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Review article

Estrogens, inflammation and cognition

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ABSTRACT

The effects of estrogens are pleiotropic, affecting multiple bodily systems. Changes from the body's natural fluctuating levels of estrogens, through surgical removal of the ovaries, natural menopause, or the administration of exogenous estrogens to menopausal women have been independently linked to an altered immune profile, and changes to cognitive processes. Here, we propose that inflammation may mediate the relationship between low levels of estrogens and cognitive decline. In order to determine what is known about this connection, we review the literature on the cognitive effects of decreased estrogens due to oophorectomy or natural menopause, decreased estrogens' role on inflammation – both peripherally and in the brain – and the relationship between inflammation and cognition. While this review demonstrates that much is unknown about the intersection between estrogens, cognition, inflammation, we propose that there is an important interaction between these literatures.

1. Introduction

Hormone manipulations are common in women; these include variations in hormones administered for cessation of menstruation, menopausal symptoms, and ovarian removal for disease prophylaxis (Barbaglia et al., 2009; Whiteman et al., 2008). The latter two cases principally affect either women in natural menopause or young women who carry the Breast Cancer 1 and 2 gene variant (BRCA1 and BRCA2). In spite of the fact that the former is due to the natural process of aging, and the latter, to the removal of the ovaries, they are similar in that both lead to decreased levels of 17β-estradiol (E2) that ultimately leave women with lower levels of estrogens. Converging lines of research suggest that low levels of estrogens may lead to cognitive decline. Low levels of estrogens have been implicated in the etiology of dementia in women (Rocca et al., 2014; Yaffe et al., 1998) – for instance, there is a greater proportion of women with Alzheimer's disease (AD) than men, not always accounted for by women having a greater longevity (Andersen et al., 1999; Fratiglioni et al., 1997) – and an increased risk of dementia in women who have undergone surgical removal of the ovaries at a young age (Rocca et al., 2007). An outstanding question is whether the relationship between low levels of estrogens, cognitive decline and dementia is due to the direct effect of the lack of E2 on neurons or indirect effects on other body systems and, in particular, the immune system.

For the most part, the mechanism for this cognitive decline has been attributed to the effects of low levels on neurons directly. Animal studies in female rodents have shown that low levels of E2 have direct effects on neurons leading to synapse loss and lower connectivity (e.g. Woolley and McEwen, 1994; Woolley, 2007), which are important hallmarks of AD in humans (Terry et al., 1991). Young female rats that have had their ovaries removed (ovariectomized; OVX'd) have significantly lower levels of the synaptic proteins phosphosynapsin and synaptophysin in the hippocampus (O'Leary et al., 2009; Velázquez-Zamora et al., 2012), while OVX'd females with E2 treatment show increased spine density of hippocampal CA1 pyramidal cells (Woolley and McEwen, 1994) that form synaptic contacts, producing increased neuronal excitability (Woolley et al., 1997).

However, another possible mechanism for cognitive decline might be brain inflammation due to the response of the immune system to decreased levels of E2 (Straub, 2007). Women who have had their ovaries removed as well as those in natural menopausal exhibit systematic inflammation (e.g. Cioffi et al., 2002; Abu-Taha et al., 2009). Increased levels of pro-inflammatory markers such as interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α) have been found in women who have had their ovaries surgically removed (e.g. Pacifici et al., 1991). Levels of pro-inflammatory markers interleukin-6 (IL-6), IL-1, TNF-α increase significantly in menopausal women when E2 synthesis declines (Pfeilschifter et al., 2002). Inflammation is also implicated in the pathophysiology of AD in both men and women (e.g. Altsteil and Sperber,

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1991; Breitner, 1996; Mrak et al., 1995) suggesting a strong link between cognitive decline, low levels of estrogens, and inflammation.

Support for the idea that peripheral inflammation might affect cognition comes from research looking at inflammation and cognition directly. Male mice given an intravenous injection of human interleukin-1α (IL-1α) take significantly more trials to learn the response that would allow them to avoid a shock, but this memory impairment reverses when an antibody against IL-1α is injected first (Banks et al., 2001). Lastly, that inflammatory molecules can breach the blood–brain barrier (BBB) and are linked to cognitive impairment (Banks et al., 2002) provide the premise that inflammation may mediate the relationship between low levels of estrogens and cognitive changes. This idea is elaborated upon in a review exploring the evidence that AD is an inflammatory neurodegenerative disease as a result of disruption of the BBB (Sohrabji, 2007). This review provides one of the only cohesive discussions of estrogens in relation to inflammation in the pathogenesis of AD, a condition of cognitive decline.

The BBB functions as a physical barrier made up of astrocytes, endothelial cells and pericytes that barricade circulating immune cells from the central nervous system (Abbott et al., 2006). Tight junctions between adjacent microvascular endothelial cells are regulated by the transmembrane proteins, claudin, occludin, and junction adhesion molecules, which are important for maintaining the integrity of the BBB (Mandell and Parkos, 2005). Thus, the BBB is normally closed to most immune cells that cannot easily traverse these barriers. However, decreased E2 has been shown to increase the permeability of the BBB in female rats (Bake and Sohrabji, 2004) and in female mice (Burek et al., 2010). Specifically, following treatment with 2 μg/kg E2 per day, endothelial cells extracted from the brains of female mice show an upregulated expression of the tight junction protein, claudin-5, and an increased transendothelial electric resistance, suggesting that E2 is important in maintaining the BBB's integrity (Burek et al., 2010). As well, in response to high hydrostatic pressure, the BBB of OVX'd female rats show a 500% increase in permeability as compared to that of rats with intact ovaries. With the administration of 0.5 mg E2 and 5 mg estriol, differences between the estrogens-treated group and those with intact ovaries disappeared (Cipolla et al., 2009). Young, untreated OVX'd rats also show significantly greater dye transfer across the BBB, further indicating that low levels of E2 levels are associated with a compromised BBB integrity (Bake and Sohrabji, 2004).

Other research in female rodents support these findings. OVX'd mice treated with lipopolysaccharide (LPS), an endotoxin used to experimentally induce systemic inflammation, have increased levels of cytokines in their brains (Brown et al., 2010). Increased dye transfer into the brain was observed, but E2 treated mice did not show this increase dye transfer suggesting that breakdown of the BBB due to low levels of E2 plays a role in the ensuing neuroinflammation. Independent of the levels of E2, cytokines can degrade the BBB on their own; exposure to cytokines like IL-6 and interleukin-1β (IL-1β) can degrade the BBB (de Vries et al., 1996).

More research will be needed to disentangle whether low levels of E2 and increased levels of cytokines independently contribute to a breakdown of the BBB, or whether they act synergistically to potentiate this effect. That said, experiments as previously described support the possibility that breakdown of the BBB may be a mechanism by which low levels of E2 affect cognition via systemic inflammation.

Based on the evidence that there might be convergence between low levels of estrogens (E2, primarily), decreases in cognition, and brain inflammation along with a possible mechanism, the objective of this review is to describe some of works from these literatures in order to explore the hypothesis that inflammation may mediate the relationship between low levels of E2 and cognitive decline. The relationship between estrogens and cognition has previously been reviewed elsewhere (e.g. Henderson and Sherwin, 2007; Vearncombe and Pachana, 2009), as have the literatures on inflammation and cognition (e.g. Cunningham and Hennessy, 2015; Goshen and Yirmiya, 2007; Trollor and Agars, 2010) and on estrogens and the immune system (e.g. Fish, 2008; Kovats, 2015; Straub, 2007). Our specific objective is to report on a focused selection of research in both animal models and humans that interfaces the interactions between low levels of estrogens, cognition, and inflammation.

2. Literature search

A literature search was conducted using combinations of the following key words: (1) menopause, oophorectomy, ovariectomy, estradiol, estrogen replacement, hormone replacement, (2) inflamm*, neuroinflamm* (wildcards used to respectively to search for variations of the terms inflammation, neuroinflammation), cytokine, interleukin, interferon or (3) memory, cognit*, verbal, spatial, attention, dementia. Searches were conducted using the PubMed, Web of Science and PsychINFO databases, allowing us to survey the biomedical and behavioral literature. Articles published between 1980 and May 2015 were selected based the relevance of their titles and abstracts. We excluded articles that were primarily focused on mental health, obesity, asthma, HIV, endometriosis, and cancer. We also excluded articles that focused on health comorbidities unrelated to inflammation or cognitive changes. Where possible, we selected research conducted on female animals. However, if a particular area lacked research conducted on females alone, we reported on experiments using mixed sex populations or males. The interconnections between subjects and number of hits are illustrated in Fig. 1. Although we have provided the number of queries returned from each combination of search terms, they are presented only to illustrate the breadth of the literature. This strategy left us with 1023 studies in both animals and humans that we believe are key to exploring what is known about low levels of estrogens, cognition, and inflammation.

3. Cognition and low levels of estrogens

In this section, we describe the research exploring the relationship between low levels of estrogens and cognitive functioning in humans and in animal models. In humans, neuropsychological tests are used to assess various cognitive domains that are subserved by different areas of the brain. Global cognition is assessed across a number of domains, and the most common assessment to measure this in humans is the Mini Mental State Examination (MMSE; Folstein et al., 1975), especially in participants that may have cognitive impairment. A common experimental paradigm in animals includes training them to perform a task followed by memory testing after a certain amount of time has elapsed (Kinnavane et al., 2015).

We found 341 relevant studies that discussed low levels of estrogens and cognitive changes or dementia. Of these, 170 focused on humans and 171 focused on animal models. One hundred and eighty-four articles used oophorectomy or ovariectomy (a combined figure for humans and animal models) and 155 used natural menopause in humans.

This literature focuses primarily on E2 and the following conditions of low levels of E2: (1) women with bilateral oophorectomy and (2) women in natural menopause. Ovarian removal, as opposed to natural menopause, is a procedure that induces an abrupt loss of E2, as the ovaries are a woman's primary source of endogenous E2 (Ryan, 1982). Endocrine

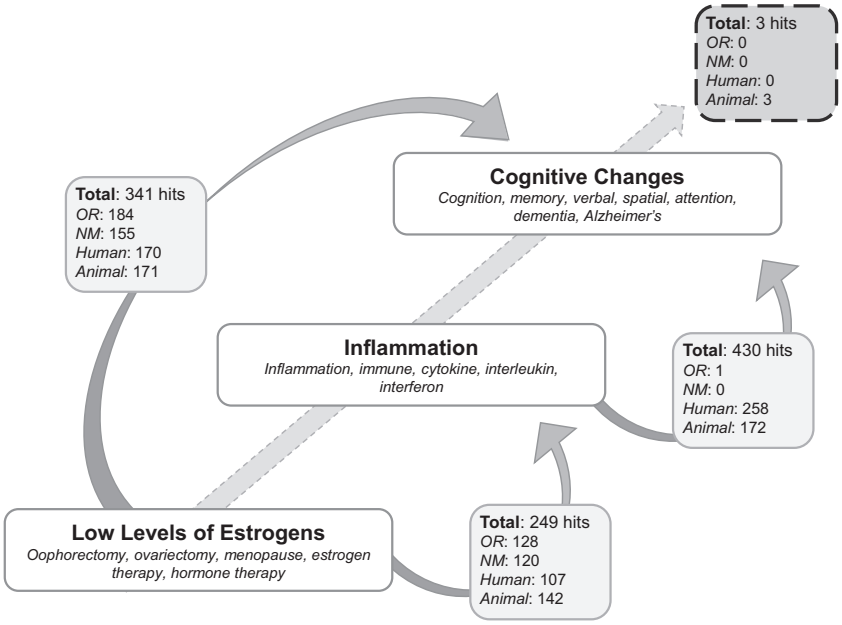

Fig. 1. We proposed that the relationship between low levels of estrogens and cognitive changes is mediated by inflammation. The interrelationships between estrogens, inflammation and cognition have been studied extensively as seen by the number of hits returned per combination of search terms. To date, there has yet to be an investigation of whether inflammation mediates the relationship between low levels of estrogens and cognitive changes in women. Note that the breakdown of articles into the categories of ovary removal, natural menopause, human and animals are not mutually exclusive. OR = ovary removal; NM = natural menopause.

Table 1
Serum E2 levels at different phases in women.

Phase	E2 range (pg/mL)	Average age	Onset
Cycling women, menses	30–50[a]	12[e,f]–51[g]	n/a
Cycling women, follicular phase	130–400[a]	12[e,f]–51[g]	n/a
Cycling women, luteal phase	100–150[a]	12[e,f]–51[g]	n/a
Pregnancy, first trimester	118–2947[b]	Reproductive age	n/a
Pregnancy, second trimester	1278–7192[b]	Reproductive age	n/a
Pregnancy, third trimester	3460–6137[b]	Reproductive age	n/a
Natural Menopause	2–46[c]	51[g]	Gradual
Bilateral oophorectomy	6–35[d]	Recommended < 35 for BRCA mutation carriers[h]; Variable age for other indications	Immediate

[a] Chabbert Buffet et al. (1998).
[b] Abbassi-Ghanavati et al. (2009).
[c] Measured two to three years after menopause, at a mean age of 52.3. Range calculated as ±2 standard deviations from the mean, Longcope et al. (1986).
[d] Measured two to three years after oophorectomy, at a mean age of 48.6 from Chakravarti et al. (1977).
[e] Anderson and Must (2005).
[f] Al-Sahab et al. (2010).
[g] In North America, from Palacios et al. (2010).
[h] Finch et al. (2014).

changes following bilateral oophorectomy include decreased levels of E2 and testosterone (Chakravarti et al., 1977; Korse et al., 2009). Natural menopause yields a more gradual and less extreme loss of E2; in natural menopause E2 levels gradually fall approximately 75% during the menopause transition (Overlie et al., 1999). Although average levels of endogenous E2 do not significantly differ in women who are naturally menopausal and those who have bilateral oophorectomy (Chakravarti et al., 1977), there is a greater range of possible E2 levels in naturally menopausal women as the ovaries continue to secrete small amounts of E2 following menopause (Judd et al., 1974). Table 1 presents typical ranges of serum E2 in women allowing comparison to be made across different types of reproductive hormone changes, and demonstrating that there is considerable variability in what low estrogens mean in a given study.

3.1. Cognition and oophorectomy

3.1.1. The effects of low levels of E2 and replacement

In general, the literature on women who undergo oophorectomy prior to natural menopause suggests there is a post-operative cognitive decline, notably in verbal memory (Sherwin, 1988; Phillips and Sherwin, 1992). In a small randomized controlled trial (RCT), women with bilateral salpingo-oophorectomy (BSO; surgical removal of the ovaries and fallopian tubes) at a mean age of 45 when tested four months post-surgically performed significantly better on measures of memory, perceptual speed, and abstract reasoning with injections of E2 valerate (three injections of 10 mg each over three months) compared to the placebo phase (Sherwin, 1988). Women with hysterectomy (surgical removal of the uterus) have no significant cognitive changes

post-surgically (Sherwin, 1988). Another RCT replicated this verbal memory decline; compared to their pre-surgical performance, women tested at a mean age of 48, three months post-BSO performed significantly worse on the Associate Learning task measuring verbal memory if they received a placebo (Phillips and Sherwin, 1992). In contrast, women who received monthly injections of E2 valerate (10 mg) showed no decline from their pre- to post-operative performance. Thus, in the placebo group, memory decline was related to low levels of E2.

Changes in global cognition, or cognitive ability across multiple domains, has also been found in women post-oophorectomy. Women with BSO (mean age = 41) show a significant decrease in performance on the MMSE and subtests of the Wechsler Memory Scale compared to their own pre-surgical baseline (Farrag et al., 2002). In this study, the MMSE was administered prior to BSO, and then again at three and six-months post-surgically. Scores on the MMSE and all subtests of the Wechsler Memory Scale were significantly lower at six months post-BSO compared to baseline. Performance was related to E2 levels; women with more than a 50% decrease in serum E2 experienced greater memory decline, suggesting changes were linked to low levels of E2. Further, based on a composite of 17 tests, surgical menopause, whether induced by hysterectomy or oophorectomy, are associated with a steeper decline on global cognition in elderly women (mean age = 78) (Bove et al., 2014). Results suggest that in addition to memory, cognition in general, may be compromised by oophorectomy.

Recent epidemiological studies show that oophorectomy prior to natural menopause is associated with a higher risk for dementia (Phung et al., 2010; Rocca et al., 2007) and parkinsonism in later life (Rocca et al., 2008). The incidence of dementia is higher in women who undergo the surgery at a younger age (Rocca et al., 2007). Furthermore, the study reported that the risk of dementia is higher in women who had a bilateral oophorectomy compared to a unilateral oophorectomy (removal of one ovary), and use of estrogen replacement up to age 50 in women with oophorectomy eliminates the increased risk of dementia. On the other hand, oophorectomy in women after menopause does not alter the risk of AD (Imtiaz et al., 2014).

Thus, results from RCTs, observational, and epidemiological studies provide evidence that loss of the ovaries that produce E2 before natural menopause induces changes in memory, and that the higher incidence of dementia in women with oophorectomies may be related to the severity and number of years since E2 withdrawal. Taken together, decline on measures of verbal and global cognition suggest that young women with oophorectomy and hence, low levels of estrogens, with no E2 replacement may be at risk for further cognitive decline since verbal, episodic memory tasks are highly sensitive predictors of progression to AD (Bastin and Salmon, 2014; Tierney et al., 2005). Epidemiological studies showing higher incidence of dementia in women with oophorectomy prior to natural menopause support the decline toward dementia.

Similar to the cognitive changes observed in humans following oophorectomy, ovariectomy (OVX) in animal models have been linked to deficits in memory and learning (e.g. Singh et al., 1994). Female rats OVX'd between three to four months of age and tested at five or 28 weeks post-OVX performed significantly worse on the active avoidance task compared to OVX'd rats that received implants restoring physiological levels of E2 starting three weeks post-surgically (Singh et al., 1994). Both two and twenty-five weeks of continuous E2 treatment was associated with significantly better performance and accelerated learning. Similarly, rhesus macaques tested at a mean age of 21 (OVX'd at a mean age of 9) on the delayed nonmatching-to-sample task, a measure of visual recognition, had significantly fewer correct responses than intact macaques of a comparable age (mean age = 23) when tested with a 10-min delay period after the recognition phase (Lacreuse et al., 2000). These studies not only demonstrate the importance of higher levels of E2 for performance on certain cognitive tasks but also a potential homology across mammals of the effects of ovarian removal with removal at a young age, detrimental to cognition.

3.1.2. Animal models

Animal models are instrumental in elucidating possible mechanisms underlying changes in cognition following oophorectomy. One of these mechanisms might be decreased connectivity in regions mediating cognition. A lower synaptic density in the CA1 region of the hippocampus (Silva et al., 2003), and a lower dendritic spine density in the CA1 and CA3 hippocampal pyramidal cells as well as in pyramidal cells of the prefrontal cortex (Wallace et al., 2006) are found in OVX'd, female rats. Similarly, a significant spine synapse loss in the CA1 region of the hippocampus is found in female mice following OVX or treatment with letrozole, an aromatase inhibitor that reduces levels of E2 synthesized (Zhou et al., 2010). In addition, E2 attenuates neuronal death by inhibiting the expression of the anti-apoptotic gene Bax and decreasing expression of the pro-apoptotic gene Bcl-2 (Sales et al., 2010). Linking these findings with the human condition of dementia, synapse loss is recognized as the basis for cognitive impairment in patients with AD (Terry et al., 1991), and detectable at autopsy in the CA1 region of older adults with mild AD (Scheff et al., 2007). Thus, by facilitating communication between neurons by increasing spine density and supporting the viability of neurons by preventing apoptosis, E2 may be important to staving off cognitive decline.

3.2. Cognition and natural menopause

Natural menopause is often used to model a state of E2 withdrawal despite the fact that the ovaries continue to make and secrete androgens that can be aromatized to E2 (Longcope et al., 1980). In addition to the continued synthesis of estrogens, natural menopause is also confounded by cultural expectations and perceptions of aging (Hogervorst et al., 2000). Perhaps because of both the biological and the socio-cultural aspects of natural menopause as well as large variations in circulating E2 levels in menopausal women (Toniolo et al., 1994), the literature using this model is rife with small effect sizes and inconsistent findings (Hogervorst et al., 2000; McCarrey and Resnick, 2015).

Studies examining cognition in menopause have been conducted cross-sectionally comparing different groups of women, or longitudinally to determine changes over the menopause transition. One cross-sectional study reports no cognitive differences between women whether they are categorized as pre-menopausal (mean age = 48), early peri-menopausal, late peri-menopausal, or post-menopausal (mean age = 52) after adjusting for sociodemographic variables and menopause-related symptoms (Luetters et al., 2007). However, other cross-sectional studies report that untreated menopausal women show frontal dysfunction (Keenan et al., 2001), or a performance decrement on measures of verbal learning, memory, motor ability, and working memory in the first year after the final menstrual period (Weber et al., 2013). Some longitudinal studies also show small decreases in verbal fluency (Fuh et al., 2006) and processing speed on the Symbol Digit Modalities Test (Greendale et al., 2010) through the menopause transition. While one literature review reports no significant relationship between levels of endogenous E2 and episodic memory or executive functioning in menopausal women (Henderson and Popat, 2011), another meta-analysis reports lower scores on measures of delayed verbal memory and phonemic fluency as well as higher depressive symptoms in menopausal

women (Weber et al., 2014). Since depression is associated with cognitive impairment (Burt et al., 1995), the increased risk for depressive disorders in menopause may be a source of variability across studies.

Results from various RCTs looking at the effects of estradiol-based hormone therapy (HT) in menopausal women show varying effects (Lethaby et al., 2008). Results from the Women's Health Initiative Study of Cognitive Aging (WHISCA) suggest that HT is detrimental to menopausal women. This large-scale drug trial found a significant increase in the risk of dementia and mild cognitive impairment (Shumaker et al., 2003), as well as lower scores on measures of verbal memory and learning in women treated with 0.625 mg/day equine estrogen (EE) and 2.5 mg/day medroxyprogesterone acetate (Resnick et al., 2006). Thus, results disagree with the oophorectomy literature, and in reconciling these findings, the hypothesis of a critical period for beneficial effects of HT is now a major consideration (Maki, 2013). Since a major weakness of the WHISCA was the age of participants – women were age 65 or older upon study enrolment – there is concern that the detrimental effects on cognition are due to the age of administration. There is evidence that estradiol-based HT is beneficial for maintenance of cognitive functioning if administered in the perimenopause, but yields at best, null, or at worst, detrimental effects if administered later than the early stages of menopause (Maki, 2013). Thus, the administration of HT in the WHISCA may have been outside the critical window of positive estrogenic effects, underscoring that when studying the effects of HT on cognition, it is important to take into account the type of HT as well as the method, age, and mode of administration (Miranda et al., 1999).

3.2.1. Animal models

In non-human primates such as the rhesus macaque or the baboon that, as a species, have a cessation of the reproductive cycle like menopause, females typically do not live long enough to undergo menopause (Bellino and Wise, 2003), making it difficult to study them during this life stage. However, when menopausal rhesus macaques have been tested as late as 20–27 years old, they perform significantly worse on a delayed response task compared to age-matched, premenopausal macaques (Roberts et al., 1997). Further, perimenopausal and menopausal rhesus macaques (mean age = 29) perform more poorly on the delayed nonmatching-to-sample task compared to an age-matched, premenopausal group, demonstrating a deficit in delayed recall (Hara et al., 2012). Although research on cognitive changes in non-human primates is limited, both studies suggest that the reduction in ovarian hormone secretion with menopause is associated with a performance decrement on memory recall that is assessed following a longer delay period.

While the non-human primate model has a scarcity of studies, rodents are often used in studies of hormone depletion with aging. However, evidence from rodent models of menopause is more difficult to interpret because neither rats nor mice undergo a human-like menopause. Instead, rodents undergo reproductive senescence characterized by the cessation of reproductive cycles due to the secretion of either constant high or low levels of ovarian hormones (Nelson et al., 1981). The first stage of reproductive senescence is persistent estrus, where E2 is elevated, followed by persistent diestrus, where E2 is diminished (Kermath and Gore, 2012). This pattern is substantially different from the endocrine changes observed in women in whom, after their last menstrual period, E2 typically decreases over one year (Longcope et al., 1986).

Nevertheless, studies of reproductive senescence in rats and mice can be instructive. One experimental manipulation to female rodents that simulates the endocrine conditions of human menopause is the administration of 4-vinyl cyclohexane diepoxide (VCD), which accelerates ovarian follicle atresia in order to deplete the primordial and primary follicles (Springer et al., 1996). After treatment of VCD in mice, levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) increase with a concomitant decrease of E2, mimicking the pattern of endocrine changes in menopausal women (Mayer et al., 2004). VCD models are valuable as they allow comparisons to be made in rodent models between a transitional and a surgical menopause. For example when middle-aged, female rats were treated with VCD or OVX'd and then tested on the water radial arm maze task, it was found that rats treated with VCD before OVX perform better than rats with OVX alone (Acosta et al., 2009). These results support the idea that a gradual and incomplete decrease in the levels of estrogens has less of an effect on cognitive outcomes than the abrupt E2 cessation that comes with oophorectomy or OVX. Thus, the data from natural menopause in both humans and animals is far less certain as to the effects of low levels of estrogens on cognition.

4. Inflammation and low levels of estrogens

The following section will discuss how estrogens affect levels of cytokines involved in cell signaling, changes in macrophage activity and cell adhesion molecules that facilitate the extravasation of leukocytes through the endothelium, all of which contribute to inflammation. We found 249 studies on low levels of estrogen and inflammation, of which 107 focused on humans and 142 on animal models. There were 128 studies that looked at inflammation and oophorectomy, and 120 studies that looked at inflammation and natural menopause.

Studies discussed here describe mainly the detrimental effects of inflammation, but it should be acknowledged that inflammation can sometime be beneficial. Neuroinflammation can attenuate damage in the brain by promoting controlled cell death and neuronal growth after injury (Ekdahl et al., 2009). Some proteins are associated with an anti-inflammatory response such as the cytokines interleukin-10 (IL-10), which can inhibit NF-KB mediated upregulation of other cytokines (Clarke et al., 1998), or the IL-1RA (interleukin-1 receptor antagonist) that inhibits the family of IL-1 cytokines (Dinarello, 1994). However, chronicity of an inflammatory state may be cytotoxic (e.g. Willard et al., 2000), and increased levels of markers such as TNF-α and IL-1β have been implicated in the pathogenesis of dementia (Blasko et al., 2004).

4.1. Inflammation and oophorectomy

4.1.1. Peripheral immune system

The literature suggests that, in general, reduction of endogenous E2 following oophorectomy is associated with increased peripheral inflammatory markers (e.g. Kalyan et al., 2011; Kumru et al., 2004) just as oophorectomy is associated with cognitive decline in young women. Levels of C-reactive protein (CRP; an acute phase inflammatory protein) measured from serum are three times higher in women after BSO with hysterectomy than in age-matched women with intact ovaries (Kalyan et al., 2011). There are other changes in inflammatory markers in women with BSO plus hysterectomy (mean age = 49) when compared to these markers pre-surgically including significant increases in CD8+ cytotoxic T-cells, a significant decrease of CD19+ B-cells, a decrease in the CD4+ (T-helper) to CD8+ ratio, and decrease of the cytokines interleukin-4 (IL-4), and interferon-gamma (IFN-γ) (Kumru et al., 2004). Following four weeks of treatment with 50 μg transdermal E2 patches applied once per week, changes in the levels of CD19+, the CD4+ to CD8+ ratio, and IFN-γ reverse, suggesting that these changes are due to low levels of E2.

While surgeries themselves have been documented to cause elevation of CRP, IL-6 and other inflammatory markers due to

trauma (Vittimberga et al., 1998), several studies have included women with hysterectomy only as a control group for surgical trauma (e.g. Pacifici et al., 1991; Cantatore et al., 1995). In women who undergo BSO and hysterectomy prior to natural menopause, there are higher levels of IL-1, TNF-α, and granulocyte–macrophage colony-stimulating factor (GM-CSF) post-surgically whereas there were no changes in the hysterectomy-only controls (Pacifici et al., 1991). The increase of these inflammatory markers occurs concomitantly with a significant decrease of endogenous E2 measured at a week post-BSO. Following a daily regime of 0.625 mg/-day oral conjugated equine estrogen, levels of IL-1, TNF-α, and GM-CSF all return to pre-surgical levels within four weeks of treatment. Hysterectomy only is not associated with any changes in cytokine levels, indicating that the increased cytokine levels are due to the changes in levels of E2 post-BSO and not to a urogenital surgery per se (Pacifici et al., 1991). Levels of IL-1 and IL-6 are significantly elevated at six months post-BSO compared to pre-surgical levels, supporting the idea that inflammatory changes after BSO are due to low levels of E2 and that they are sustained unless E2 is replaced (Cantatore et al., 1995).

Animal models for low levels of E2 and inflammation corroborate human studies, by showing that OVX is associated with changes in the peripheral immune response with increases in inflammatory markers such as: TNF-α, IL-1β, macrophage inflammatory protein-1, and macrophage colony-stimulating factor (e.g. Benedusi et al., 2012; Cenci et al., 2000). One possible mechanism for this may be induction of the transcription factor NF-KB via binding of estrogens on the two estrogen receptors ERα and ERβ (Kalaitzidis and Gilmore, 2005), which in turn regulates the expression of cytokines, cell adhesion molecules, chemokines and others inflammatory genes (O'Neill and Kaltschmidt, 1997). Treating OVX'd mice with 17α-ethinylestradiol (EE) leads to suppression of NF-KB-induced genes and subsequently decreases levels of vascular cell adhesion molecule (VCAM-1), TNF-α and the chemokine RANTES (Evans et al., 2001). Treatment with the estrogen receptor antagonist ICI 182, 780 also inhibits the reduction of VCAM-1, TNF-α and RANTES by EE treatment, suggesting that EE binding to the ERs leads to anti-inflammatory effects, although the receptor subtype is not specified in the study (Evans et al., 2001). Taken together, the effects of OVX on increased inflammatory markers and the reduction of markers mediated by the estrogen receptors underscores the relationship between inflammation and low levels of estrogens.

Another component of the peripheral immune system on which estrogens may act are T-cells (Straub, 2007). Increased T-cell proliferation has been observed in the bone marrow of mice OVX'd at four weeks, and in turn, there is an increase in TNF-α (Cenci et al., 2000). Likewise, mice OVX'd at four weeks have significantly decreased levels of IFN-γ, an inhibitor of T helper 17 (Th17) cells (Maret et al., 2003). Low levels of E2 leading to increased levels of TNF may stimulate Th17 T-cells, causing a downstream effect of increased interleukin-17 (IL-17), which plays a primary role in chronic inflammation (Straub, 2007).

4.1.2. Central nervous system

The central nervous system is also affected by peripheral immune system response. T-cells are implicated in the etiology of multiple sclerosis (MS), an autoimmune disease of the central and peripheral nervous system which affects approximately two to three times more women than men worldwide (Disanto and Ramagopalan, 2013). A hallmark of MS is demyelination of the axons and inflammation of the CNS, resulting in motor changes, fatigue, pain, vision loss, and cognitive symptoms (Lublin and Reingold, 1996).

Animal models of multiple sclerosis such as experimental autoimmune encephalomyelitis (EAE), causes inflammatory damage to the myelin sheaths of neurons via the action of Th1 and Th17 helper T-cells (Constantinescu et al., 2011). Low levels of estrogens also affect this disease model. Eight to twelve week-old OVX'd mice treated with EAE have an earlier disease onset compared to control females, and EAE mice – OVX'd or intact – treated with 3.2 μg of E2 benzoate show significant delays in the onset of symptoms (Jansson et al., 1994). OVX'd EAE mice also show a significantly earlier onset and disease severity than sham operated females, suggesting that estrogens modulate the presentation of EAE pathology (Offner et al., 2000). Furthermore, E2 treatment is associated with a dose-dependent inhibition of EAE in which higher doses produce lower scores on the cumulative disease index, a method for quantifying the pathological signs of EAE. Thus, levels of estrogens affect a nervous system disease that is influenced by inflammation.

Brain inflammatory mechanisms are upregulated after OVX too, as brain macrophages (microglia) are affected by low levels of E2 (Vegeto et al., 2001). After treatment with LPS, OVX'd, six-week old rats show microglial activation that was significantly reduced after administration of 50 μg/kg E2 (Vegeto et al., 2003). Activated microglia, or the primed microglia phenotype, is associated with the ability to synthesize pro- or anti-inflammatory cytokines depending on the microenvironment of the central nervous system (Perry and Holmes, 2014). One way that low levels of E2 may increase neuroinflammation is therefore through activation of microglia.

4.2. Inflammation and natural menopause

4.2.1. Peripheral immune system

Natural menopause brings peripheral immune system changes (Gameiro et al., 2010). Menopausal women (mean age = 56) show increased leukocyte adhesion and expression of interleukin-8 (IL-8), monocyte chemotactic protein-1 (MCP-1), RANTES and macrophage inflammatory protein-1α (MIP-1α), suggesting a low-grade, systematic inflammation (Abu-Taha et al., 2009). Menopausal women compared to pre-menopausal controls show elevated levels of cytokines, including IL-6, IL-18, IL-2, IL-4, GM-CSF, and granulocyte-colony stimulating factor (G-CSF) (Cioffi et al., 2002; Yasui et al., 2007), suggesting that the lower levels of E2 following menopause are associated with a pro-inflammatory phenotype.

HT seems to reverse the increase of pro-inflammatory markers in menopausal women (Störk et al., 2002). Menopausal women (mean age = 60) treated for 48 weeks with 1 mg/day E2 in combination with a low dose progestin have reduced levels of intercellular adhesion molecule 1 (ICAM-1), VCAM-1, and E-selectin, all involved in leukocyte extravasation or movement through the endothelium (Störk et al., 2002). An even lower dose of HT (0.25 mg/day E2) given for 12 weeks in menopausal women (mean age = 75) is associated with significantly reduced levels of CRP compared to the placebo (Prestwood et al., 2004).

4.2.2. Central nervous system

Menopausal women also show immune changes localized to the brain (Sárvári et al., 2012). Tissue from the National Institute on Aging Alzheimer's Disease brain banks show that macrophage-associated gene expression is upregulated in samples from the postcentral and superior frontal gyrus in menopausal women compared to younger, pre-menopausal women (Sárvári et al., 2012). Since menopausal women are older, one might conclude that such changes in gene expression were related to age (Franceschi et al., 2000). However, genes related to inflammation and the immune system are proportionally more highly expressed in older women than in older men (Berchtold et al., 2008). Taken together, results suggest that upregulation of inflammatory genes

in the brain are not solely driven by age, but may be related to E2 withdrawal in menopause.

Also suggestive of the effects of low levels of estrogens on central nervous system inflammation is the observation that the severity of MS symptoms varies across a woman's lifespan (Smith and Studd, 1992). There is a modulation of MS by hormone fluctuation most notably linked with remission of symptoms during the third trimester of pregnancy – when estriol and estradiol levels are elevated – and followed by a relapse postpartum when E2 levels are at their lowest (Korn-Lubetzki et al., 1984; Nott et al., 1976). Fifty-four percent of women with MS report worsening of symptoms following menopause, but 75% of women using HT report significantly better functioning compared to those not taking HT (Smith and Studd, 1992). These findings demonstrate that the severity of MS is linked to levels of circulating estrogens in women as symptoms are intensified when E2 is low. Taken together, observations of both peripheral and central nervous system inflammation at different reproductive stages of a women's life suggest that the immune system, especially inflammatory markers and inflammatory conditions are affected by levels of estrogens.

5. Inflammation and cognitive changes

We found 430 studies that discussed inflammation and cognitive changes or dementia, of which 258 focused on humans and 172 focused on animals. Although there is research on older humans (both males and females), the proportion of menopausal participants is seldom reported, and menopause status could only be inferred on the basis of age.

5.1. Human studies

There is a vast literature on inflammation and dementia that typically considers both sexes together. Nevertheless, it is worth considering as it points to the role of inflammation in cognitive decline. The observation that individuals (without regard to sex of participants) with rheumatoid arthritis who have used anti-inflammatory medications also had a lower incidence of AD generated a subsequent body of literature on inflammation and AD (McGeer et al., 1990, 1996). For the population at large, self-reported non-steroidal anti-inflammatory drugs (NSAID) use of two years or more is associated with a significant decrease in the relative risk of AD (Stewart et al., 1997). This finding has been replicated in the Rotterdam study, which also reports that usage of NSAIDs for over two year according to prescription records reduces the relative risk of AD approximately fivefold (in't Veld et al., 2001). Thus it appears that decreasing inflammation by use of NSAIDs confer protection against AD (Szekely et al., 2004) with one caveat: several clinical trials of cyclooxygenase-2 (COX-2) inhibitors – a form of NSAID – in older adults with AD have had limited success suggesting that decreasing inflammation after neurodegeneration has started does not curtail ongoing neurodegeneration and cognitive decline (McGeer and McGeer, 2007).

Inflammation may have a role in the etiology of mild cognitive impairment (MCI), a transitional stage between normal cognitive changes with aging and probable AD (Petersen et al., 1997), in older women (Trollor et al., 2011). Older women between ages 70 and 90 (presumed to be menopausal by age) with MCI, but not men, have significantly elevated levels of TNF-α (Trollor et al., 2011), suggesting a potential sex difference in the relationship between inflammation and cognitive impairment.

That said, in older, healthy women without MCI, the evidence that NSAID use affects cognitive functioning is mixed. A study of NSAID use in women between ages 70 and 81 shows that use of eight or more years confers better global cognition scores and lower odds of cognitive decline compared to never-users (Kang and Grodstein, 2003). However, an RCT assessing the effect of a low dose of aspirin in women aged 65 and older failed to find any significant differences between the treated and placebo group, except for a slightly decreased risk of decline on categorical fluency performance in the group taking aspirin (Kang et al., 2007). It should be noted, however, that aspirin is a relatively weak NSAID and the strongest findings have been using ibuprofen (Anthony et al., 2000). Ovarian status was not discussed in these studies, hence there is no information as to whether any of the participants have had an oophorectomy. To date, there have been no other clinical trials on the effects of other NSAIDs on cognitive functioning in healthy women.

Most of the studies examining cognitive performance in association with inflammatory markers have been conducted using both sexes. In a community-based sample of older women and men, levels of IL-6 and CRP are negatively associated with global cognition and executive function (Jefferson et al., 2011; Schram et al., 2007). Higher levels of IL-6 in plasma are associated with lower scores on the Telephone Interview for Cognitive Status-modified (Economos et al., 2013). Older adults (mean age = 71) with metabolic syndrome who have higher than mean levels of IL-6 and CRP have significantly lower scores on the modified Mini Mental State Examination, suggesting an association between inflammation and global cognitive decline (Yaffe et al., 2004). Despite some inconsistencies in the literature, CRP and IL-6 have been most frequently reported to be associated with lower cognitive performance in healthy, older adults (Trollor and Agars, 2010). Thus the data suggest that decreasing inflammation protects against AD, and high levels of CRP and IL-6 is correlated with lower scores on tests of global cognition.

5.2. Animal models

Animal models using LPS treatment have provided more insights into inflammation and cognitive impairment. Male mice treated with seven injections of 250 μg/kg LPS over one week exhibit memory and learning deficits, attributed to neuronal apoptosis in the hippocampus and cortex (Lee et al., 2008). LPS-induced neuroinflammation is also linked to an elevation of beta amyloid levels in male mice, which is associated with neuronal apoptosis (Lee et al., 2008). Further, a single intracerebroventricular injection of 5 μL LPS to male rats leads to ultrastructural damage to the hippocampal CA1 pyramidal neurons, including irregular chromatin masses, thickening of the perinuclear space, swelling of the mitochondria and rupture of the mitochondrial membranes (Gong et al., 2010). LPS male rats treated with 40 mg/kg ibuprofen or 5 mg/kg hydrogen sulfide, an anti-inflammatory compound that inhibits NF-KB, do not show impairment on the Morris water maze and treatment further attenuates damage to the CA1 pyramidal neurons (Gong et al., 2010). The relationship between LPS-induced inflammation and cognitive changes has been replicated by other groups on fear conditioning and water maze performance (Pugh et al., 1998; Zarifkar et al., 2010). Further, administration of a 2 μL injection of LPS to the hippocampus and anterior cortex of 4.5-month old mice transgenic for a tau mutation (both sexes) induces a significant increase of CD45, a microglial marker, as well as an increase of tau phosphorylated at the Ser396 position in the hippocampal CA1 which reduces its ability for binding to microtubules (Lee et al., 2010; Bramblett et al., 1993), demonstrating that inflammation may facilitate tau phosphorylation and the formation of neurofibrillary tangles observed in AD.

When female animal models are used to study the relationship of inflammation and cognition, inflammation is again associated with memory deficits. Year-old female mice given five days of

250 μg/kg LPS injections take significantly longer to complete the Morris water maze task than rats given saline injections (Sparkman et al., 2005). Furthermore, the effects of LPS are exacerbated by age; two-month old mice do not show the same degree of impairment as year-old mice. A single 1 mg/kg LPS exposure to female rats is associated with a 240% increase of activated microglia in the dentate gyrus and 35% reduction of hippocampal neurogenesis, showing that inflammation in the CNS can suppress processes that support learning and memory (Monje et al., 2003). The hippocampus and particularly the CA1 pyramidal neurons is one of the earliest brain regions to acquire neurofibrillary tangles and neuropil threads (Braak and Braak, 1991). Thus, there is a role for inflammation in the formation of neurofibrillary tangles, a hallmark neuropathology of AD.

Inflammation also has a detrimental effect on long term potentiation (LTP) in the hippocampus, the long-lasting, enhanced synaptic transmission induced by the high-frequency stimulation of coincident afferent nerve fibers, usually measured in the CA1 pyramidal neurons and thought to underlie the formation of memories (Kerchner and Nicoll, 2008; Shors and Matzel, 1997). LTP is a form of synaptic plasticity, playing a central role in the maintenance of cognitive function (Kerchner and Nicoll, 2008; Matynia et al., 2002). Injection of LPS in male rats induces attenuation of LTP in the dentate gyrus of the hippocampus (Hauss-Wegrzyniak et al., 2002) and entorhinal cortex (Vereker et al., 2000) resulting in a significant decrease of the excitatory post-synaptic potential in two key regions for the consolidation of memory. Injection of LPS also leads to an increase in reactive oxygen species production, which results in increased caspase-1 activity, an IL-1 converting enzyme (Vereker et al., 2000). IL-1β increase then leads to increased c-Jun N-terminal protein kinases (JNK) phosphorylation and decreased glutamate release and therefore impairment in learning and memory. Taken together, these studies support an association between LPS-induced inflammation and AD pathology as well as impairment of the underlying mechanism for memory formation leading to cognitive decline on hippocampal-dependent tasks. However, they do not shed much light on the effects of ovarian hormones on inflammation and cognition.

6. Estrogens, inflammation, and cognitive changes

In this section, we discuss what is known about the intersection of estrogens, inflammation, and cognition. With the exception of the previously discussed review exploring the evidence that AD is an inflammatory neurodegenerative disease and, in women, is due to low levels of estrogens modulating BBB permeability allowing peripheral immune response to enter the brain (Sohrabji, 2007), there is no further empirical support for the idea that inflammation may mediate the relationship between low levels of estrogens and cognition in women. There are only three studies of inflammation and estrogens that consider their combined effects on cognitive changes in OVX'd rats.

One of the very few studies to consider the relationship between inflammation and cognition in the context of low levels of estrogen is a study on Huntington's disease induced by 3-Nitropropionic acid (3-NPA), a mitochrondrial toxin that produces lesions and memory impairments (Menze et al., 2015). While inflammation was not studied directly, levels of inflammatory mediators changed in the brain with the administration of either E2 or a phytoestrogen, genistein. 3-NPA, OVX'd rats treated with E2 (2.5 mg/kg) or genistein (5, 10 and 20 mg/kg), perform significantly better than rats with no hormone treatment. In addition, the expression of COX-2, an inflammatory mediator, was significantly lower in the hippocampus of rats treated with E2, while 20 mg/kg of genistein reduced expression of COX-2 in both the hippocampus and cortex. Since treatment with E2 and genistein lowered both COX-2 expression and improved memory, results suggest that the improvement may be attributable to the anti-inflammatory effect of E2 or phytoestrogens.

In LPS (250 μg/kg) rats, passive avoidance performance is detrimentally affected by OVX at 12 weeks (Pourganji et al., 2014). In the training phase, rats in an apparatus with both light and dark compartments separated by a door are given a shock in the dark compartment. After a period of time in their cages, rats were returned to the apparatus for the test phase at one, and 24 h later. LPS-OVX'd rats spend significantly more time in the dark compartment compared to OVX-only or LPS-only mice in spite of conditioning to the shock stimulus. These results suggest that memory impairment caused by LPS is exacerbated in the OVX'd rats that have low levels of endogenous E2.

In addition to the absolute levels of E2, how and when E2 treatment is administered can have differential effects. In a study using rats also OVX'd at 12 weeks and treated with LPS, continuous administration of E2 (maintaining blood levels of 30 pg/mL) for two months is paradoxically associated with significant impairment on the water maze task compared to LPS-OVX'd rats given the placebo (Marriott et al., 2002). These results are conflicting with those previously reporting that even 25 weeks of continuous E2-treatment starting three weeks after OVX in rats is associated with improvements on the passive avoidance task (Singh et al., 1994). Despite the counterintuitive results in light of the research previously presented in support of E2 treatment in OVX'd animals being beneficial, this study points to the fact that timing and dosage of E2 require careful calibration. At the same time, results also suggest that research into anti-inflammatory treatments for early cognitive changes may be fruitful. Clearly, more studies are needed not only in humans, but in animal models using OVX and LPS that evaluate cognition.

7. Discussion

Given the number of women who undergo oophorectomy (Whiteman et al., 2008), and that women represent two thirds of current AD patients (Hebert et al., 2013), it is increasingly important to understand the mechanisms mediating cognitive decline in women. Older women have lower levels of estrogens and these are linked with both cognitive changes and inflammation. Thus, inflammation may be an important mediator to these cognitive changes.

We have reviewed the literature on estrogens and cognition, estrogens and inflammation, inflammation and cognition, and on the combination of all three in order to determine what is known about inflammation as a mediator of cognitive changes in women. We included as a proxy for low levels of estrogens, oophorectomy, OVX, and natural menopause. We have found that while there are studies in humans and animal models supporting the effects of estrogens on cognition and on inflammation individually, there is little directly linking inflammation with cognitive changes and almost none on the interaction between low levels of estrogens, inflammation, and cognitive changes.

7.1. Summary of the literature

Our search revealed numerous studies demonstrating that chronic, low E2 levels following oophorectomy are associated with cognitive impairments in both humans and animal models (e.g. Sherwin, 1988; Wallace et al., 2006). There are also many studies that have found elevated inflammatory markers in women with oophorectomies (Kumru et al., 2004). Further supporting the hypothesis that inflammation is associated with low levels of

estrogens, there are anti-inflammatory effects of E2 treatment on naturally menopausal women (Störk et al., 2002), suggesting that low levels of E2 elicit an inflammatory response that can be reversed by HT. We also found papers linking inflammation to cognition by showing that inflammation can inhibit neurogenesis (Ekdahl et al., 2003), affect differentiation of hippocampal precursor cells (Monje et al., 2003), and decrease LTP in the hippocampus (Yirmiya and Goshen, 2011). Despite the fact that all the pieces are present to suggest that low levels of E2 leading to inflammation which in turn, affects cognition, we found scant literature putting all of these pieces together with only one review making the direct link between low levels of estrogens, inflammation and dementia in women (Sohrabji, 2007).

Thus, one may question why, in spite of these links, more research has not emerged on the secondary effects of E2 withdrawal. One possibility is that the animal literature contains powerful examples of estrogens' direct effects on neurons (e.g. Woolley and McEwen, 1994; Woolley, 2007). Another possibility is that estrogens have often been described in the literature as "neuroprotective" (e.g. Wise et al., 2011), which taken out of context, may lend to the discourse that estrogens alone, act directly on neuronal health and therefore cognitive functioning. As a result, less attention is paid to pathways by which E2 withdrawal might affect cognition other than by its direct effects on neurons.

One example of such a pathway might be through the vasomotor symptoms experienced during menopause, which manifest in the form of hot flashes and night sweats (McKinlay and Jefferys, 1974). As the pathophysiology is currently understood, E2 reduction with natural or surgical menopause leads to upregulation of the serotonin receptor 5-HT_{2A} in the hypothalamus, which upon activation, is associated with a hyperthermic response (Berendsen, 2002). In naturally menopausal women who are not using hormone therapy, the frequency of hot flashes measured with a skin conductance monitor is associated with lower verbal memory and verbal fluency performance (Maki et al., 2008), supporting that vasomotor symptoms are correlated with declines in specific cognitive domains. While hormone therapy is commonly prescribed as an add-back for the decline in E2, the principal actor in this case is not E2, but rather secondary mechanisms in the CNS (Archer et al., 2011). Thus, in a similar way that lower levels of E2 can indirectly affect cognition through hot flashes, lower levels of E2 may affect cognition through inflammation.

7.2. Menopause and hormone therapy as a model for replacement of endogenous estrogens

There is a wealth of literature on E2 and cognition at the age of natural menopause. This may reflect a pragmatic consideration based on the sheer number of women being treated with HT. It is estimated that 2.7% of women between ages 45 and 64 in the USA were using an estrogen-progestin in 2010 (Jewett et al., 2014).

While studying menopause and HT can be helpful in understanding the broad effects of ovarian aging and HT as an ameliorating factor, using menopause and HT as models of low levels of estrogens and replenishing of hormones to determine cognitive decline or inflammation are problematic. First, menopause is not simply the gradual reduction of ovarian function but it also includes other effects of aging on the entire body. These other changes might also affect cognition or inflammation but not be directly related to ovarian involution and low levels of estrogens. We see an example of that in the observational studies on NSAIDs not matching the clinical trials of NSAIDs.

As well, despite the abundance of studies that use HT as an experimental manipulation in examining estrogens and cognition as well as estrogens and inflammation, there is considerable heterogeneity around the parameters associated with HT-use and its administration. HT is commonly formulated as estrogens only, or in combination with progesterone (Furness et al., 2012). For women who have undergone a hysterectomy, estrogens-only HT are commonly administered (Hickey et al., 2012), which can either be naturally derived (e.g. from pregnant mare urine), or synthetic (Scharbo-Dehaan, 1996). For women with an intact uterus, estrogen and progesterone combinations are given because the addition of progesterone, or its synthetic analogues, protects against uterine cancer (Hickey et al., 2012). Progesterone is administered either orally, using an intrauterine device, or transdermally, while estrogen is administered orally, intravaginally, or transdermally (Hickey et al., 2012). Thus, formulations, dosage, age, timing, and modes of administration differ across studies, rendering it difficult to compare results from experiment to experiment.

7.3. Studies using AD as a proxy for cognitive change when studying inflammation and cognition

Our review shows a broad literature linking inflammation with cognition. However, human studies in women alone or that include an analysis disaggregated by sex are limited. A major focus has been on inflammation and AD, and this literature has included men and women, often without disaggregating the data by sex for analysis. A bibliometric analysis of articles published in 2009 that were sampled from four high-impact journals of each subject area reveal that for human studies in immunology, <10% of data were analyzed by sex, and this figure was estimated to be 20% for studies in neuroscience (Beery and Zucker, 2011). Thus, it is challenging to interpret results for women due to the underrepresentation of female participants in research as well as how data are analyzed and reported.

Since a number of clinical trials with COX-2 inhibitors in AD have not resulted in significant improvement of symptomology or prognosis (McGeer and McGeer, 2007), it may be prudent to direct greater efforts to understanding the relationship between inflammation and cognition in the preclinical stages of AD. In addition, more research on the relationship between inflammatory markers and cognition in women would be helpful. Lastly, medical histories such as oophorectomy, HT, breast cancer treatment have an effect on both the immune and the nervous systems and thus, need to be taken into account. This will have important ramifications since exploring how downstream effects of estrogen withdrawal could affect cognitive functioning, such as by increasing inflammation, might lead to the development of therapeutics other than HT and for both women and men.

7.4. Hormones other than estrogens and inflammation

The synthesis of other reproductive hormones, such as progesterone, is affected by menopause and removal of the ovaries (Overlie et al., 1999). There is some evidence that low levels of progesterone are implicated in inflammation and that progesterone replacement can attenuate inflammation in rats. After traumatic brain injury (TBI), treatment with progesterone (two 16 mg/kg injections) reduces levels of inflammatory markers in male rat brains (Pettus et al., 2005). In preclinical models, progesterone also has a positive effect on spatial learning and memory test performance after TBI in male rats (Si et al., 2013). In male rats with AD-like symptoms, administration of progesterone (4, 8 or 16 mg/kg) improves cognition and decrease levels of TNF-α and IL-1β (Liu et al., 2013). Research in a female-only mice model of EAE shows that a progesterone implant decreases secretion of inflammatory markers IL-2 and IL-17 compared to placebo treatment (Yates et al., 2010). Another study in female mice reveal decreases in TNF-α, microglial marker CD11b and increased myelination with progesterone implants compared to controls (Garay

et al., 2012). Thus, while low levels of E2 might be responsible for direct effects on neurons, low levels of progesterone might also affect inflammation and thereby, cognition.

While evidence in preclinical models of progesterone treatment for inflammation have been promising, research in humans is more inconclusive. Some clinical trials of progesterone treatment in patients of both sexes with TBI (1 mg/kg twice daily for five days) show reduced mortality (Xiao et al., 2008) and in patients of both sexes with ischemia there is improvement in functional outcomes with a low dose (<1 mg/kg) treatment (Wright et al., 2007). Nevertheless, a recent clinical trial failed to demonstrate any benefit of progesterone treatment (0.05 mg/kg per mL of infusate) for acute TBI in a population of both sexes, and even a trend suggesting a detrimental effect in women (Wright et al., 2014). Given the current state of mixed findings in humans, more research will be needed to assess the efficacy of progesterone treatment for inflammation.

Testosterone is also secreted by the ovaries and is an important hormone for both women and men. Thus, it is not surprising that there is a parallel literature in studying the effects of low levels of testosterone on inflammation as a potential mediator of neurodegeneration in men. Low levels of free testosterone are found in men with dementia (Bowen et al., 2000; Hogervorst et al., 2001; Rosario, 2004). Men with AD also have higher levels of LH, and a positive association between LH and TNF-α (Butchart et al., 2012). Reproductive hormones, in general, may therefore be implicated in the etiology of cognitive changes acting through inflammatory mechanisms.

7.5. Clinical implications

In 2006, 3.3 women per 1000 in the USA had undergone an oophorectomy (Oliphant et al., 2010). Women undergo the surgery for various indications, and carrying a deleterious BRCA1 or BRCA2 mutation is amongst one of them. A prophylactic oophorectomy confers optimal cancer protection before age 35 in female carriers of a BRCA1/2 mutation with a family history of breast and ovarian cancer (Finch et al., 2014). For this population electing oophorectomy could induce cessation of ovarian function over fifteen years prior to the mean age of natural menopause. This means living longer with low levels of estrogens, and as discussed, these women are at higher risk of dementia than women who enter natural menopause. Although short-term HT does not increase the risk of cancer in BRCA mutation carriers who have not yet had cancer (Rebbeck et al., 2005), it is contraindicated for women with active or suspected breast or endometrial cancer (Ross et al., 2000; Weiderpass et al., 1999). As well, compliance to HT may be limited (Castelo-Branco et al., 1999; Faulkner et al., 1998), and compliance may decline over time due to cancer anxieties (Read et al., 2010). Thus, it is important to understand any and all mechanisms leading to these cognitive changes in order to develop novel therapies. Determining whether inflammation mediates the relationship between low levels of E2 and cognition would open opportunities for alternate, immunotherapies for attenuating cognitive changes in women with oophorectomies.

7.6. Future directions

It is important to conduct research that directly links low levels of estrogens, inflammation and cognition together. To test whether inflammation is one of the mediators of cognitive decline, we propose that a study should first demonstrate that low levels of E2 following BSO that is performed prior to natural menopause are associated with inflammation, and that inflammation is associated with cognitive changes. Then, inflammation should be inhibited and ensuing cognition evaluated. This two-step process would allow us to assess whether inflammation mediates the relationship between cognitive decline and low E2 levels. As previously suggested, support of this hypothesis would open opportunities for clinical trials of anti-inflammatories or other therapeutics to prevent cognitive decline in women who have had their ovaries removed prior to natural menopause.

While we have proposed inflammation as one of the potential mediators of the relationship between low levels of E2 and cognitive changes, the effects of E2 loss on other bodily systems and how they interact with the immune system cannot be understated. For instance, IL-6 and TNF-α have been shown to elicit an elevated response of the hypothalamic–pituitary–adrenal (HPA) axis (Turnbull and Rivier, 1999). A low dose of LPS to menopausal women stimulates release of adrenocorticotropic hormone (ACTH), cortisol and cytokine release, but levels are significantly lower in the group treated with transdermal E2 (Puder et al., 2001). Since lower levels of IL-1, IL-6 and TNF-α are found in the blood of E2-treated women, one possibility is that E2's suppression of the cytokines subsequently inhibits activation of the HPA axis and hence, a chronic stress response. Another downstream effect of low E2 in women is inflammation-related hypertension (Sandberg et al., in press). In turn, hypertension is predictive of decrements in cognitive functioning (van den Berg et al., 2009). Given the multiplicity of E2's effects throughout the body and the number of women who undergo oophorectomy, other effects secondary to low levels of E2 also merit further investigation.

8. Conclusion

We have reviewed the literature and presented examples of what is known about the intersection of estrogens, cognitive changes and inflammation in order to better understand the effects of oophorectomy prior to natural menopause as well as to provide a platform for new research directions. We have found that while there is literature supporting an interaction between low levels of estrogens, inflammation, and cognitive changes, there is no research to date that has provided empirical support in women. We call for these studies to be undertaken in order to spur the development of treatments both for women following natural menopause or oophorectomy, allowing for the development for treatments beyond HT.

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References

Abbott, N.J., Rönnbäck, L., Hansson, E., 2006. Astrocyte-endothelial interactions at the blood-brain barrier. Nat. Rev. Neurosci. 7, 41–53. http://dx.doi.org/10.1038/nrn1824.

Abbassi-Ghanavati, M., Greer, L.G., Cunningham, F.G., 2009. Pregnancy and laboratory studies: a reference table for clinicians. Obstet. Gynecol. 114, 1326–1331. http://dx.doi.org/10.1097/AOG.0b013e3181c2bde8.

Abu-Taha, M., Rius, C., Hermenegildo, C., Noguera, I., Cerda-Nicolas, J.-M., Issekutz, A.C., Jose, P.J., Cortijo, J., Morcillo, E.J., Sanz, M.-J., 2009. Menopause and ovariectomy cause a low grade of systemic inflammation that may be prevented by chronic treatment with low doses of estrogen or losartan. J. Immunol. 183, 1393–1402. http://dx.doi.org/10.4049/jimmunol.0803157.

Acosta, J.I., Mayer, L., Talboom, J.S., Tsang, C.W.S., Smith, C.J., Enders, C.K., Bimonte-Nelson, H.A., 2009. Transitional versus surgical menopause in a rodent model: etiology of ovarian hormone loss impacts memory and the acetylcholine system. Endocrinology 150, 4248–4259. http://dx.doi.org/10.1210/en.2008-1802.

Al-Sahab, B., Ardern, C.I., Hamadeh, M.J., Tamim, H., 2010. Age at menarche in Canada: results from the National Longitudinal Survey of Children & Youth. BMC Public Health 10, 736. http://dx.doi.org/10.1186/1471-2458-10-736.

Altsteil, L.D., Sperber, K., 1991. Cytokines in Alzheimer's disease. Neuro-Psychoparmacol. Biol. Psychiat. 15, 481–495.

Andersen, K., Launer, L.J., Dewey, M.E., Letenneur, L., Ott, A., Copeland, J.R.M., Dartigues, J.-F., Kragh-Sorensen, P., Baldereschi, M., Brayne, C., Lobo, A., Martinez-Lage, J.M., Stijnen, T., Hofman, A., 1999. Gender differences in the incidence of AD and vascular dementia: the EURODEM Studies. Neurology 53. http://dx.doi.org/10.1212/WNL.53.9.1992, 1992–1992.

Anderson, S.E., Must, A., 2005. Interpreting the continued decline in the average age at menarche: results from two nationally representative surveys of U.S. girls studied 10 years apart. J. Pediatr. 147, 753–760. http://dx.doi.org/10.1016/j.jpeds.2005.07.016.

Anthony, J.C., Breitner, J.C.S., Zandi, P.P., Meyer, M.R., Jurasova, I., Norton, M.C., Stone, S.V.on behalf of the Cache County Memory Study Group, 2000. Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists: the Cache County Study. Neurology 54, 2066–2071. http://dx.doi.org/10.1212/WNL.54.11.2066.

Archer, D.F., Sturdee, D.W., Baber, R., de Villiers, T.J., Pines, A., Freedman, R.R., Gompel, A., Hickey, M., Hunter, M.S., Lobo, R.A., Lumsden, M.A., MacLennan, A. H., Maki, P., Palacios, S., Shah, D., Villaseca, P., Warren, M., 2011. Menopausal hot flushes and night sweats: where are we now? Climacteric 14, 515–528. http://dx.doi.org/10.3109/13697137.2011.608596.

Bake, S., Sohrabji, F., 2004. 17Beta-Estradiol differentially regulates blood-brain barrier permeability in young and aging female rats. Endocrinology 145, 5471–5475. http://dx.doi.org/10.1210/en.2004-0984.

Banks, W.A., Farr, S.A., Morley, J.E., 2002. Entry of blood-borne cytokines into the central nervous system: effects on cognitive processes. Neuroimmunomodulation 10, 319–327. http://dx.doi.org/10.1159/000071472.

Banks, W.A., Farr, S.A., La Scola, M.E., Morley, J.E., 2001. Intravenous human interleukin-1alpha impairs memory processing in mice: dependence on blood-brain barrier transport into posterior division of the septum. J. Pharmacol. Exp. Ther. 299, 536–541.

Barbaglia, G., Macià, F., Comas, M., Sala, M., del Mar Vernet, M., Casamitjana, M., Castells, X., 2009. Trends in hormone therapy use before and after publication of the Women's Health Initiative trial: 10 years of follow-up. Menopause 16, 1061–1064. http://dx.doi.org/10.1097/gme.0b013e3181a02b44.

Bastin, C., Salmon, E., 2014. Early neuropsychological detection of Alzheimer's disease. Eur. J. Clin. Nutr. 68, 1192–1199. http://dx.doi.org/10.1038/ejcn.2014.176.

Bellino, F.L., Wise, P.M., 2003. Nonhuman primate models of menopause workshop. Biol. Reprod. http://dx.doi.org/10.1095/biolreprod.102.005215.

Benedusi, V., Meda, C., Della Torre, S., Monteleone, G., Vegeto, E., Maggi, A., 2012. A lack of ovarian function increases neuroinflammation in aged mice. Endocrinology 153, 2777–2788. http://dx.doi.org/10.1210/en.2011-1925.

Berchtold, N.C., Cribbs, D.H., Coleman, P.D., Rogers, J., Head, E., Kim, R., Beach, T., Miller, C., Troncoso, J., Trojanowski, J.Q., Zielke, H.R., Cotman, C.W., 2008. Gene expression changes in the course of normal brain aging are sexually dimorphic. Proc. Natl. Acad. Sci. USA 105, 15605–15610. http://dx.doi.org/10.1073/pnas.0806883105.

Berendsen, H.H., 2002. Hot flushes and serotonin. Menopause Int. 8, 30–34. http://dx.doi.org/10.1258/136218002100321569.

Beery, A.K., Zucker, I., 2011. Sex bias in neuroscience and biomedical research. Neurosci. Biobehav. Rev. 35, 565–572. http://dx.doi.org/10.1016/j.neubiorev.2010.07.002.

Blasko, I., Stampfer-Kountchev, M., Robatscher, P., Veerhuis, R., Eikelenboom, P., Grubeck-Loebenstein, B., 2004. How chronic inflammation can affect the brain and support the development of Alzheimer's disease in old age: the role of microglia and astrocytes. Aging Cell 3, 169–176. http://dx.doi.org/10.1111/j.1474-9728.2004.00101.x.

Bove, R., Secor, E., Chibnik, L.B., Barnes, L.L., Schneider, J.A., Bennett, D.A., De Jager, P. L., 2014. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology 82, 222–229. http://dx.doi.org/10.1212/WNL.0000000000000033.

Bowen, R.L., Isley, J.P., Atkinson, R.L., 2000. An association of elevated serum gonadotropin concentrations and Alzheimer disease? J. Neuroendocrinol. 12, 351–354. http://dx.doi.org/10.1046/j.1365-2826.2000.00461.x.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259. http://dx.doi.org/10.1007/BF00308809.

Bramblett, G.T., Goedert, M., Jakes, R., Merrick, S.E., Trojanowski, J.Q., Lee, V.M., 1993. Abnormal tau phosphorylation at Ser396 in Alzheimer's disease recapitulates development and contributes to reduced microtubule binding. Neuron 10, 1089–1099. http://dx.doi.org/10.1016/0896-6273(93)90057-X.

Breitner, J.C.S., 1996. Inflammatory processes and antiinflammatory drugs in Alzheimer's disease: a current appraisal. Neurobiol. Aging 17, 789–794. http://dx.doi.org/10.1016/0197-4580(96)00109-1.

Brown, C.M., Mulcahey, T.A., Filipek, N.C., Wise, P.M., 2010. Production of proinflammatory cytokines and chemokines during neuroinflammation: novel roles for estrogen receptors alpha and beta. Endocrinology 151, 4916–4925. http://dx.doi.org/10.1210/en.2010-0371.

Burek, M., Arias-Loza, P.A., Roewer, N., Förster, C.Y., 2010. Claudin-5 as a novel estrogen target in vascular endothelium. Arterioscler. Thromb. Vasc. Biol. 30, 298–304. http://dx.doi.org/10.1161/ATVBAHA.109.197582.

Burt, D.B., Zembar, M.J., Niederehe, G., 1995. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psychol. Bull. 117, 285–305. http://dx.doi.org/10.1037/0033-2909.117.2.285.

Butchart, J., Birch, B., Bassily, R., Wolfe, L., Holmes, C., 2012. Male sex hormones and systemic inflammation in Alzheimer disease. Alzheimer Dis. Assoc. Disord. 27, 1. http://dx.doi.org/10.1097/WAD.0b013e318258cd63.

Cantatore, F.P., Loverro, G., Ingrosso, A.M., Lacanna, R., Sassanelli, E., Selvaggi, L., Carrozzo, M., 1995. Effect of oestrogen replacement on bone metabolism and cytokines in surgical menopause. Clin. Rheumatol. 14, 157–160.

Castelo-Branco, C., Figueras, F., Sanjuan, A., Vicente, J.J., Martínez de Osaba, M.J., Pons, F., Balasch, J., Vanrell, J.A., 1999. Long-term compliance with estrogen replacement therapy in surgical postmenopausal women: benefits to bone and analysis of factors associated with discontinuation. Menopause 6, 307–311. http://dx.doi.org/10.1097/00042192-199906040-00006.

Cenci, S., Weitzmann, M.N., Roggia, C., Namba, N., Novack, D., Woodring, J., Pacifici, R., 2000. Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-a. J. Clin. Invest. 106, 1229–1237. http://dx.doi.org/10.1172/JCI11066.

Chabbert Buffet, N., Djakoure, C., Maitre, S.C., Bouchard, P., 1998. Regulation of the human menstrual cycle. Front. Neuroendocrinol. 19, 151–186. http://dx.doi.org/10.1006/frne.1998.0167.

Chakravarti, S., Collins, W.P., Newton, J.R., Oram, D.H., Studd, J.W., 1977. Endocrine changes and symptomatology after oophorectomy in premenopausal women. Br. J. Obstet. Gynaecol. 84, 769–775.

Cioffi, M., Esposito, K., Vietri, M.T., Gazzerro, P., D'Auria, A., Ardovino, I., Puca, G.A., Molinari, A.M., 2002. Cytokine pattern in postmenopause. Maturitas 41, 187–192. http://dx.doi.org/10.1016/S0378-5122(01)00286-9.

Cipolla, M.J., Godfrey, J.A., Wiegman, M.J., 2009. The effect of ovariectomy and estrogen on penetrating brain arterioles and blood-brain barrier permeability. Microcirculation 16, 685–693. http://dx.doi.org/10.3109/10739680903164131.

Clarke, C.J., Hales, A., Hunt, A., Foxwell, B.M., 1998. IL-10-mediated suppression of TNF-alpha production is independent of its ability to inhibit NF kappa B activity. Eur. J. Immunol. 28, 1719–1726. http://dx.doi.org/10.1002/(SICI)1521-4141(199805)28.

Constantinescu, C.S., Farooqi, N., O'Brien, K., Gran, B., 2011. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). Br. J. Pharmacol. 164, 1079–1106. http://dx.doi.org/10.1111/j.1476-5381.2011.01302.x.

Cunningham, C., Hennessy, E., 2015. Co-morbidity and systemic inflammation as drivers of cognitive decline: new experimental models adopting a broader paradigm in dementia research. Alzheimers. Res. Ther. 7, 1–13. http://dx.doi.org/10.1186/s13195-015-0117-2.

de Vries, H.E., Blom-Roosemalen, M.C.M., van Oosten, M., de Boer, A.G., van Berkel, T.J.C., Breimer, D.D., Kuiper, J., 1996. The influence of cytokines on the integrity of the blood-brain barrier in vitro. J. Neuroimmunol. 64, 37–43. http://dx.doi.org/10.1016/0165-5728(95)00148-4.

Dinarello, C.A., 1994. The interleukin-1 family: 10 years of discovery. FASEB J. 8, 1314–1325, Retrieved from <http://www.fasebj.org/content/8/15/1314.short>.

Disanto, G., Ramagopalan, S.V., 2013. On the sex ratio of multiple sclerosis. Mult. Scler. J. 19, 3–4. http://dx.doi.org/10.1177/1352458512447594.

Economos, A., Wright, C.B., Moon, Y.P., Rundek, T., Rabbani, L., Paik, M.C., Sacco, R.L., Elkind, M.S.V., 2013. Interleukin 6 plasma concentration associates with cognitive decline: the northern Manhattan study. Neuroepidemiology 40, 253–259. http://dx.doi.org/10.1159/000343276.

Ekdahl, C.T., Claasen, J.-H., Bonde, S., Kokaia, Z., Lindvall, O., 2003. Inflammation is detrimental for neurogenesis in adult brain. Proc. Natl. Acad. Sci. USA 100, 13632–13637. http://dx.doi.org/10.1073/pnas.2234031100.

Ekdahl, C.T., Kokaia, Z., Lindvall, O., 2009. Brain inflammation and adult neurogenesis: the dual role of microglia. Neuroscience 158, 1021–1029. http://dx.doi.org/10.1016/j.neuroscience.2008.06.052.

Evans, M.J., Eckert, A., Lai, K., Adelman, S.J., Harnish, D.C., 2001. Reciprocal antagonism between estrogen receptor and NF-KB activity in vivo. Circ. Res. 89, 823–830. http://dx.doi.org/10.1161/hh2101.098543.

Farrag, A.F., Khedr, E.M., Abdel-Aleem, H., Rageh, T.A., 2002. Effect of surgical menopause on cognitive functions. Dement. Geriatr. Cogn. Disord. 13, 193–198. http://dx.doi.org/10.1159/000048652.

Faulkner, D.L., Young, C., Hutchins, D., McCollam, J.S., 1998. Patient noncompliance with hormone replacement therapy: a nationwide estimate using a large prescription claims database. Menopause 5, 226–229.

Finch, A.P.M., Lubinski, J., Møller, P., Singer, C.F., Karlan, B., Senter, L., Rosen, B., Maehle, L., Ghadirian, P., Cybulski, C., Huzarski, T., Eisen, A., Foulkes, W.D., Kim-Sing, C., Ainsworth, P., Tung, N., Lynch, H.T., Neuhausen, S., Metcalfe, K.A., Thompson, I., Murphy, J., Sun, P., Narod, S.A., 2014. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J. Clin. Oncol. 32, 1547–1553. http://dx.doi.org/10.1200/JCO.2013.53.2820.

Fish, E.N., 2008. The X-files in immunity: sex-based differences predispose immune responses. Nat. Rev. Immunol. 8, 737–744. http://dx.doi.org/10.1038/nri2394.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198. http://dx.doi.org/10.1016/0022-3956(75)90026-6.

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann. N.Y. Acad. Sci. 908, 244–254. http://dx.doi.org/10.1111/j.1749-6632.2000.tb06651.x.

Fratiglioni, L., Viitanen, M., von Strauss, E., Tontodonati, V., Herlitz, A., Winblad, B., 1997. Very old women at highest risk of dementia and Alzheimer's disease incidence data from the Kungsholmen Project, Stockholm. Neurology 48, 132–138. http://dx.doi.org/10.1212/WNL.48.1.132.

Fuh, J.L., Wang, S.J., Lee, S.J., Lu, S.R., Juang, K.D., 2006. A longitudinal study of cognition change during early menopausal transition in a rural community. Maturitas 53, 447–453. http://dx.doi.org/10.1016/j.maturitas.2005.07.009.

Furness, S., Roberts, H., Marjoribanks, J., Lethaby, A., 2012. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst. Rev. 8, CD000402. http://dx.doi.org/10.1002/14651858.CD000402.pub4.

Gameiro, C.M., Romão, F., Castelo-Branco, C., 2010. Menopause and aging: changes in the immune system – a review. Maturitas 67, 316–320. http://dx.doi.org/10.1016/j.maturitas.2010.08.003.

Garay, L.I., González Deniselle, M.C., Brocca, M.E., Lima, A., Roig, P., De Nicola, A.F., 2012. Progesterone down-regulates spinal cord inflammatory mediators and increases myelination in experimental autoimmune encephalomyelitis. Neuroscience 226, 40–50. http://dx.doi.org/10.1016/j.neuroscience.2012.09.032.

Gong, Q.-H., Wang, Q., Pan, L.-L., Liu, X.-H., Huang, H., Zhu, Y.-Z., 2010. Hydrogen sulfide attenuates lipopolysaccharide-induced cognitive impairment: a pro-inflammatory pathway in rats. Pharmacol. Biochem. Behav. 96, 52–58. http://dx.doi.org/10.1016/j.pbb.2010.04.006.

Goshen, I., Yirmiya, R., 2007. The role of pro-inflammatory cytokines in memory processes and neural plasticity. In: Ader, R. (Ed.), Psychoneuroimmunology, forth ed. Elsevier Academic Press, Burlington, pp. 337–377.

Greendale, G.A., Wight, R.G., Huang, M.-H., Avis, N., Gold, E.B., Joffe, H., Seeman, T., Vuge, M., Karlamangla, A.S., 2010. Menopause-associated symptoms and cognitive performance: results from the study of women's health across the nation. Am. J. Epidemiol. 171, 1214–1224. http://dx.doi.org/10.1093/aje/kwq067.

Hara, Y., Park, C.S., Janssen, W.G.M., Roberts, M.T., Morrison, J.H., Rapp, P.R., 2012. Synaptic correlates of memory and menopause in the hippocampal dentate gyrus in rhesus monkeys. Neurobiol. Aging 33, 421.e17–421.e28. http://dx.doi.org/10.1016/j.neurobiolaging.2010.09.014.

Hauss-Wegrzyniak, B., Lynch, M.A., Vraniak, P.D., Wenk, G.L., 2002. Chronic brain inflammation results in cell loss in the entorhinal cortex and impaired LTP in perforant path-granule cell synapses. Exp. Neurol. 176, 336–341. http://dx.doi.org/10.1006/exnr.2002.7966.

Hebert, L.E., Weuve, J., Scherr, P.A., Evans, D.A., 2013. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology 80, 1778–1783. http://dx.doi.org/10.1212/WNL.0b013e31828726f5.

Henderson, V.W., Popat, R.A., 2011. Effects of endogenous and exogenous estrogen exposures in midlife and late-life women on episodic memory and executive functions. Neuroscience 191, 129–138. http://dx.doi.org/10.1016/j.neuroscience.2011.05.059.

Henderson, V.W., Sherwin, B.B., 2007. Surgical versus natural menopause: cognitive issues. Menopause 14, 572–579. http://dx.doi.org/10.1097/gme.0b013e31803df49c.

Hickey, M., Elliott, J., Davison, S.L., 2012. Hormone replacement therapy. BMJ 344. http://dx.doi.org/10.1136/bmj.e763, e763–e763.

Hogervorst, E., Williams, J., Budge, M., Barnetson, L., Combrinck, M., Smith, A.D., 2001. Serum total testosterone is lower in men with Alzheimer's Disease. Neuroendocrinol. Lett. 22, 163–168.

Hogervorst, E., Williams, J., Budge, M., Riedel, W., Jolles, J., 2000. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience 101, 485–512. http://dx.doi.org/10.1016/S0306-4522(00)00410-3.

Imtiaz, B., Tuppurainen, M., Tiihonen, M., Kivipelto, M., Soininen, H., Hartikainen, S., Tolppanen, A.-M., 2014. Oophorectomy, hysterectomy, and risk of Alzheimer's disease: a nationwide case-control study. J. Alzheimers Dis. 42, 575–581. http://dx.doi.org/10.3233/JAD-140336.

in't Veld, B.A., Ruitenberg, A., Hofman, A., Launer, L.J., van Duijn, C.M., Stijnen, T., Breteler, M.M.B., Stricker, B.H.C., 2001. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N. Engl. J. Med. 345, 1515–1521. http://dx.doi.org/10.1056/NEJMoa010178.

Jansson, L., Olsson, T., Holmdahl, R., 1994. Estrogen induces a potent suppression of experimental autoimmune encephalomyelities and collagen-induced arthritis in mice. J. Neuroimmunol. 53, 203–207. http://dx.doi.org/10.1016/0165-5728(94)90030-2.

Jefferson, A.L., Massaro, J.M., Beiser, A.S., Seshadri, S., Larson, M.G., Wolf, P.A., Au, R., Benjamin, E.J., 2011. Inflammatory markers and neuropsychological functioning: the Framingham Heart Study. Neuroepidemiology 37, 21–30. http://dx.doi.org/10.1159/000328864.

Jewett, P.I., Gangnon, R.E., Trentham-Dietz, A., Sprague, B.L., 2014. Trends of postmenopausal estrogen plus progestin prevalence in the United States between 1970 and 2010. Obstet. Gynecol. 124, 727–733. http://dx.doi.org/10.1097/AOG.0000000000000469.

Judd, H.L., Judd, G.E., Lucas, W.E., Yen, S.S., 1974. Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. J. Clin Endocrinol. Metab. 39, 1020–1024. http://dx.doi.org/10.1210/jcem-39-6-1020.

Kalaitzidis, D., Gilmore, T.D., 2005. Transcription factor cross-talk: the estrogen receptor and NF-kappaB. Trends Endocrinol. Metab. 16, 46–52. http://dx.doi.org/10.1016/j.tem.2005.01.004.

Kalyan, S., Hitchcock, C.L., Pudek, M., Prior, J.C., 2011. Acute effects of premenopausal hysterectomy with bilateral oophorectomy on serum lipids, hormonal values, inflammatory markers, and metabolism. J. Gynecol. Surg. 27, 9–15. http://dx.doi.org/10.1089/gyn.2009.0098.

Kang, J.H., Cook, N., Manson, J., Buring, J.E., Grodstein, F., 2007. Low dose aspirin and cognitive function in the women's health study cognitive cohort. BMJ 334, 987. http://dx.doi.org/10.1136/bmj.39166.597836.BE.

Kang, J.H., Grodstein, F., 2003. Regular use of nonsteroidal anti-inflammatory drugs and cognitive function in aging women. Neurology 60, 1591–1597. http://dx.doi.org/10.1212/01.WNL.0000065980.33594.B7.

Keenan, P.A., Ezzat, W.H., Ginsburg, K., Moore, G.J., 2001. Prefrontal cortex as the site of estrogen's effect on cognition. Psychoneuroendocrinology 26, 577–590. http://dx.doi.org/10.1016/S0306-4530(01)00013-0.

Kerchner, G.A., Nicoll, R.A., 2008. Silent synapses and the emergence of a postsynaptic mechanism for LTP. Nat. Rev. Neurosci. 9, 813–825. http://dx.doi.org/10.1038/nrn2501.

Kermath, B.A., Gore, A.C., 2012. Neuroendocrine control of the transition to reproductive senescence: lessons learned from the female rodent model. Neuroendocrinology 96, 1–12. http://dx.doi.org/10.1159/000335994.

Kinnavane, L., Albasser, M.M., Aggleton, J.P., 2015. Advances in the behavioural testing and network imaging of rodent recognition memory. Behav. Brain Res. 285, 67–78. http://dx.doi.org/10.1016/j.bbr.2014.07.049.

Korn-Lubetzki, I., Kahana, E., Cooper, G., Abramsky, O., 1984. Activity of multiple sclerosis during pregnancy and puerperium. Ann. Neurol. 16, 229–231. http://dx.doi.org/10.1002/ana.410180120.

Korse, C.M., Bonfrer, J.M.G., van Beurden, M., Verheijen, R.H.M., Rookus, M.A., 2009. Estradiol and testosterone levels are lower after oophorectomy than after natural menopause. Tumor Biol. 30, 37–42. http://dx.doi.org/10.1159/000199449.

Kovats, S., 2015. Estrogen receptors regulate innate immune cells and signaling pathways. Cell. Immunol. 294, 63–69. http://dx.doi.org/10.1016/j.cellimm.2015.01.018.

Kumru, S., Godekmerdan, A., Yilmaz, B., 2004. Immune effects of surgical menopause and estrogen replacement therapy in peri-menopausal women. J. Reprod. Immunol. 63, 31–38. http://dx.doi.org/10.1016/j.jri.2004.02.001.

Lacreuse, A., Herndon, J.G., Moss, M.B., 2000. Cognitive function in aged ovariectomized female rhesus monkeys. Behav. Neurosci. 114, 506–513. http://dx.doi.org/10.1037//0735-7044.114.3.506.

Lethaby, A., Hogervorst, E., Richards, M., Yesufu, A., Yaffe, K., 2008. Hormone replacement therapy for cognitive function in postmenopausal women. Cochrane Database Syst. Rev. 4, 1–43. http://dx.doi.org/10.1002/14651858.CD003122.pub2.

Lee, J.W., Lee, Y.K., Yuk, D.Y., Choi, D.Y., Ban, S.B., Oh, K.W., Hong, J.T., 2008. Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. J. Neuroinflammation 5, 37. http://dx.doi.org/10.1186/1742-2094-5-37.

Lee, D.C., Rizer, J., Selenica, M.-L.B., Reid, P., Kraft, C., Johnson, A., Blair, L., Gordon, M. N., Dickey, C.A., Morgan, D., 2010. LPS- induced inflammation exacerbates phospho-tau pathology in rTg4510 mice. J. Neuroinflammation 7, 56. http://dx.doi.org/10.1186/1742-2094-7-56.

Liu, S., Wu, H., Gai Xue, X.M., Wu, J., Qin, Y., Hou, Y., 2013. Metabolic alteration of neuroactive steroids and protective effect of progesterone in Alzheimer's disease-like rats. Neural. Regen. Res. 8, 2800–2810. http://dx.doi.org/10.3969/j.issn.1673-5374.2013.30.002.

Longcope, C., Franz, C., Morello, C., Baker, R., Johnston, C.C., 1986. Steroid and gonadotropin levels in women during the peri-menopausal years. Maturitas 8, 189–196. http://dx.doi.org/10.1016/0378-5122(86)90025-3.

Longcope, C., Hunter, R., Franz, C., 1980. Steroid secretion by the postmenopausal ovary. Am. J. Obstet. Gynecol. 138, 564–568. http://dx.doi.org/10.1097/00006254-198104000-00017.

Lublin, F.D., Reingold, S.C., 1996. Defining the clinical course of multiple sclerosis results of an international survey. Neurology 46, 907–911. http://dx.doi.org/10.1212/WNL.46.4.907.

Luetters, C., Huang, M.-H., Seeman, T., Buckwalter, G., Meyer, P.M., Avis, N.E., Sternfeld, B., Johnston, J.M., Greendale, G.A., 2007. Menopause transition stage and endogenous estradiol and follicle-stimulating hormone levels are not related to cognitive performance: cross-sectional results from the Study of Women's Health across the Nation (SWAN). J. Women's Heal. 16, 331–344. http://dx.doi.org/10.1089/jwh.2006.0057.

Maki, P.M., 2013. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. Menopause 20, 695–709. http://dx.doi.org/10.1097/gme.0b013e3182960cf8.

Maki, P.M., Drogos, L.L., Rubin, L.H., Banuvar, S., Shulman, L.P., Geller, S.E., 2008. Objective hot flashes are negatively related to verbal memory performance in midlife women. Menopause 15, 848–856. http://dx.doi.org/10.1097/gme.0b013e31816d815e.Objective.

Mandell, K.J., Parkos, C.A., 2005. The JAM family of proteins. Adv. Drug Deliv. Rev. 57, 857–867. http://dx.doi.org/10.1016/j.addr.2005.01.005.

Maret, A., Coudert, J.D., Garidou, L., Foucras, G., Gourdy, P., Krust, A., Dupont, S., Chambon, P., Druet, P., Bayard, F., Guéry, J.-C., 2003. Estradiol enhances primary antigen-specific CD4 T cell responses and Th1 development in vivo. Essential role of estrogen receptor alpha expression in hematopoietic cells. Eur. J. Immunol. 33, 512–521. http://dx.doi.org/10.1002/immu.200310027.

Marriott, L.K., Hauss-Wegrzyniak, B., Benton, R.S., Vraniak, P.D., Wenk, G.L., 2002. Long-term estrogen therapy worsens the behavioral and neuropathological

consequences of chronic brain inflammation. Behav. Neurosci. 116, 902–911. http://dx.doi.org/10.1037/0735-7044.116.5.902.
Matynia, A., Kushner, S.A., Silva, A.J., 2002. Genetic approaches to molecular and cellular cognition: a focus on LTP and learning and memory. Annu. Rev. Genet. 36, 687–720. http://dx.doi.org/10.1146/annurev.genet.36.062802.091007.
Mayer, L.P., Devine, P.J., Dyer, C.A., Hoyer, P.B., 2004. The follicle-deplete mouse ovary produces androgen. Biol. Reprod. 71, 130–138. http://dx.doi.org/10.1095/biolreprod.103.016113.
McCarrey, A.C., Resnick, S.M., 2015. Postmenopausal hormone therapy and cognition. Horm. Behav. http://dx.doi.org/10.1016/j.yhbeh.2015.04.018.
McGeer, P.L., McGeer, E.G., 2007. NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. Neurobiol. Aging 28, 639–647. http://dx.doi.org/10.1016/j.neurobiolaging.2006.03.013.
McGeer, P.L., McGeer, E., Rogers, J., Sibley, J., 1990. Anti-inflammatory drugs and Alzheimer disease. Lancet 335, 1037.
McGeer, P.L., Schulzer, M., McGeer, E.G., 1996. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. Neurology 47, 425–432. http://dx.doi.org/10.1212/WNL.47.2.425.
McKinlay, S.M., Jefferys, M., 1974. The menopausal syndrome. J. Epidemiol. Community Heal. 28, 108–115. http://dx.doi.org/10.1136/jech.28.2.108.
Menze, E.T., Esmat, A., Tadros, M.G., Abdel-Naim, A.B., Khalifa, A.E., 2015. Genistein improves 3-NPA-induced memory impairment in ovariectomized rats: impact of its antioxidant, anti-inflammatory and acetylcholinesterase modulatory properties. PLoS One 10, e0117223. http://dx.doi.org/10.1371/journal.pone.0117223.
Miranda, P., Williams, C.L., Einstein, G., 1999. Granule cells in aging rats are sexually dimorphic in their response to estradiol. J. Neurosci. 19, 3316–3325.
Monje, M.L., Toda, H., Palmer, T.D., 2003. Inflammatory blockade restores adult hippocampal neurogenesis. Science 302, 1760–1765. http://dx.doi.org/10.1126/science.1088417.
Mrak, R.E., Sheng, J.G., Griffin, W.S., 1995. Glial cytokines in Alzheimer's disease: review and pathogenic implications. Hum. Pathol. 26, 816–823. http://dx.doi.org/10.1016/0046-8177(95)90001-2.
Nelson, J.F., Felicio, L.S., Osterburg, H.H., Finch, C.E., 1981. Altered profiles of estradiol and progesterone associated with prolonged estrous cycles and persistent vaginal cornification in aging C57BL/6J mice. Biol. Reprod. 24, 784–794. http://dx.doi.org/10.1095/biolreprod24.4.784.
Nott, P.M., Franklin, M., Armitage, C., Gelder, M.G., 1976. Hormonal changes and mood in the puerperium. Br. J. Psychiatry 128, 379–383. http://dx.doi.org/10.1192/bjp.128.4.379.
O'Leary, O.F., Wu, X., Castren, E., 2009. Chronic fluoxetine treatment increases expression of synaptic proteins in the hippocampus of the ovariectomized rat: role of BDNF signalling. Psychoneuroendocrinology 34, 367–381. http://dx.doi.org/10.1016/j.psyneuen.2008.09.015.
Offner, H., Adlard, K., Zamora, A., Vandenbark, A.A., 2000. Estrogen potentiates treatment with T-cell receptor protein of female mice with experimental encephalomyelitis. J. Clin. Invest. 105, 1465–1472. http://dx.doi.org/10.1172/JCI9213.
Oliphant, S.S., Jones, K.A., Wang, L., Bunker, C.H., Lowder, J.L., 2010. Trends over time with commonly performed obstetric and gynecologic inpatient procedures. Obstet. Gynecol. 116, 926–931. http://dx.doi.org/10.1097/AOG.0b013e3181f38599.
O'Neill, L.A.J., Kaltschmidt, C., 1997. NF-KB: a crucial transcription factor for glial and neuronal cell function. Trends Neurosci. 20, 252–258. http://dx.doi.org/10.1016/S0166-2236(96)01035-1.
Overlie, I., Moen, M.H., Morkrid, L., Skjaeraasen, J.S., Holte, A., 1999. The endocrine transition around menopause–a five years prospective study with profiles of gonadotropines, estrogens, androgens and SHBG among healthy women. Acta Obstet. Gynecol. Scand. 78, 642–647. http://dx.doi.org/10.1034/j.1600-0412.1999.780714.x.
Pacifici, R., Brown, C., Puscheck, E., Friedrich, E., Slatopolsky, E., Maggio, D., McCracken, R., Avioli, L.V., 1991. Effect of surgical menopause and estrogen replacement on cytokine release from human blood mononuclear cells. Proc. Natl. Acad. Sci. USA 88, 5134–5138. http://dx.doi.org/10.1073/pnas.88.12.5134.
Palacios, S., Henderson, V.W., Siseles, N., Tan, D., Villaseca, P., 2010. Age of menopause and impact of climacteric symptoms by geographical region. Climacteric 13, 419–428. http://dx.doi.org/10.3109/13697137.2010.507886.
Perry, V.H., Holmes, C., 2014. Microglial priming in neurodegenerative disease. Nat. Rev. Neurol. 10, 217–224. http://dx.doi.org/10.1038/nrneurol.2014.38.
Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Kokmen, E., Tangelos, E.G., 1997. Aging, memory, and mild cognitive impairment. Int. Psychogeriatr. 9 (Suppl. 1), 65–69. http://dx.doi.org/10.1017/S1041610297004717.
Pettus, E.H., Wright, D.W., Stein, D.G., Hoffman, S.W., 2005. Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury. Brain Res. 1049, 112–119. http://dx.doi.org/10.1016/j.brainres.2005.05.004.
Pfeilschifter, J., Köditz, R., Pfohl, M., Schatz, H., 2002. Changes in proinflammatory cytokine activity after menopause. Endocr. Rev. 23, 90–119. http://dx.doi.org/10.1210/er.23.1.90.
Phillips, S.M., Sherwin, B.B., 1992. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 17, 485–495. http://dx.doi.org/10.1016/0306-4530(92)90007-T.
Phung, T.K.T., Waltoft, B.L., Laursen, T.M., Settnes, A., Kessing, L.V., Mortensen, P.B., Waldemar, G., 2010. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. Dement. Geriatr. Cogn. Disord. 30, 43–50. http://dx.doi.org/10.1159/000314681.
Pourganji, M., Hosseini, M., Soukhtanloo, M., Zabihi, H., Hadjzadeh, M.A.-R., 2014. Protective role of endogenous ovarian hormones against learning and memory impairments and brain tissues oxidative damage induced by lipopolysaccharide. Iran. Red Crescent Med. J. 16, e13954. http://dx.doi.org/10.5812/ircmj.13954.
Prestwood, K.M., Unson, C., Kulldorff, M., Cushman, M., 2004. The effect of different doses of micronized 17beta-estradiol on C-reactive protein, interleukin-6, and lipids in older women. J. Gerontol. A. Biol. Sci. Med. Sci. 59, 827–832, doi:59/8/M827.
Puder, J.J., Freda, P.U., Goland, R.S., Wardlaw, S.L., 2001. Estrogen modulates the hypothalamic–pituitary–adrenal and inflammatory cytokine responses to endotoxin in women. J. Clin. Endocrinol. Metab. 86, 2403–2408. http://dx.doi.org/10.1210/jc.86.6.2403.
Pugh, C.R., Kumagawa, K., Fleshner, M., Watkins, L.R., Maier, S.F., Rudy, J.W., 1998. Selective effects of peripheral lipopolysaccharide administration on contextual and auditory-cue fear conditioning. Brain. Behav. Immun. 12, 212–229. http://dx.doi.org/10.1006/brbi.1998.0524.
Read, M.D., Edey, K.A., Hapeshi, J., Foy, C., 2010. Compliance with estrogen hormone replacement therapy after oophorectomy: a prospective study. Menopause Int. 16, 60–64. http://dx.doi.org/10.1258/mi.2010.010023.
Rebbeck, T.R., Friebel, T., Wagner, T., Lynch, H.T., Garber, J.E., Daly, M.B., Isaacs, C., Olopade, O.I., Neuhausen, S.L., van 't Veer, L., Eeles, R., Evans, D.G., Tomlinson, G., Matloff, E., Narod, S.A., Eisen, A., Domchek, S., Armstrong, K., Weber, B.L., 2005. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J. Clin. Oncol. 23, 7804–7810. http://dx.doi.org/10.1200/JCO.2004.00.8151.
Resnick, S.M., Maki, P.M., Rapp, S.R., Espeland, M.A., Brunner, R., Coker, L.H., Granek, I.A., Hogan, P., Ockene, J.K., Shumaker, S.A., 2006. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J. Clin. Endocrinol. Metab. 91, 1802–1810. http://dx.doi.org/10.1210/jc.2005-2097.
Roberts, J.A., Gilardi, K.V., Lasley, B., Rapp, P.R., 1997. Reproductive senescence predicts cognitive decline in aged female monkeys. Neuroreport 8, 2047–2051. http://dx.doi.org/10.1097/00001756-199705260-00048.
Rocca, W.A., Bower, J.H., Maraganore, D.M., Ahlskog, J.E., Grossardt, B.R., de Andrade, M., Melton, L.J., 2007. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 69, 1074–1083. http://dx.doi.org/10.1212/01.wnl.0000276984.19542.e6.
Rocca, W.A., Bower, J.H., Maraganore, D.M., Ahlskog, J.E., Grossardt, B.R., de Andrade, M., Melton, L.J., 2008. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology 70, 200–209. http://dx.doi.org/10.1212/01.wnl.0000280573.30975.6a.
Rocca, W.A., Grossardt, B.R., Shuster, L.T., 2014. Oophorectomy, estrogen, and dementia: a 2014 update. Mol. Cell. Endocrinol. 389, 7–12. http://dx.doi.org/10.1016/j.mce.2014.01.020.
Rosario, E.R., 2004. Age-related testosterone depletion and the development of Alzheimer disease. JAMA J. Am. Med. Assoc. 292, 1431–1432. http://dx.doi.org/10.1001/jama.292.12.1431-b.
Ross, R.K., Paganini-Hill, A., Wan, P.C., Pike, M.C., 2000. Effect of hormone replace ment therapy on breast cancer risk: estrogen versus estrogen plus progestin. J. Natl. Cancer Inst. 92, 328–332. http://dx.doi.org/10.1093/jnci/92.4.328.
Ryan, K.J., 1982. Biochemistry of aromatase: significance to female reproductive physiology. Cancer Res. 42, 3342s–3344s.
Sales, S., Ureshino, R.P., Pereira, R.T.D.S., Luna, M.S.A., Pires de Oliveira, M., Yamanouye, N., Godinho, R.O., Smaili, S.S., Porto, C.S., Abdalla, F.M.F., 2010. Effects of 17β-estradiol replacement on the apoptotic effects caused by ovariectomy in the rat hippocampus. Life Sci. 86, 832–838. http://dx.doi.org/10.1016/j.lfs.2010.04.002.
Sandberg, K., Ji, H., Einstein, G., Au, A., Hay M., 2015. Is immune system related hypertension associated with ovarian hormone deficiency? Exp. Physiol. (in press). doi: http://dx.doi.org/10.1113/EP085149.
Sárvári, M., Hrabovszky, E., Kalló, I., Solymosi, N., Likó, I., Berchtold, N., Cotman, C., Liposits, Z., 2012. Menopause leads to elevated expression of macrophage-associated genes in the aging frontal cortex: rat and human studies identify strikingly similar changes. J. Neuroinflammation 9, 264. http://dx.doi.org/10.1186/1742-2094-9-264.
Scharbo-Dehaan, M., 1996. Hormone replacement therapy. Nurse Pract. 21, 1–13.
Scheff, S.W., Price, D.A., Schmitt, F.A., Dekosky, S.T., Mufson, E.J., 2007. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. Neurology 68, 1501–1508. http://dx.doi.org/10.1212/01.wnl.0000260698.46517.8f.
Schram, M.T., Euser, S.M., de Craen, A.J.M., Witteman, J.C., Frölich, M., Hofman, A., Jolles, J., Breteler, M.M.B., Westendorp, R.G.J., 2007. Systemic markers of inflammation and cognitive decline in old age. J. Am. Geriatr. Soc. 55, 708–716. http://dx.doi.org/10.1111/j.1532-5415.2007.01159.x.
Sherwin, B.B., 1988. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. Psychoneuroendocrinology 13, 345–357. http://dx.doi.org/10.1016/0306-4530(88)90060-1.
Shors, T., Matzel, L., 1997. Long-term potentiation: what's learning got to do with it? Behav. Brain Sci. 20, 597–655.
Shumaker, S.A., Legault, C., Rapp, S.R., Thal, L., Wallace, R.B., Ockene, J.K., Hendrix, S.L., Jones III, B.N., Assaf, A.R., Jackson, R.D., Morley Kotchen, J., Wassertheil-Smoller, S., Wactawski-Wende, J.for the WHIMS Investigators, 2003. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. JAMA 289, 2651. http://dx.doi.org/10.1001/jama.289.20.2651.

Si, D., Wang, H., Wang, Q., Zhang, C., Sun, J., Wang, Z., Zhang, Z., Zhang, Y., 2013. Progesterone treatment improves cognitive outcome following experimental traumatic brain injury in rats. Neurosci. Lett. 553, 18–23. http://dx.doi.org/10.1016/j.neulet.2013.07.052.

Silva, I., Mello, L.E.A.M., Freymüller, E., Haidar, M.A., Baracat, E.C., 2003. Onset of estrogen replacement has a critical effect on synaptic density of CA1 hippocampus in ovariectomized adult rats. Menopause 10, 406–411. http://dx.doi.org/10.1097/01.GME.0000064816.74043.E9.

Singh, M., Meyer, E.M., Millard, W.J., Simpkins, J.W., 1994. Ovarian steroid deprivation results in a reversible learning impairment and compromised cholinergic function in female Sprague-Dawley rats. Brain Res. 644, 305–312. http://dx.doi.org/10.1016/0006-8993(94)91694-2.

Smith, R., Studd, J., 1992. A pilot study of the effect upon multiple sclerosis of the menopause, hormone replacement therapy and the menstrual cycle. J. R. Soc. Med. 85, 612–613, Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/1433038>.

Sohrabji, F., 2007. Guarding the blood-brain barrier: a role for estrogen in the etiology of neurodegenerative disease. Gene Expr. 13, 311–319. http://dx.doi.org/10.3727/000000006781510723.

Sparkman, N.L., Martin, L.A., Calvert, W.S., Boehm, G.W., 2005. Effects of intraperitoneal lipopolysaccharide on Morris maze performance in year-old and 2-month-old female C57BL/6J mice. Behav. Brain Res. 159, 145–151. http://dx.doi.org/10.1016/j.bbr.2004.10.011.

Springer, L.N., Flaws, J.A., Sipes, I.G., Hoyer, P.B., 1996. Follicular mechanisms associated with 4-vinylcyclohexene diepoxide-induced ovotoxicity in rats. Reprod. Toxicol. 10, 137–143. http://dx.doi.org/10.1016/0890-6238(95)02056-X.

Stewart, W.F., Kawas, C., Corrada, M., Metter, E.J., 1997. Risk of Alzheimer's disease and duration of NSAID use. Neurology 48, 626–632. http://dx.doi.org/10.1212/WNL.48.3.626.

Störk, S., von Schacky, C., Angerer, P., 2002. The effect of 17β-estradiol on endothelial and inflammatory markers in postmenopausal women: a randomized, controlled trial. Atherosclerosis 165, 301–307. http://dx.doi.org/10.1016/S0021-9150(02)00242-3.

Straub, R.H., 2007. The complex role of estrogens in inflammation. Endocr. Rev. 28, 521–574. http://dx.doi.org/10.1210/er.2007-0001.

Szekely, C.A., Thorne, J.E., Zandi, P.P., Ek, M., Messias, E., Breitner, J.C.S., Goodman, S. N., 2004. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. Neuroepidemiology 23, 159–169. http://dx.doi.org/10.1159/000078501.

Terry, R.D., Masliah, E., Salmon, D.P., Butters, N., DeTeresa, R., Hill, R., Hansen, L.A., Katzman, R., 1991. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann. Neurol. 30, 572–580. http://dx.doi.org/10.1002/ana.410300410.

Tierney, M.C., Yao, C., Kiss, A., McDowell, I., 2005. Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. Neurology 64, 1853–1859. http://dx.doi.org/10.1212/01.WNL.0000163773.21794.0B.

Toniolo, P., Koenig, K.L., Pasternack, B.S., Banerjee, S., Rosenberg, C., Shore, R.E., Strax, P., Levitz, M., 1994. Reliability of measurements of total, protein-bound, and unbound estradiol in serum. Cancer Epidemiol. Biomarkers Prev. 3, 47–50, Retrieved from <http://cebp.aacrjournals.org/content/3/1/47.short>.

Trollor, J., Agars, E., 2010. Systemic inflammation and cognition in the elderly. In: Miyoshi, K., Moriumura, Y., Maeda, K. (Eds.), Neuropsychiatric Disorders. Springer, Tokyo, pp. 177–198.

Trollor, J.N., Smith, E., Baune, B.T., Kochan, N.A., Campbell, L., Samaras, K., Crawford, J., Brodaty, H., Sachdev, P., 2011. Systemic inflammation is associated with MCI and its subtypes: the Sydney memory and aging study. Dement. Geriatr. Cogn. Disord. 30, 569–578. http://dx.doi.org/10.1159/000322092.

Turnbull, A.V., Rivier, C.L., 1999. Regulation of the hypothalamic–pituitary–adrenal axis by cytokines: actions and mechanisms of action. Physiol. Rev. 79, 1–71, Retrieved from <http://physrev.physiology.org/content/79/1/1>.

van den Berg, E., Kloppenborg, R.P., Kessels, R.P.C., Kappelle, L.J., Biessels, G.J., 2009. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition. Biochim. Biophys. Acta – Mol. Basis Dis. 1792, 470–481. http://dx.doi.org/10.1016/j.bbadis.2008.09.004.

Vearncombe, K.J., Pachana, N.A., 2009. Is cognitive functioning detrimentally affected after early, induced menopause? Menopause 16, 188–198. http://dx.doi.org/10.1097/gme.0b013e3181775eb4.

Vegeto, E., Belcredito, S., Etteri, S., Ghisletti, S., Brusadelli, A., Meda, C., Krust, A., Dupont, S., Ciana, P., Chambon, P., Maggi, A., 2003. Estrogen receptor-a mediates the brain antiinflammatory activity of estradiol. Proc. Natl. Acad. Sci. 100, 9614–9619. http://dx.doi.org/10.1073/pnas.1531957100.

Vegeto, E., Bonincontro, C., Pollio, G., Sala, A., Viappiani, S., Nardi, F., Brusadelli, A., Viviani, B., Ciana, P., Maggi, A., 2001. Estrogen prevents the lipopolysaccharide-induced inflammatory response in microglia. J. Neurosci. 21, 1809–1818.

Velázquez-Zamora, D.A., González-Tapia, D., González-Ramírez, M.M., Flores-Soto, M.E., Vázquez-Valls, E., Cervantes, M., González-Burgos, I., 2012. Plastic changes in dendritic spines of hippocampal CA1 pyramidal neurons from ovariectomized rats after estradiol treatment. Brain Res. 1470, 1–10. http://dx.doi.org/10.1016/j.brainres.2012.06.012.

Vereker, E., Campbell, V., Roche, E., McEntee, E., Lynch, M.A., 2000. Lipopolysaccharide inhibits long term potentiation in the rat dentate gyrus by activating caspase-1. J. Biol. Chem. 275, 26252–26258. http://dx.doi.org/10.1074/jbc.M002226200.

Vittimberga, F.J., Foley, D.P., Meyers, W.C., Callery, M.P., 1998. Laparoscopic surgery and the systemic immune response. Ann Surg. 227, 326–334.

Wallace, M., Luine, V., Arellanos, A., Frankfurt, M., 2006. Ovariectomized rats show decreased recognition memory and spine density in the hippocampus and prefrontal cortex. Brain Res. 1126, 176–182. http://dx.doi.org/10.1016/j.brainres.2006.07.064.

Weber, M.T., Maki, P.M., McDermott, M.P., 2013. Cognition and mood in perimenopause: a systematic review and meta-analysis. J. Steroid Biochem. Mol. Biol. 1–9. http://dx.doi.org/10.1016/j.jsbmb.2013.06.001.

Weber, M.T., Rubin, L.H., Maki, P.M., 2014. Cognition in perimenopause: the effect of transition stage. Menopause 20, 511–517. http://dx.doi.org/10.1097/gme.0b013e31827655e5.

Weiderpass, E., Adami, H.O., Baron, J.A., Magnusson, C., Bergström, R., Lindgren, A., Correia, N., Persson, I., 1999. Risk of endometrial cancer following estrogen replacement with and without progestins. J. Natl. Cancer Inst. 91, 1131–1137. http://dx.doi.org/10.1093/jnci/91.13.1131.

Whiteman, M.K., Hillis, S.D., Jamieson, D.J., Morrow, B., Podgornik, M.N., Brett, K.M., Marchbanks, P.A., 2008. Inpatient hysterectomy surveillance in the United States, 2000–2004. Am. J. Obstet. Gynecol. 198 (34), e1–7. http://dx.doi.org/10.1016/j.ajog.2007.05.039.

Willard, L.B., Hauss-Wegrzyniak, B., Danysz, W., Wenk, G.L., 2000. The cytotoxicity of chronic neuroinflammation upon basal forebrain cholinergic neurons of rats can be attenuated by glutamatergic antagonism or cyclooxygenase-2 inhibition. Exp. Brain Res. 134, 58–65. http://dx.doi.org/10.1007/s002210000446.

Wise, P.M., Dubal, D.B., Wilson, M.E., Rau, S.W., Böttner, M., 2011. Minireview: neuroprotective effects of estrogen—new insights into mechanisms of action. Endocrinology 142, 969–973. http://dx.doi.org/10.1210/endo.142.3.8033#sthash.H11hcdhV.dpuf.

Woolley, C.S., 2007. Acute effects of estrogen on neuronal physiology. Annu. Rev. Pharmacol. Toxicol. 47, 657–680. http://dx.doi.org/10.1146/annurev.pharmtox.47.120505.105219.

Woolley, C.S., Weiland, N.G., McEwen, B.S., Schwartzkroin, P.A., 1997. Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. J. Neurosci. 17, 1848–1859.

Woolley, S., McEwen, B.S., 1994. Estradiol regulates hippocampal dendritic spine density via an N-Methyl-D-aspartate receptor-dependent mechanism. J Neurosci 74, 7680–7687.

Wright, D.W., Kellermann, A.L., Hertzberg, V.S., Clark, P.L., Frankel, M., Goldstein, F. C., Salomone, J.P., Dent, L.L., Harris, O.A., Ander, D.S., Lowery, D.W., Patel, M.M., Denson, D.D., Gordon, A.B., Wald, M.M., Gupta, S., Hoffman, S.W., Stein, D.G., 2007. ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. Ann. Emerg. Med. 49, 391–402. http://dx.doi.org/10.1016/j.annemergmed.2006.07.932.

Wright, D.W., Yeatts, S.D., Silbergleit, R., Palesch, Y.Y., Hertzberg, V.S., Frankel, M., Goldstein, F.C., Caveney, A.F., Howlett-Smith, H., Bengelink, E.M., Manley, G.T., Merck, L.H., Janis, L.S., Barsan, W.G., 2014. Very early administration of progesterone for acute traumatic brain injury. N. Engl. J. Med. 371, 2457–2466. http://dx.doi.org/10.1056/NEJMoa1404304.

Xiao, G., Wei, J., Yan, W., Wang, W., Lu, Z., 2008. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. Crit. Care 12, R61. http://dx.doi.org/10.1186/cc6887.

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E.M., Harris, T., Shorr, R.I., Tylavsky, F. A., Newman, A.B., 2004. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 292, 2237–2242. http://dx.doi.org/10.1001/jama.292.18.2237.

Yaffe, K., Sawaya, G., Lieberburg, I., Grady, D., 1998. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA 279, 688–695. http://dx.doi.org/10.1001/jama.279.9.688.

Yasui, T., Maegawa, M., Tomita, J., Miyatani, Y., Yamada, M., Uemura, H., Matsuzaki, T., Kuwahara, A., Kamada, M., Tsuchiya, N., Yuzurihara, M., Takeda, S., Irahara, M., 2007. Changes in serum cytokine concentrations during the menopausal transition. Maturitas 56, 396–403. http://dx.doi.org/10.1016/j.maturitas.2006.11.002.

Yates, M.A., Li, Y., Chlebeck, P., Proctor, T., Vandenbark, A.A., Offner, H., 2010. Progesterone treatment reduces disease severity and increases IL-10 in experimental autoimmune encephalomyelitis. J. Neuroimmunol. 220, 136–139. http://dx.doi.org/10.1016/j.jneuroim.2010.01.013.

Yirmiya, R., Goshen, I., 2011. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain. Behav. Immun. 25, 181–213. http://dx.doi.org/10.1016/j.bbi.2010.10.015.

Zarifkar, A., Choopani, S., Ghasemi, R., Naghdi, N., Maghsoudi, A.H., Maghsoudi, N., Rastegar, K., Moosavi, M., 2010. Agmatine prevents LPS-induced spatial memory impairment and hippocampal apoptosis. Eur. J. Pharmacol. 634, 84–88. http://dx.doi.org/10.1016/j.ejphar.2010.02.029.

Zhou, L., Fester, L., Von Blittersdorff, B., Hassu, B., Nogens, H., Prange-Kiel, J., Jarry, H., Wegscheider, K., Rune, G.M., 2010. Aromatase inhibitors induce spine synapse loss in the hippocampus of ovariectomized mice. Endocrinology 151, 1153–1160. http://dx.doi.org/10.1210/en.2009-0254.