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Review article

Estrogens, inflammation and cognition

April Au *, Anita Feher, Lucy McPhee, Ailya Jessa, Soojin Oh, Gillian Einstein

University of Toronto, 100 St. George Street, 4F Sidney Smith Hall, Dept. of Psychology, Toronto, ON M5S 3G3, Canada

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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,

* Corresponding author.
E-mail addresses: april.au@mail.utoronto.ca (A. Au), afeher2@uwo.ca (A. Feher), lucy.mcphee@mail.utoronto.ca (L. McPhee), ailya.jessa@mail.utoronto.ca (A. Jessa), soojin.oh@mail.utoronto.ca (S. Oh), gillian.einstein@utoronto.ca (G. Einstein).

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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