not only by increasing inflammation, but also by increasing A β deposition (Asti and Gioglio, 2014). In general, infections are associated with increased risk of AD (Alonso et al., 2014; Miklossy, 2011; Nee and Lipka, 1999; Perry et al., 2003) and some viral infections may actively contribute to AD pathogenesis, since pathogens that evade elimination by the immune system lead to chronic inflammation, neuronal damage and A β deposition (Hill et al., 2009; Miklossy, 2011; Zhao and Lukiw, 2015).

Interestingly, there are sex differences in the microbiome. In microbiome transplantation experiments, the sex of the microbiome donor determined the metabolic outcomes in the recipient. Specifically, female mice that received a male microbiome transplant showed increased levels of serum testosterone and lowered serum concentrations of

glycerophospholipid and sphingolipid long-chain fatty acids, which are characteristically male (Markle et al., 2013). Moreover, blocking AR signaling attenuated all of the male microbiome-specific changes in female host metabolites, suggesting that the increased testosterone from the male microbiome transfer was critical for the generation of host metabolomic phenotypes (Markle et al., 2013). Other studies have also demonstrated sex differences in microbiome manipulations, including altered BDNF and serotonin levels in germ-free male animals but not in females, which suggests that the sexes differ in their sensitivity to microbiome changes (Clarke et al., 2012).

Obesity and AD are both characterized by sex differences and regulated by sex steroid hormones. Moreover, inflammation represents a point of interaction between obesity and AD, which can also be modulated by sex steroid hormones. Adipose tissue, liver, and gut contribute to the systemic inflammation and impaired glucose homeostasis associated with obesity, as well as to cognitive deficits. Thus, obesity may accelerate the onset of AD and exacerbate its progression at least in part through inflammatory pathways, which can be modulated by sex steroid hormones, offering an opportunity for therapeutic interventions.

3. Air pollution

An environmental risk factor for AD that may contribute to the relationships between AD, inflammation, and sex is air pollution. Polluted air is a mixture of gases and particulate matter (PM) of heterogeneous size and composition. Epidemiological data indicates that air pollution is responsible for 5.5 million deaths worldwide and 141.5 million disabilities (Forouzanfar et al., 2015). One well established effect of air pollution is cognitive decline. For example, women chronically exposed to coarse (2.5 μm – 10 μm diameter) and fine (< 2.5 μm diameter) particles show faster cognitive decline with aging (Weuve et al., 2012). Likewise, middle-aged and old men and women living in areas with high concentrations of fine particles show worse cognitive performance (Ailshire and Clarke, 2015). Similar results have been reported other components of air pollution, including ozone (Chen and Schwartz, 2009). Findings in human populations have been reproduced in rodent models, with varying degrees of memory impairment associated with both acute and chronic exposure to air pollution paradigms (Avila-Costa et al., 1999; Cheng et al., 2016b; Fonken et al., 2011; Rivas-Arancibia et al., 2010; Zanchi et al., 2010).

Strikingly, neurodegeneration has been found in people who live in areas with extreme levels of PM, regardless of age. Some of these findings indicate that exposure to air pollution environments can increase A β production and deposition as well as elevate neuroinflammation in children and young adults (Calderon-Garciduenas et al., 2003; 2008). Similar links between air pollution and A β have been reported in mice and dogs (Bhatt et al., 2015; Calderón-Garcidueñas et al., 2003), which collectively point to an interaction between air pollution and AD pathogenesis (Block and Calderón-Garcidueñas, 2009). Given the role of inflammation in the pathogenesis of AD, it seems reasonable that air pollution may be acting through pro-inflammatory pathways to increase AD risk. Perhaps consistent with this idea is evidence that persons with factors that increase inflammation, like *APOE4*, are at even greater risk of developing AD-like neuropathology when exposed to air pollution (Calderon-Garciduenas et al., 2008; 2015).

Air pollution induces systemic inflammation and brain inflammation—An

important deleterious effect of air pollution exposure is induction of focal as well as systemic inflammation. Ultrafine particles (< 100nm) are able to translocate into the lung epithelia (Semmler-Behnke et al., 2007), can be taken up by resident macrophages (Donaldson et al., 1998), and can form ultrafine particulate-protein complexes (Kreyling et al., 2006). These complexes allow air pollution particles to circulate throughout the body and deposit in organs including the heart and liver (Kreyling et al., 2002; Semmler et al., 2004) and perhaps brain. Therefore, air pollution exposure represents a risk for other major inflammatory diseases like pulmonary disease, cardiovascular disease, and stroke (Brook et al., 2010; Chauhan and Johnston, 2003; Liu et al., 2016). The presence of PM in tissue leads to macrophage recruitment and leukocyte infiltration, as well as systemic microvascular dysfunction (Nurkiewicz et al., 2005), and production of cytokines and acute-phase proteins, which can be detected in the bloodstream (Goldsmith et al., 1998; Tan et al., 2000; van Eeden et al., 2001). Air pollution not only induces chronic inflammation, but also has synergistic effects with other inflammatory conditions including aging, diabetes or hypertension (Dubowsky et al., 2006; Genc et al., 2012). Behavioral changes triggered by air pollution include memory impairment and depressive-like behaviors (Avila-Costa et al., 1999; Cheng et al., 2016a; Davis et al., 2013; Fonken et al., 2011; Morgan et al., 2011).

In the brain, PM exposure can directly induce degeneration and neuroinflammation. PM can also indirectly contribute to the effects of air pollution through systemic inflammation. Inhalation of PMs can induce oxidative stress (Zhang et al., 2012), inflammation, and even neuronal cell death, and particles can be taken up by the olfactory neurons into the brain (Cheng et al., 2016b; Oberdoster et al., 2004). The effects of cytokines and PM exposure on the microvasculature can also lead to blood brain barrier breakdown (Calderon-Garciduenas et al., 2008). Additionally, PM can directly affect glutamatergic neuronal health through downregulation of GluA1 and increased susceptibility to excitotoxicity (Morgan et al., 2011). PM also activate glial cells and induce cytokine release (Cheng et al., 2016a; Fonken et al., 2011; Levesque et al., 2011; Morgan et al., 2011), which is associated with fewer dendritic spines in the hippocampus and impaired memory (Fonken et al., 2011). Thus, air pollution induces a range of systemic and neural effects that may increase vulnerability to AD.

Exposure to air pollution affects males and females differently—Deleterious

effects of air pollution show sex differences. In terms of mortality, exposure to coarse and fine particles and to ozone were strongly correlated with lung cancer deaths, systemic inflammation, and all natural cause mortality only in males (Abbey et al., 1999; Hoffmann et al., 2009), although other studies identified no sex differences in air pollution-related all-cause mortality rates (Naess et al., 2007; Pope et al., 1995). The interaction of age and sex may be more important than sex alone. Age-dependent reduction in sex hormone levels, which is more drastic in women, may affect susceptibility to air pollution. Women > 60 years of age are at a five-fold greater risk for coarse particle-associated heart mortality than women < 60. In comparison, men aged > 60 years are only two-fold more likely to have coarse particle-associated heart death than young men (Zeka et al., 2006). In line with this, female patients are more sensitive to the effects of air pollution before the age of 15 and

after age 65, indicating that the reduced levels of sex steroid hormones during these ages may play a role in susceptibility to air pollution in women (Wang and Chau, 2013). In terms of neural effects, a comparison of cognitive impairment in children exposed to air pollution found the greatest deficits in girls that were both obese and *APOE4* carriers (Calderón-Garcidueñas et al., 2016).

Sex steroid hormones have been shown to interact with air pollution. Estrogen treatment protects against neurodegeneration and oxidative stress induced by ozone inhalation in ovariectomized rats (Angoa-Pérez et al., 2006). Air pollution can also affect sex steroid production. One study demonstrated that traffic policemen exposed to urban pollutants have lower free testosterone values than control administrative staff policemen (Sancini et al., 2010). It is likely that different components of air pollution and different exposure times will have distinct effects on the interaction with sex steroid hormones, but few studies have examined this relationship. One study shows that male rats exposed to oil paint vapor for 10 weeks have increased serum testosterone levels if exposed for 1 hour/day, but significantly lower levels if exposed for 8 hours/day (Ahmadi et al., 2015). Several compounds in air pollution are described as endocrine disruptors and can act on multiple organs by affecting metabolism, which links air pollution to obesity, diabetes, cardiovascular problems and AD (Maqbool et al., 2016; Newbold et al., 2008; Rudel et al., 2003). Despite the compelling advances in this area, this relationship between air pollution and sex remains to be fully elucidated.

Air-pollution associated neurodegeneration may be the result of chronic systemic inflammation, as well as of oxidative stress, neuroinflammation, and A β production. Exposure to air pollution increases risk of cognitive impairment and AD, which may be exacerbated by other factors that increase inflammation, such as *APOE4*, aging, and decrease in sex steroid hormone levels.

Conclusion

AD is a multifactorial disease for which sex differences are observed in both the vulnerability to its development and the manifestation of its pathology. How sex affects AD has only been partially determined. Risk for AD in both men and women appears to be increased by the normal, age-related decrease in their primary sex steroid hormones, testosterone and estradiol, respectively. As has been reviewed previously (Brinton, 2008; Li and Singh, 2014; Pike et al., 2009), the increased risk for AD associated with hormone depletion is generally thought to result from the loss of numerous neuroprotective actions of estradiol, testosterone, and other neurosteroids. With the increasing appreciation of the contributions of both systemic and neural inflammation in AD pathogenesis, the established role of sex steroid hormones as regulators of glial function and inhibitors of inflammatory signaling has acquired new significance. Nonetheless, the translation of the potential therapeutic benefits of sex steroids to the prevention and perhaps treatment of AD has yet to be realized.

In addition to age-related reductions in sex steroid levels, AD risk is also increased by numerous genetic and environmental factors (Figure 1). Among these, perhaps the most

important is *APOE4*. The interactions among sex, sex steroid hormones, and *APOE4* have been noted for many years, yet they remain poorly defined. Notably, the AD risk associated with *APOE4* disproportionately affects females both in humans (Altmann et al., 2014; Farrer et al., 1997; Payami et al., 1994) and rodents (Cacciottolo et al., 2016). Interestingly, whereas sex steroid hormones generally exert anti-inflammatory effects, *APOE4* is linked with exaggerated pro-inflammatory responses. The associations between sex, sexual differentiation, and microglia (Lenz et al., 2013; Schwarz et al., 2012) suggest interesting possible links with *APOE4* that may be relevant to AD.

AD risk is also increased by a range of lifestyle and environmental factors, including obesity and air pollution (Figure 1). The gene – environment interactions among *APOE4*, obesity and air pollution as they apply to AD are largely unknown. As suggested by initial evidence, AD risk is predictably worsened by the combination of risk factors. However, the nature of such interactions is unclear, including how they are affected by sex, whether they share common mechanisms such as inflammation, and whether they are mitigated by sex steroids. For example, obesity appears to have more deleterious effects on men than women, whereas women are more impacted by *APOE4*. In an interactive context, how do the combination of obesity and *APOE4* status affect AD risk in men versus women? Similar arguments can be made for air pollution and a host of other risk factors. Moving forward, it appears untenable to focus on individual components of pathogenesis in solving the AD crisis. Like cancers and other complex age-related diseases, AD is multifactorial and differs according to sex and, by extension, by sex steroid hormones. Progress in identifying at-risk populations and both developing and applying therapeutics will require attention to individual gene profiles, lifestyle and environmental exposures, sex, and how these variables interact.

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Highlights

- Multiple factors regulate vulnerability to Alzheimer's disease
- Alzheimer's pathology is promoted by inflammation and inhibited by sex steroids
- Alzheimer's risk is also affected by sex, *APOE*, obesity and air pollution
- Evidence suggest numerous interactions among Alzheimer's risk factors

Figure 1.

Inflammation is widely theorized to act as a significant contributor to Alzheimer's disease pathogenesis. Neuroinflammation is associated with activation of microglia and astrocytes, which increase expression of pro-inflammatory cytokines that can promote accumulation of the pathological proteins β -amyloid and hyper-phosphorylated tau. Genetic (*APOE4*), environmental (obesity, air pollution) factors that increase Alzheimer's risk are associated with elevated inflammation. Sex steroid hormones may affect Alzheimer's risk in part by inhibiting inflammation, modulating glial cells, and regulating interactions among risk factors. Illustration was generated using images from www.mindthegraph.com.