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Review

Long-term consequences of estrogens administered in midlife on female cognitive aging

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ABSTRACT

This article is part of a Special Issue "Estradiol and cognition".

Many of the biochemical, structural, and functional changes that occur as the female brain ages are influenced by changes in levels of estrogens. Administration of estrogens begun during a critical window near menopause is hypothesized to prevent or delay age-associated cognitive decline. However, due to potential health risks women often limit use of estrogen therapy to a few years to treat menopausal symptoms. The long-term consequences for the brain of short-term use of estrogens are unknown. Interestingly, there are preliminary data to suggest that short-term use of estrogens during the menopausal transition may afford long-term cognitive benefits to women as they age. Thus, there is the intriguing possibility that short-term estrogen therapy may provide lasting benefits to the brain and cognition. The focus of the current review is an examination of the long-term impact for cognition of midlife use of estrogens. We review data from our lab and others indicating that the ability of midlife estrogens to impact estrogen receptors in the hippocampus may contribute to its ability to exert lasting impacts on cognition in aging females.

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Results of research conducted over the last two decades support a role for estrogens in the modulation of cognitive function (reviewed in Boulware et al., 2012; Luine, 2014; Bimonte-Nelson et al., 2010). Many, although not all, randomized clinical trials and observational studies have reported that postmenopausal estrogen therapy is associated with improved cognition if treatment is initiated within a critical period after loss of ovarian function (Sherwin, 2009). However the potential health risks associated with exposure to estrogens (Chen and Colditz, 2007; Chen et al., 2006; but see Harman et al., 2011) may preclude their long-term use. Therefore, current recommendations include limiting the use of hormone therapy to a few years to treat menopausal symptoms. It is currently unknown if estrogen use for a few years in midlife will reduce risk of dementia or improve cognitive aging later in life. The current report provides an overview of the literature describing the long-term impact for cognition of midlife estradiol use. We also describe our recent work investigating mechanisms by which short-term estradiol administration in midlife can exert long-term benefits for memory.

Estrogens and cognitive aging

Effects of estrogens on cognition in women

At menopause, circulating levels of estradiol, the main estrogen produced by the ovaries, drops to one-tenth of those during menstruating years (Rannevik et al., 2008). This dramatic change in hormonal state is proposed to have functional consequences for cognition (Sherwin, 1998), either directly or by interaction with other normal or pathological aging-related physiological alterations. In support of this hypothesis, many, though not all, randomized clinical trials and observational studies have reported a link between estrogen therapy initiated after naturally occurring or surgically-induced menopause in healthy women and improved cognition (reviewed in Sherwin, 2002). Findings of early randomized clinical trials that estrogen therapy positively influenced cognition suggested a possible protective role of estrogens against Alzheimer's disease. Supporting evidence was provided by many (Fillit et al., 1986; Honjo et al., 1995; Kawas et al., 1997; Ohkura et al., 1994; Paganini-Hill and Henderson, 1996; Tang et al., 1996), but not all (Brenner et al., 1994; Mulnard et al., 2000) studies demonstrating estrogen therapy was associated with reduced risk and severity, and delayed onset of Alzheimer's disease.

In order to systematically and fully evaluate the efficacy of hormone therapy, the National Institutes of Health established the Women's Health Initiative (WHI), a longitudinal study initiated in the 1990s that was designed to assess the efficacy of hormone therapy on the incidence, prevalence, and severity of cardiovascular disease, cancer, and osteoporosis in postmenopausal women. The objective of the auxiliary Women's Health Initiative Memory Study (WHIMS) was to determine the effect of postmenopausal hormone therapy on the development and progression of dementia and global cognitive function. Surprisingly, the results of the WHI and WHIMS indicated that hormone therapy regimens consisting of chronic conjugated equine estrogens (CEE) or CEE plus medroxyprogesterone as compared to placebo treatment, had no effect, or under certain conditions increased the risks of cardiovascular disease, breast cancer, stroke, dementia, and global cognitive decline (Chlebowski et al., 2003; Craig et al., 2005; Espeland et al., 2004; Rapp et al., 2003b; Rossouw et al., 2002; Shumaker et al., 2003, 2004; Wassertheil-Smoller et al., 2003). Scrutiny of the WHIMS design, population, specifics of hormone therapy regimen used, and tests of cognitive functioning has led to hypotheses that the failure of the WHIMS to demonstrate the predicted beneficial effects of hormone therapy may be explained by various confounding factors such as the advanced age and health problems of the participants, treatment specifics (agent, regimen, dose, and route of administration), and years of ovarian hormone deprivation the participants had already experienced (Harman et al., 2005).

Critical period hypothesis of effects of estrogens on cognition

In the WHIMS, the average age of the participants at the beginning of hormone treatment was 69 (Coker et al., 2009). Importantly, these women had been without ovarian hormones for nearly two decades. The "critical period" hypothesis of hormone therapy states that there is a crucial window following the onset of menopause during which hormone therapy must be initiated in order to have beneficial effects (Gibbs and Gabor, 2003; Resnick and Henderson, 2002). The brain may lose its responsivity to estrogens after a prolonged absence of the steroids and estrogen sensitivity may remain only with a timely onset of hormone therapy. Furthermore, once brain structures have been without estrogens for too long, hormone therapy may have detrimental effects (Brinton, 2005; Suzuki et al., 2007). Therefore, the negative outcomes seen in the WHIMS may be due to the timing of hormone therapy initiation. A recent review summarizes the clinical literature including observational studies and small randomized clinical trials examining the impact of early initiation of hormone therapy on cognitive outcomes and concludes that there exists initial support for the critical period hypothesis (Maki, 2013). Results of ongoing or recently completed randomized, placebo-controlled clinical trials should provide additional insights (Wharton et al., 2013; Hodis et al., 2015).

Experimental tests of the critical period hypothesis using animal models provide corroborating evidence. For instance, nonhuman primate studies have reported that estrogens administered 30 weeks, but not 10 years post ovariectomy improves performance on tests of working memory (Lacreuse et al., 2002; Rapp et al., 2003a). In rodent models, Gibbs (2000b) first showed that long-term hormone deprivation prevented the ability of later estradiol administration to enhance hippocampus-dependent memory in aging female rats. Middle-aged rats were ovariectomized and chronically treated with estradiol beginning either immediately, 3 months, or 10 months later. Only rats treated immediately or 3 months post-ovariectomy showed enhanced performance on a delayed matching-to-position maze task when tested in old age. Similarly, our lab demonstrated that the length of hormone deprivation impacts the ability of exogenous estradiol treatment to enhance hippocampus-dependent memory in aging female rats (Daniel et al., 2006). Rats ovariectomized at either 12 or 17 months of age and immediately implanted with estradiol capsules outperformed ovariectomized controls when tested at 17.5 months of age. However, rats ovariectomized at 12 months of age and implanted with estradiol capsules at 17 months did not show enhanced memory compared to controls. Therefore, both a short-term (2 weeks) and long-term (5 months) estradiol regimen was effective at enhancing memory when initiated immediately following ovariectomy, but estradiol treatment initiated 5 months post-ovariectomy was ineffective. Furthermore, a related study in our lab showed that this effect is not limited to hippocampus-dependent tasks (Bohacek and Daniel, 2010). Middle-aged rats that were immediately implanted with estradiol capsules following ovariectomy displayed enhanced performance on the 5-choice serial reaction time task, an attentional task dependent upon the prefrontal cortex, compared to ovariectomized control rats. However, estradiol treatment initiated 5 months post-ovariectomy did not enhance performance on the task compared to controls. Collectively, these results support the idea that there is a critical time window following the cessation of ovarian function during which estradiol administration must be initiated in order to exert positive effects on cognition.

Long-term effects on cognition of short-term estrogen use within the critical period

The critical period encompassing the menopausal transition, during which evidence suggests estrogen therapy must be initiated in order to benefit cognition, is reminiscent of the hormone-sensitive period in early development during which hormones act on the brain to exert permanent influences on adult behavioral responsiveness to hormones

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