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Review

The critical period hypothesis of estrogen effects on cognition: Insights from basic research

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ABSTRACT

Background: In addition to its primary role in reproduction estrogen impacts brain areas important for cognition, including the hippocampus and prefrontal cortex. It has been hypothesized that decline in estrogen levels in women following menopause is associated with, or can exacerbate, age-related cognitive decline. However, clinical evidence to support a role for estrogen in preventing cognitive decline in women as they age is equivocal. The critical period hypothesis of estrogen effects on cognition, which proposes that estrogen administration has to be initiated within a critical time period following the loss of ovarian function in order for it to exert positive effects on the central nervous system, is offered as one explanation for inconsistencies across studies.

Scope of review: This review details results from basic research using rodent models investigating the effects of estrogen on cognition in the aging female. Emphasis is placed on work investigating effects of timing of initiation of estrogen administration on its subsequent efficacy.

Major conclusions: Results of basic research provide support for the critical period hypothesis. Furthermore, results of work in rodent models suggest mechanisms by which the response to estrogen is altered if treatment is initiated following long-term ovarian hormone deprivation.

General significance: Understanding if and under what conditions hormone administration following the loss of ovarian function positively affects the brain and behavior could have important implications with regard to female cognitive aging. Results of basic research can contribute to this understanding and provide insight into the complex mechanisms by which estrogen affects cognition.

1. Introduction

Because of the increase in life expectancy over the last century, women now live a significantly longer portion of their lives following the cessation of ovarian function. Many of the biochemical, structural, and functional changes that occur as the female brain ages are influenced by changes in estrogen levels [1]. Whereas the function of some cognitive domains, such as language and reasoning skills, is often maintained throughout the lifespan, age-related deficits are frequently noted in other areas including declarative memory and attentional processes [2]. These functions are subserved by the hippocampus and prefrontal cortex, areas of the brain that are not only particularly vulnerable to aging, but also significantly impacted by estrogen [3,4]. Many of the effects of estrogen on the structure and function of the hippocampus and prefrontal cortex are opposite to those of aging. Thus, estrogen administration is hypothesized as a potential treatment to prevent or delay age-associated cognitive decline [5].

The role of postmenopausal hormone therapy (HT) in the maintenance of cognitive skills as women age is unresolved. Although results of basic research as well as many early clinical studies support a role for HT in the prevention of age-related cognitive decline [for review, see 6], results of the large Women's Health Initiative Memory Study (WHIMS) conducted by the National Institutes of Health indicated that HT regimens consisting of chronic conjugated equine estrogens [7,8] or chronic conjugated equine estrogens plus medroxyprogesterone [9,10] do not improve cognition and may actually increase risk of dementia. Furthermore, a follow-up study to the WHIMS revealed that in older postmenopausal women HT is associated with greater brain atrophy in the hippocampus and prefrontal cortex as measured by MRI relative to the placebo control treatment [11]. Attempts to reconcile the unexpected results of WHIMS with previous research results have focused on many methodological discrepancies across studies including forms of hormones used, regimens, and routes of administration. In addition, much attention has focused on the importance of the timing of initiation of HT. In contrast to most other clinical studies, HT in the

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WHIMS was administered to women aged 65 years and older (mean age of 73 years), which is on average more than two decades after ovarian hormone levels have declined at menopause. The critical period hypothesis, which proposes that cognitive benefits of estrogen may only be apparent if administered near the time of menopause, is being investigated as a possible explanation for the discrepant results across studies [6,12,13]. Furthermore, the "healthy-cell bias" of estrogen action proposes that estrogen will provide neuroprotection when the exposure takes place before neurodegeneration is present [14]. However, if exposure takes place after neurodegeneration is present, estrogen is detrimental to neurons. There is evidence in support of the critical period hypothesis of estrogen effects on cognition in women. HT initiated during or soon after menopause exerted positive effects on measures of cognitive function in women, while later initiation of treatment was associated with no effects or impairment [15–17]. Moreover, there is preliminary evidence to suggest that a transient exposure to HT near the time of menopause may afford long-term benefits on cognition [18].

The current review details work completed by us and others focused on the investigation of how estrogen impacts cognition in aging females. Specifically, we hope to demonstrate how basic research using rodent models can help elucidate the mechanisms by which the timing of initiation of estrogen administration following the loss of ovarian function can be a critical factor in determining its efficacy.

2. Use of rodent models to investigate the critical period hypothesis

Long before the link between ovarian hormones and cognition had been appreciated, there was evidence from basic research in rodents to indicate that the responsiveness of the mammalian nervous system to estrogen is altered after a period of ovarian hormone deprivation. Results of several reproductive behavior studies revealed decreased ability of estradiol, the primary estrogen produced by the ovaries, to induce sexual behavior in ovariectomized rats if it is administered after prolonged hormone deprivation [19–22]. Furthermore, three years prior to the publication of the results of the WHIMS, there was evidence from research using a rat model to support the critical period hypothesis of estrogen effects on cognition. In this first report on the importance of timing of initiation of estrogen on its ability to affect cognition, estradiol treatment initiated within 3 months, but not 10 months, after ovariectomy enhanced acquisition of a T-maze spatial memory task in aged rats [23]. Thus, results of these early studies using rodent models provided evidence that the timing of initiation of estrogen treatment following cessation of ovarian function is a critical factor in determining its efficacy.

As these reports illustrate, the study of the effects of aging and estrogen on cognitive function can be advanced by the experimental control afforded by the use of nonhuman animal models. Scientists have developed a foundation for the study of how aging affects cognition using rodent models [for review, see 2]. As in humans and other mammals, biological vulnerability to aging in rodents is evident in areas of the brain important for cognition, including the hippocampus [24] and the prefrontal cortex [25]. Likewise, performance on behavioral tasks designed to measure cognitive functions in rodents mediated by these brain areas is also vulnerable to aging effects [26].

Rodent models also have been used extensively to characterize neuroendocrine aging [27]. Female rats undergo some of the same processes of reproductive aging as women including cessation of reproductive cycles and loss of fertility. However, rats differ from humans in that during middle age estradiol levels in rats do not drop immediately, but often remain temporarily elevated, a state referred to as constant estrus. Eventually, aged animals enter constant diestrus that is characterized by very low levels of estradiol. Therefore, ovariectomy to induce cessation of ovarian function in rats during the chronological equivalent of middle age is a commonly used model for menopause because it captures the reproductive senescence, the drop in gonadal steroid levels, and the advanced age that characterize human menopause [1,28].

Despite obvious limitations, we propose that a rodent model is a strong one to use to explore the effects of estrogen and aging on cognition. In addition to the high level of experimental control it provides, it allows for direct investigation of neural mechanisms underlying behavioral effects. And important for understanding changes in responsiveness to estrogen in aging mammals, the relatively short life span of rodents allows for the use of longitudinal designs.

3. The critical period hypothesis and targets of estrogen action

3.1. Hippocampus

Memory for acquisition of new declarative or explicit memories is dependent upon the hippocampus and becomes compromised with increasing age [29]. Explicit memory is considered the cognitive function most vulnerable to the loss of estrogen during menopause and many studies report that estrogen administered to postmenopausal women protects against this vulnerability [6]. Results of a series of studies conducted in rats in the 1990s suggest a mechanism by which changes in estrogen levels impact hippocampal function. Dendritic spine density in pyramidal neurons in the CA1 subfield of the hippocampus fluctuates across the female rat estrous cycle, with spine and synapse density being highest at proestrus when estradiol levels are high [30,31]. Furthermore, dendritic spine density of CA1 pyramidal neurons in the hippocampus is lowered in ovariectomized rats, but can be restored to levels of intact animals upon exogenous estradiol administration [32]. The estrogen-induced increase in spine and synapse density is associated with increased NMDA-receptor binding and sensitivity to NMDA-receptor mediated synaptic input [33]. The hippocampal response to estradiol is not specific to rats as a similar effect was reported in nonhuman primates [34]. As increases in levels of hippocampal spine density and NMDA-receptor levels are related to enhancements on performance on tasks of learning and memory [35,36], the ability of estrogen to induce these changes in the hippocampus has important implications with regard to its effects on hippocampus-dependent behavior [37].

Interestingly, effects of estrogen on the hippocampus differ in young and aged animals. The increase in spine density in response to estrogen observed in young adult ovariectomized rats is not evident in aged ovariectomized rats [38]. Furthermore, in aged ovariectomized rats, acute estradiol exposure increases spine density of dentate granule cells, whereas no such effects are apparent in young animals [39]. What remains to be determined is if the differential response of the hippocampus to estradiol in young and aged animals is due to effects of aging *per se* or instead due to changes in responsiveness to estradiol resulting from a period of hormone deprivation that occurs in the aging female. Results of a recent study suggest the latter. Estradiol administered 10 weeks after ovariectomy was less effective at increasing hippocampal CA1 spine density compared to estradiol administered immediately following ovariectomy [40], thus indicating that the timing of administration of estradiol is an important factor in determining its efficacy. These results provide support for the critical period hypothesis with regard to the ability of estrogen to impact the structure of the hippocampus.

3.2. Hippocampus-dependent behavior

In rodents, performance on a variety of tasks that require flexible memory use that is characteristic of the explicit or declarative memory system is dependent upon the hippocampus [41]. Results

of basic research indicate that the changes exerted by estrogen on the hippocampus translate into changes in hippocampus-dependent tasks of cognition. For example, the same regimen of estradiol administration in ovariectomized rats that results in increased spine density and NMDA-receptor binding [33] enhances performance on a matching-to-place water-maze task [42]. Additionally, we demonstrated that pharmacologically blocking the ability of estradiol to effect change in the hippocampus also blocks the ability of estradiol to enhance performance on a working memory task in a radial-arm maze [43]. A large literature indicates that estrogen enhances performances on tasks dependent on the hippocampus, although the effects are complex and can be affected by many factors, including regimen and dose of hormone administration [for reviews, see 44–46].

Like the differential effects exerted by estrogen on the hippocampus, differences in the effects of estrogen treatment on learning and memory performance of young vs. aged ovariectomized rats and mice have also been demonstrated. Estradiol enhanced spatial water-maze acquisition in young and middle-aged, but not in aged rats [47]. Furthermore, estradiol treatment enhanced object recognition and reference memory in the water maze in middle-aged but not aged mice [48]. It is unclear whether these reported decreases in responsiveness to estrogen in aged animals are due to age, or due to the changes in ovarian hormone status that occur with aging. However, the results of one study indicate that the performance of ovariectomized aged rats on a task of learning and memory can be enhanced by estradiol, but only if the treatment was begun during young adulthood [23].

The idea that the duration of ovarian hormone deprivation rather than age determines subsequent estrogen treatment efficacy is supported by results of a study from our lab. We determined if estradiol treatment in middle-aged rats is affected by the age at which it is initiated, the duration of exposure and importantly, the length of hormone deprivation prior to administration [49]. We compared the ability of physiological levels of chronic estrogen treatment initiated at different time points to affect performance on a hippocampus-dependent working memory task in a radial-arm maze in 17-month old ovariectomized rats (Fig. 1). Effects of treatments were assessed during acquisition of the maze task (Fig. 1A). In addition, because the impact of estrogen on working memory may be most apparent when the memory load increases [50], we also assessed the effects of our treatments on delay trials in which a 2.5 hour delay was imposed between the fourth and fifth arm choices (Fig. 1B). Results indicate that estradiol treatment loses its ability to positively affect working memory in middle-aged rats when it is initiated after a long period of ovarian hormone deprivation. Whereas chronic estradiol administration was effective in ameliorating ovariectomy-induced deficits in working memory when initiated immediately after ovariectomy either at 12 months of age or at 17 months of age, it was not effective when initiated after a 5-month period of hormone deprivation. Interestingly, factors such as the length of estradiol treatment prior to training and the age at which the animals were ovariectomized did not influence the efficacy of estradiol treatment. These results provide support for the critical period hypothesis and indicate that the ability of estrogen treatment to affect hippocampus-dependent behavior is attenuated following long-term ovarian hormone deprivation.

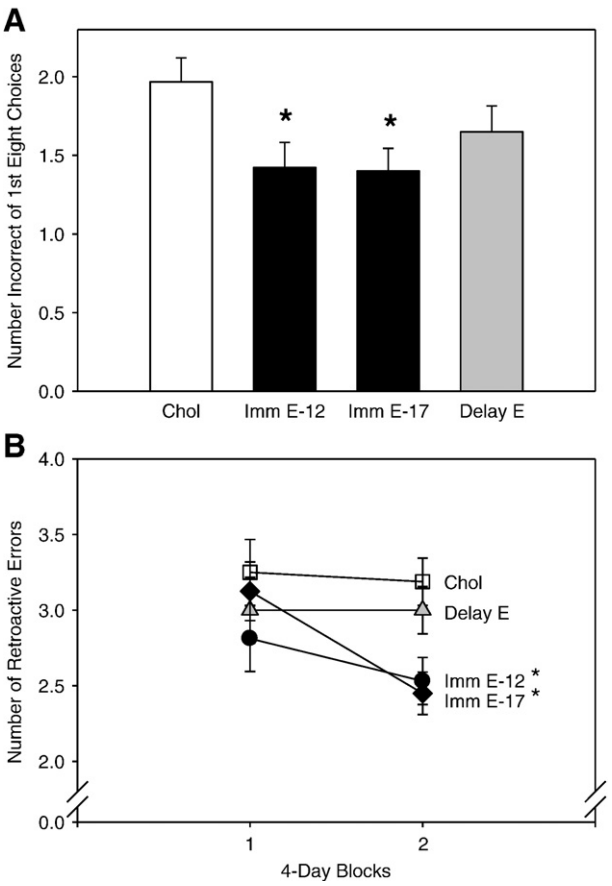

Fig. 1. Effects of timing of initiation of estradiol treatment on a hippocampal-dependent task in a radial-arm maze. Three groups of rats were ovariectomized at 12 months of age and received cholesterol control treatment via implanted capsules 5 months before and during training (Chol), estradiol treatment 5 months before and during training (Imm E-12), or cholesterol treatment for 5 months followed by estradiol treatment beginning 1 week before training (Delay E). A fourth group underwent sham surgery at 12 months of age and was ovariectomized and treated with estradiol 1 week before training at 17 months of age (Imm E-17). Following 24 days of acquisition training on the maze, rats received an additional 8 days of delay trials in which a 2.5 hour delay was imposed between the fourth and fifth arm choices. (A) Mean number of incorrect arm choices in the first eight visits (+SEM) averaged over 24 days of acquisition training (*, $P<0.05$ vs. Chol). (B) Mean number of post-delay retroactive errors (±SEM) presented as 4-day blocks over 8 days of trials (*$P<0.05$ vs. Chol) [49].

3.3. Prefrontal cortex

The prefrontal cortex in rats, monkeys, and humans is associated with higher order cognitive processes such as attention selection, resistance to interference, behavioral inhibition, task switching, and decision making [51,52]. Like the hippocampus, the prefrontal cortex is particularly vulnerable to effects of aging [53] and some reports indicate that these impairments may occur relatively early in the lifespan [2]. Although as compared to the hippocampus, relatively less is known about the effects of estrogen on the prefrontal cortex using rodent models, there is evidence that the prefrontal cortex is a target of estrogen action. For example, ovariectomized rats have a lower spine density on pyramidal cells in the medial prefrontal cortex than gonadally intact females [54] and phytoestrogens increase spine density of pyramidal cells in the medial prefrontal cortex of ovariectomized rats [55]. To date, effects of timing of initiation of estrogen treatment on its ability to impact the structure of the prefrontal cortex have not been investigated.

3.4. Prefrontal cortex-dependent behavior

Compared to the extensive literature available regarding effects of estrogen on hippocampus-sensitive tasks, relatively little is known about the behavioral implications of estrogen effects on the prefrontal cortex in rodents. One well-characterized, prefrontal cortex-sensitive task for rodents is the 5-choice serial reaction time task (5-CSRTT), which requires the animal to scan a horizontal array of five holes and quickly respond to a visual stimulus (light) with a nose poke into the illuminated hole. The 5-CSRTT task measures attentional capacity but also behavioral inhibition, impulse control, perseveration, and resistance to interference [for review, see 56]. This task has been used

to investigate estrogen effects on prefrontal cortex-associated behaviors. When the intertrial interval was varied to decrease predictability, young adult ovariectomized rats treated with estradiol outperformed ovariectomized controls [57], suggesting that estradiol enhances some aspects of attention, specifically when task difficulty is increased.

We used the 5-CSRTT task to investigate the validity of the critical period hypothesis as applied to prefrontal-cortex-sensitive behaviors (Fig. 2). Consistent with previous results [57], young adult estradiol-treated rats outperformed ovariectomized controls when behavior was challenged [58]. Specifically, we found that during unpredictably shortened intertrial intervals (Short ITI), estradiol-treated rats outperformed controls (Fig. 2A). In the same Short ITI condition, ovariectomized middle-aged rats receiving immediate estradiol treatment beginning at the age of 17 months, but not 12 months, outperformed controls as well as animals receiving delayed estradiol treatment (Fig. 2B). These results are in agreement with previous findings involving hippocampus-sensitive tasks [23,49] and indicate that the critical period hypothesis retains validity across cognitive domains. Unexpectedly however, long-term chronic estradiol treatment initiated at the age of 12 months immediately following ovariectomy failed to enhance 5-CSRTT performance when tested in the Short ITI condition approximately 6 months later. This contrasts with our previous report in which both short-term and long-term chronic estradiol treatments enhanced performance on a hippocampus-sensitive working memory task as compared to control treatment [see Fig. 1B and 49]. These results suggest that chronic estradiol treatment positively affects attention in rats, but that after prolonged treatment this beneficial effect is lost. In women, a similar finding has been reported, where hormone therapy for shorter than 10 years was found to enhance prefrontal cortex-sensitive performance on the Wisconsin Card Sorting Test and concomitantly increased prefrontal cortex volume as measured by MRI, whereas hormone treatment for longer than 10 years was associated with impairments on both measures [59].

3.5. The cholinergic system

Acetylcholine is a neurotransmitter implicated in the regulation of learning and memory [60]. The basal forebrain cholinergic system, which includes projections to the hippocampus and cortex, is vulnerable to the effects of aging and this vulnerability may be a causative factor in age-related cognitive decline [61]. In contrast, estrogen exerts primarily positive effects on cholinergic neurotransmission. For example, estradiol administration in ovariectomized rats increased potassium-stimulated acetylcholine release in the hippocampus and overlying cortex [62] and expression of the synthetic enzyme for acetylcholine, choline acetyltransferase, in the basal forebrain [63,64] and projection sites in the cortex and hippocampus [65]. The ability of estrogen to positively impact the cholinergic system is one hypothesized mechanism by which it is able to affect learning and memory. In the hippocampus, estradiol-induced disinhibition of CA1 pyramidal cells [66], increased NMDA-receptor binding [43], and associated enhancements of working memory [43,67] are mediated at least in part by the cholinergic system. Furthermore, estradiol administration following the cessation of ovarian function attenuates memory impairments induced by muscarinic receptor antagonism in rats [68,69], monkeys [70] and humans [71].

There is growing evidence that the ability of estradiol treatment following the cessation of ovarian function to affect the cholinergic system is particularly vulnerable to the timing of its initiation. For example, estrogen administration counteracts the memory impairing effects of a muscarinic receptor antagonist in women close to menopause, but not in older postmenopausal women [71]. Likewise in rats, estradiol produces protective effects against a cholinergic drug challenge when initiated immediately after ovariectomy in middle-aged, but not in aged rats [72]. In addition, a recent study revealed that pharmacologically augmenting cholinergic function can restore the ability of estradiol to affect cognition after long-term ovarian hormone deprivation in aged rats [73]. In that study, estradiol administered to aged rats that had been ovariectomized as young adults failed to enhance performance during acquisition of a T-maze task. However, when estradiol administration was preceded by treatment with a cholinesterase inhibitor, which increases endogenous levels of acetylcholine, performance was enhanced.

In our lab, we further investigated the validity of the critical period hypothesis with regard to the ability of estrogen to impact the cholinergic system. We determined if long-term ovarian hormone deprivation alters the ability of estradiol to affect levels of choline

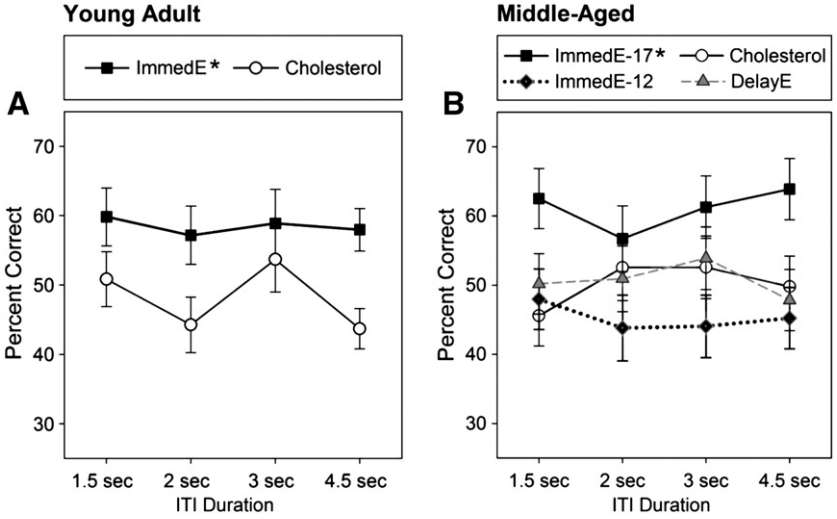

Fig. 2. Effects of timing of initiation of estradiol treatment on performance on the prefrontal cortex-dependent 5-choice serial reaction time task (5-CSRTT). Data illustrate performance when behavior was challenged by shortening the intertrial interval (ITI) across various durations. (A) Two-month old rats were trained on the 5-CSRTT, then ovariectomized and immediately implanted with capsules containing cholesterol or estradiol (ImmedE). Rats were retrained under baseline conditions and tested on the 5-CSRTT under various challenge conditions. *$P<0.05$ vs. Cholesterol. (B) Ten-month old rats were trained on the 5-CSRTT and at 12 or 17 months of age were ovariectomized and treated with estradiol or cholesterol, so that one group received continuous cholesterol control treatment (Cholesterol), two groups received estradiol treatment immediately following ovariectomy, either at 12 (ImmedE-12) or 17 (ImmedE-17) months of age, and one group received delayed estradiol treatment initiated five months following ovariectomies (DelayE). At 17 months of age, rats were retrained under baseline conditions and tested on the 5-CSRTT under challenge conditions. *$P<0.05$ vs. all other groups [58].

acetyltransferase (ChAT), the synthesizing enzyme for acetylcholine, in the hippocampus and prefrontal cortex as measured by western blotting [74]. In both young adult (data not shown) and middle-aged rats (Fig. 3), ten days of estradiol treatment initiated immediately after ovariectomy resulted in a significant increase in immunoreactivity for ChAT in the hippocampus and a non-significant trend towards an increase in the prefrontal cortex. When estradiol treatment was initiated 5 months after ovariectomy in middle-aged rats, the pattern of effects diverged. In the hippocampus, long-term ovarian hormone deprivation attenuated the ability of estradiol treatment to increase ChAT protein levels. However in the prefrontal cortex, long-term ovarian hormone deprivation sensitized the response to estradiol treatment, resulting in significantly increased levels of ChAT. These data support the critical period hypothesis, indicating that effects of estrogen treatment on the cholinergic system are altered in a brain site-specific manner if initiated long after loss of ovarian function. These results suggest that an altered ability of estradiol to regulate the cholinergic system might underlie the decreased effectiveness of estradiol to enhance memory performance after long-term hormone deprivation.

In light of the role of the cholinergic system in mediating estrogen effects in the hippocampus [43,66], attenuation of effects on markers of cholinergic function in the hippocampus could contribute to the attenuation of enhancing effects on hippocampus-dependent behavior (see Fig. 1). However, less clear is how the sensitization of effects of estradiol on cholinergic markers in the prefrontal cortex as a result of delayed estradiol treatment is associated with the attenuation of its effects on a prefrontal cortex-sensitive task (see Fig. 2). In general, enhancing the activity of the cholinergic system is thought to be associated with beneficial effects on cognitive function [75], suggesting that the increase in ChAT protein levels following long-term hormone deprivation could be linked to favorable effects on cognitive performance. However, evidence also suggests that over-enhancing cholinergic function by administration of higher doses of the cholinesterase inhibitor physostigmine can impair cognitive performance [76,77]. It may be that there is an optimal level of cholinergic activity that is associated with optimal performance on tasks of cognition.

3.6. Estrogen receptors

Estrogen exerts effects via binding and activating specific receptors. Two nuclear estrogen receptors have been described, ERα, and the more recently cloned ERβ [78,79]. Expression of these receptors has been confirmed in brain regions important for higher order cognitive functions including the hippocampus [80] and cortex [81]. The relative contributions of ERα and ERβ in mediating the effects of estrogen on cognitive function are currently unresolved. Conflicting reports, based on ER-knockout studies [82–85] and on studies using ERα and/or ERβ selective agonists [84,86–88] implicate either ERα or ERβ in the cognitive and structural effects of estradiol on the hippocampus.

ERα is implicated in age-associated changes in the response to estradiol treatment in young vs. aged animals. For example, the decreased ability of estradiol treatment to increase spine density in the hippocampus of aged rats as compared to young animals [38] is associated with a decreased number of synapses expressing ERα in aged compared to young rats [89]. Furthermore, there is decreased interaction of ERα with β-tubulin, a microtubule-associated protein involved in estrogen signaling, in aged female mice as compared to young mice [90]. In postmenopausal women, ERα polymorphisms are related to age-related cognitive decline [91,92] as well as to an increased risk of developing Alzheimer's disease [93,94]. Although data support roles for both ERα and ERβ in cognition [82,85], to our knowledge no studies have implicated alterations in ERβ in age-related changes in responsiveness to estrogen treatment.

One mechanism by which estrogen may exert effects in the brain is through regulation of estrogen receptor levels. The effects of estrogen on estrogen receptors levels are complex and vary dependent upon a number of factors, including type and regimen of estrogen exposure [81], as well as age of the animal and brain area [for review, see 27]. In the hippocampus, chronic treatment with estradiol increased ERα but

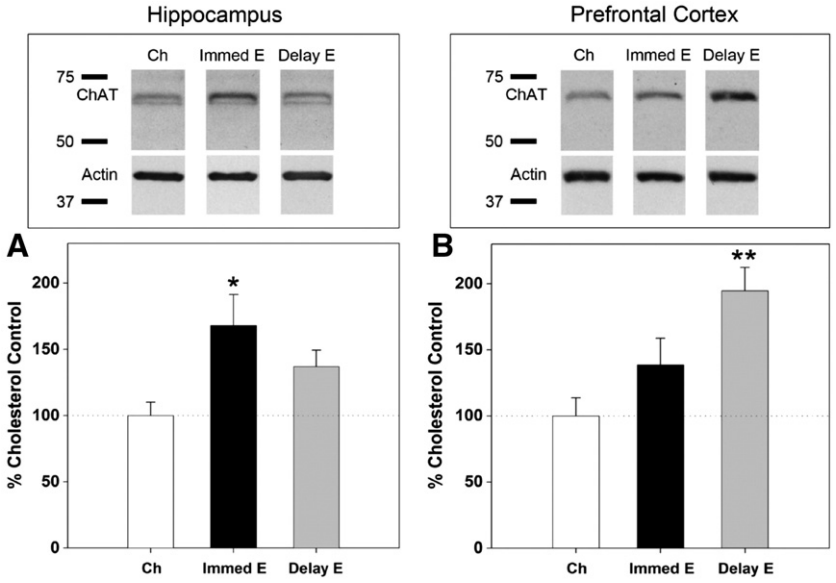

Fig. 3. Effects of timing of initiation of estradiol treatment on ChAT protein levels in hippocampus and prefrontal cortex of middle-aged rats. At 10 months of age, rats underwent either ovariectomies or sham surgeries and were maintained under these hormone conditions for a 5-month period. At 15 months of age, all rats underwent a second set of surgeries. Animals that had previously been ovariectomized underwent sham surgeries and were implanted either with cholesterol control capsules (Ch) or estradiol capsules (DelayE). Animals that had previously received sham surgeries were ovariectomized and implanted with estradiol capsules (ImmedE). Capsules were left in place for 10 days before animals were sacrificed. Mean optical density × area readings (+SEM) expressed relative to the Ch control group in the hippocampus (A) and in the prefrontal cortex (B). $^{*}P<0.05$ vs. Ch, $^{**}P<0.05$ vs. Ch and ImmedE. Representative western blot results for ChAT and the loading control, β-Actin, are shown in the insert above the graphs, including weight markers (kDa) on the left [74].

not ERβ protein levels in ovariectomized rats [80]. Exposure of hippocampal slice cultures to estradiol led to an increase of nuclear immunoreactivity for ERα, but not for ERβ [95]. We recently investigated how chronic estradiol treatment affects levels of estrogen receptor in the hippocampus and prefrontal cortex of ovariectomized rats and if the effect of estradiol on receptor levels varies with age and length of hormone deprivation [96]. Using the same tissue samples that were used to measure ChAT levels (see Fig. 3), we determined that chronic estradiol treatment influenced levels of ERα protein in these brain regions, but had no effect on ERβ (Fig. 4). In young adult rats, estradiol treatment significantly increased ERα protein levels in both the hippocampus and prefrontal cortex (data not shown). In middle-aged rats, estradiol treatment significantly increased ERα levels in the hippocampus when the treatment was initiated at the time of ovariectomy (Fig. 4A). However, the effect was attenuated when the treatment initiation was delayed until five months after ovariectomy. In the prefrontal cortex, estradiol treatment failed to significantly increase levels of ERα when initiated at the time of ovariectomy, but did so when estradiol treatment was delayed for five months (Fig. 4B). These results indicate that effects of estradiol on ERα, like effects on ChAT, are altered in a site-specific manner if initiated following long-term ovarian hormone deprivation. Whereas in the hippocampus, delaying estradiol treatment decreases the ability of estradiol to affect ERα levels, in the prefrontal cortex, the same treatment results in an increase in the ability of estradiol to affect levels of ERα.

In some circumstances and perhaps in some brain areas, high levels of ERα may be detrimental to estrogen effects. For example, estradiol treatment in young, but not middle-aged rats leads to an increase in brain-derived neurotrophic factor (BDNF) protein and neurotrophin receptor expression in the olfactory bulb [97]. The attenuation of the effects of estradiol on BDNF levels in olfactory bulb of the older rats as compared to young rats was accompanied by increases in ERα expression. A recent report indicates that

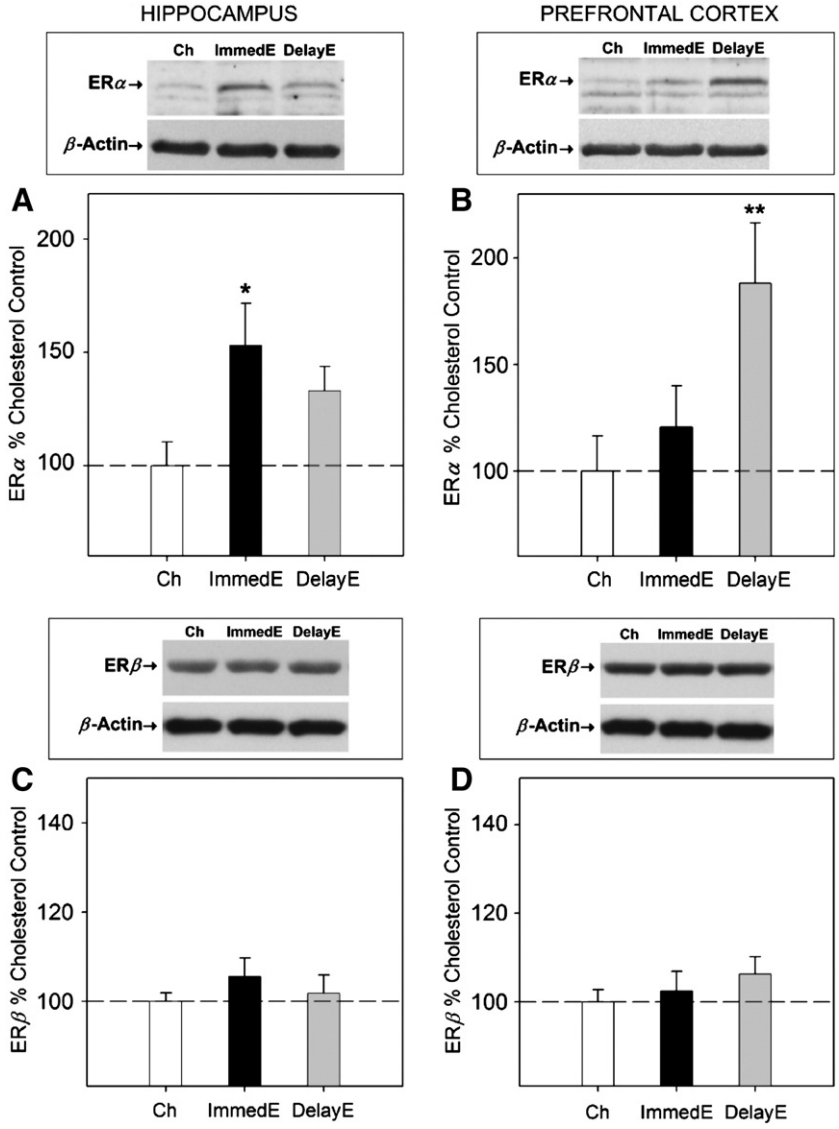

Fig. 4. Effects of timing of initiation of estradiol treatment on estrogen receptor (ER) α and ERβ protein levels in hippocampus and prefrontal cortex of middle-aged rats. At 10 months of age, rats underwent either ovariectomies or sham surgeries and were maintained under these hormone conditions for a 5-month period. At 15 months of age, all rats underwent a second set of surgeries. Animals that had previously been ovariectomized underwent sham surgeries and were implanted either with cholesterol control capsules (Ch) or estradiol capsules (DelayE). Animals that had previously received sham surgeries were ovariectomized and implanted with estradiol capsules (ImmedE). Capsules were left in place for 10 days before animals were sacrificed. Mean optical density × area readings (+SEM) expressed relative to the Ch control group in the hippocampus (A, C) and in the prefrontal cortex (B, D). *$P<0.05$ vs. Ch, **$P<0.05$ vs. Ch and ImmedE. Representative western blot results for ERα, ERβ, and the loading control, β-Actin, are shown in the insert above the graphs, including weight markers (kDa) on the left [96].

overexpression of ERα may lead to decreases in the ability of estrogen to regulate growth factors and kinases [98]. The authors suggest that there may be an optimal or homeostatic level of ERα that is necessary for estrogen to exert its trophic effects. Results of our data, in which delayed estradiol treatment results in significant increases in levels of ERα in the prefrontal cortex and yet significant impairment on performance of a prefrontal cortex-dependent task, suggest a similar relationship.

4. The critical period hypothesis of estrogen effects: hypothesized mechanisms

There is growing evidence to support a cholinergic mechanism as a basis for the critical period hypothesis of estrogen effects on cognition [73,74,99]. We hypothesize that the altered responsiveness of the cholinergic system to estradiol administration following long-term ovarian deprivation is mediated by a change in responsiveness of ERα to such treatment. The similarity between the effects of delayed estradiol treatment on ChAT (Fig. 3) and ERα (Fig. 4) in both the hippocampus and prefrontal cortex is remarkable and suggests a close link between these systems. Although it is well documented that estrogen treatment increases ChAT mRNA, protein, and enzyme activity [62,65,100,101], the precise mechanism underlying these effects has not yet been established. However, the ChAT gene contains an estrogen response element [102], and immunocytochemistry experiments have shown ERα-positive neurons in the majority of ChAT-positive cholinergic neurons in the basal forebrain that project to the hippocampus and prefrontal cortex [103]. Importantly, ERα can bind to the estrogen response element contained in the ChAT promoter region *in vitro* [104]. Therefore, it is likely that estrogen binding to ERα triggers ChAT gene transcription by activating the estrogen response element contained within the ChAT gene. In addition to this pathway, estrogen could also affect the cholinergic system via alternate routes. For example, ERα expression has been found in cholinergic terminals within the hippocampus, suggesting that estrogen can regulate acetylcholine release directly in the hippocampus [105]. Indeed, estrogen treatment increases potassium-stimulated acetylcholine release [106] as well as learning-induced acetylcholine release in the hippocampus [107]. Thus there are mechanisms by which changes in levels of ERα can directly affect the ability of estradiol to affect cholinergic neurotransmission.

In summary, we suggest that one mechanism by which the effects of estradiol on cognition are diminished after a period of ovarian hormone deprivation is due to a change in responsiveness of ERα to subsequent estradiol administration. The change in responsiveness of ERα to estradiol would likely affect the responses of many targets of estrogen action, including the responsiveness of the cholinergic system. The cholinergic system mediates, at least in part, the ability of estradiol to affect the hippocampus and associated behaviors [43,66]. Thus, an alteration in the ability of estradiol to regulate the cholinergic system might underlie the decreased effectiveness of estradiol to enhance cognition after long-term hormone deprivation.

Importantly, the currently proposed model is only one of several possible mechanisms by which the responsiveness of the nervous system to estradiol could be altered with age and/or ovarian hormone deprivation. As previously mentioned the “healthy-cell bias” of estrogen action proposes that mechanisms by estrogen will exert neuroprotective effects only before neurodegeneration has occurred [14]. Additionally, there are intriguing data to suggest that age-associated changes in the impact of estradiol on cognition may be related to its decreased ability to regulate gonadotropin levels. During the perimenopausal period in women, the hypothalamic-pituitary response becomes less sensitive to estrogen feedback resulting in elevated levels of gonadotropins including luteinizing hormone (LH) [108]. Elevated levels of LH in rats [109] and mice [110] are associated with deficits in performance on tasks of learning and memory and downregulation of LH reverses ovariectomy-induced deficits [111]. Further research will be needed to determine the validity of these mechanisms as related to the critical period hypothesis.

5. Conclusions

The results of basic research provide support for the critical period hypothesis of estrogen effects on cognition on both molecular and behavioral levels. Furthermore, these results offer insights into mechanisms by which long-term ovarian hormone deprivation alters the ability of subsequent estrogen treatment to affect cognition. Interestingly, there is preliminary evidence to suggest that in women, two to three years of hormone therapy during the critical period near the time of menopause results in long-term cognitive benefits that persist well beyond the period of exposure [18]. Results of recent work in our lab indicate that in middle-aged rats transient exposure to estradiol in the critical period following the loss of ovarian function exerts lasting effects on cognition and the brain [112]. Thus, the absence or the presence of exogenously administered estrogen during the critical period immediately following the loss of ovarian hormones may permanently alter the brain and behavior.

Continued investigation is needed to determine if the potential benefits of hormone therapy outweigh potential risks. Research using animal models can play a role in this investigation by informing clinical research as to how and under what conditions estrogen can positively impact brain systems important for cognition.

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