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Estrogenic regulation of memory consolidation: A look beyond the hippocampus, ovaries, and females

Karyn M. Frick*, Jennifer J. Tuscher, Wendy A. Koss, Jaekyoon Kim, Lisa R. Taxier

Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI 53211, United States

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ABSTRACT

The potent estrogen 17β-estradiol (E_2) has long been known to regulate the hippocampus and hippocampal-dependent memories in females, and research from the past decade has begun to shed light on the molecular mechanisms through which E_2 mediates memory formation in females. Although E_2 can also regulate hippocampal function in males, relatively little is known about how E_2 influences memory formation in males, or whether sex differences in underlying mechanisms exist. This review, based on a talk given in April 2017 at the American University symposium entitled, "Sex Differences: From Neuroscience to the Clinic and Beyond", first provides an overview of the molecular mechanisms in the dorsal hippocampus through which E_2 enhances memory consolidation in ovariectomized female mice. Next, newer research is described demonstrating key roles for the prefrontal cortex and de novo hippocampal E_2 synthesis to the memory-enhancing effects of E_2 in females. The review then discusses the effects of de novo and exogenous E_2 on hippocampal memory consolidation in both sexes, and putative sex differences in the underlying molecular mechanisms through which E_2 enhances memory formation. The review concludes by discussing the importance and implications of sex differences in the molecular mechanisms underlying E_2-induced memory consolidation for human health.

1. Introduction

Sex differences are currently a hot topic in biomedical research, thanks to recent policies enacted by funding agencies, including the National Institutes of Health, that require consideration of sex as a biological variable in all proposals [1,2]. The purpose of these policies is clear: they seek to reverse the perennial lack of females in both basic and clinical research to better understand how potential sex differences in brain and behavior may influence human health and response to therapeutic drugs. The relative merits of such policies have been debated of late on both practical and conceptual grounds. On a practical level, examining sex as a biological variable poses certain challenges [3]. Additional time and money are required to include both sexes in research studies, which strains already slim grant budgets in a time of unprecedented funding competition. Forcing researchers without backgrounds in endocrinology and genetics to address sex differences in their studies also raises potential problems for study design and interpretation. Conceptually, it has been argued that considering sex as a biological variable does not make sense for all lines of investigation, in part because this ignores social, cultural, and psychological (i.e., gender) influences on human health [3]. It has further been countered that sex is not a simple binary variable, but rather a complex phenotype involving genetic and hormonal components that are influenced by factors such as age and environment [3]. Despite these arguments, however, ignoring possible sex differences in form and function is simply no longer acceptable, given the potential adverse consequences of doing so. For example, women metabolize the drug zolpidem, the active ingredient in the sleeping pill Ambien, more slowly than men, leading to impairments in tasks such as driving the morning after women take this medication [4,5]. As such, the Food and Drug Administration reduced the recommended Ambien dosage for women by half in 2013 [5], spurring calls for increased attention to sex-specific responses to therapeutic drugs. Compelling arguments in favor of both the inclusion of females and direct examination of sex differences in biomedical research have been provided by numerous investigators [6–9], which have served to increase awareness among researchers. In addition, workshops such as that held at American University in April 2017 ("Sex Differences: From Neuroscience to the Clinic and Beyond"), and meetings sponsored by the Organization for the Study of Sex Differences, the Society for Women's Health Research, and the Society for Behavioral Neuroendocrinology, have been important venues for bringing researchers together from a variety of perspectives to discuss sex differences in multiple functional systems. Nevertheless, sex differences have yet to truly penetrate the consciousness of most

* Corresponding author at: Department of Psychology, University of Wisconsin-Milwaukee, 2441 E. Hartford Ave., Milwaukee, WI 53211, United States.
E-mail address: frickk@uwm.edu (K.M. Frick).

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researchers, precipitating the need for special issues such as this and others (e.g., [10,11]).

Sex differences in all aspects of human health are interesting and important. However, the sex difference that most piques our laboratory's interest pertains to the relative risk of Alzheimer's disease in men and women. Although age is the single greatest risk factor for Alzheimer's, women are at substantially greater risk of developing Alzheimer's than men, even when accounting for women's longer lifespans [12,13]. According to recent reports from the Alzheimer's Association, women's estimated lifetime risk of developing Alzheimer's at ages 65, 75, and 85 is approximately twice that of men [14,15]. One notable aspect of the sex difference in Alzheimer's disease risk is that it appears after menopause. Menopause marks reproductive senescence in women, and is characterized by a loss of menstrual cycling and significant hormonal alterations, including dramatic increases in gonadotropin secretion and decreases in circulating estrogen and progestin levels, that result from ovarian and hypothalamic aging. In particular, the ovarian estrogens produced by reproductively mature women are important trophic factors for neurons in regions of the brain, such as the hippocampus and prefrontal cortex [16,17], that mediate cognitive functions like learning and memory. As such, the loss of estrogens during menopause is thought to render these neurons more vulnerable to age-related decline and neurodegenerative diseases such as Alzheimer's. Indeed, elderly women with low endogenous estrogen levels experience greater risks of cognitive decline than those with higher estrogen levels [18–21].

If estrogen loss in post-menopausal women contributes to memory deficits, then estrogen replacement could potentially mitigate this loss. However, the promise of estrogen therapy for reducing and/or reversing memory loss in older women has not borne fruit. For example, treatment with conjugated equine estrogens, with or without an accompanying synthetic progestin, does not maintain or improve cognitive function in post-menopausal women over age 65, and in fact, can be detrimental to cognitive function in this population [22,23]. Moreover, hormone replacement carries small, but statistically significant, risks of breast cancer, heart disease, and stroke [24]. Despite benefits to colorectal and bone health [24], estrogen therapy is no longer generally recommended for women over age 65, including for purposes of maintaining cognition. Estrogen therapy, particularly that involving the potent estrogen 17β-estradiol (E_2), appears to have no adverse effects on cognitive function in perimenopausal women in their 50's [25–27], suggesting altered responsiveness to estrogen therapy from middle- to old-age. Somewhat similar effects have been reported in rat models of aging, in which long-term ovariectomy lasting throughout middle age diminishes the beneficial effects of E_2 on hippocampal synaptic plasticity and hippocampal-dependent memory [28–30]. As such, determining how estrogens affect brain function and why the brain's responsiveness to estrogens decreases with advanced age are important to understand why women are at greater risk of developing Alzheimer's than men.

To address these questions as they relate to learning and memory, many researchers, including ourselves, have focused on females. This approach makes sense from the perspective of understanding how estrogens work to regulate memory function in the sex most affected by Alzheimer's. Historically, our own rationale has been to first understand how estrogens influence memory in female rodents before examining this issue in males. Other labs have taken the opposite approach by examining hippocampal function in male rodents, and the resulting studies often report similar effects to those in females [31,32]. In addition, high levels of E_2 can be found endogenously in the hippocampus of both male and female rats [33,34]. Thus, numerous pieces of evidence suggest that E_2 not only affects the functioning of cognitive brain regions in males, but also that its effects are generally similar in both sexes. However, recent reports suggest that similar functional effects of E_2 in both sexes (e.g., on memory and synaptic plasticity) may be driven by different molecular mechanisms in males and females [35], which could have critical implications for the design of therapeutic interventions for men and women. As discussed below, future work must examine potential sex differences at the cellular and molecular level to determine if distinct sex-specific mechanisms underlie phenotypic differences.

In this vein, our laboratory has spent the past decade identifying molecular mechanisms in the hippocampus through which E_2 enhances hippocampal memory consolidation in female mice (for recent reviews, see [36,37]). We have primarily examined these issues in young adult females to better understand how E_2 influences memory formation in an optimally functioning system. We believe that these data from young subjects can then provide the foundation for determining how E_2, and its loss at reproductive senescence, may influence age-related memory decline and dementia in aging subjects. Therefore, most of this review discusses data collected in young females, but data from aging females is discussed at appropriate points where available. More recently, we have begun to examine these the molecular mechanisms through which E_2 may regulate memory consolidation in young males as well, and have found potentially interesting sex differences that support the notion that E_2 may exploit different molecular means in males and females to achieve similar behavioral ends. As such, the bulk of this review will focus on our data from females, with particular emphasis on new directions that illustrate the importance of hippocampally-synthesized E_2 and interactions between the hippocampus and prefrontal cortex. The remainder of the review will discuss work from our lab and others describing effects of E_2 on hippocampal function in males, and putative roles for sex differences in underlying mechanism. We then conclude with recommendations for future research.

2. Molecular mechanisms through which E_2 regulates memory consolidation in female mice

2.1. Background

Our laboratory's work on this subject has focused on the hippocampus because this brain region regulates the formation of numerous types of memory (e.g., spatial, contextual, object recognition) that are affected by aging and Alzheimer's disease [38–42]. The hippocampus is also exquisitely sensitive to levels of E_2. For example, acute E_2 treatment in young female rodents increases dendritic spine density in the CA1 region, neurogenesis in the dentate gyrus, and various forms of synaptic plasticity including long-term potentiation (LTP) (e.g., [43–53]). These effects can occur quite rapidly, as increases in CA1 dendritic spine density have been observed in vitro or in vivo as early as 20–30 min after bath application, systemic injection, or dorsal hippocampal infusion [54–58]. E_2 also swiftly triggers hippocampal cell signaling within minutes of application (e.g., [59–62]), suggesting rapid effects through non-classical estrogen receptor (ER) mechanisms in addition to potentially longer-lasting classical ER mechanisms that regulate gene transcription via estrogen response elements on DNA. Indeed, the canonical ERs, ERα and ERβ, can act both classically as nuclear transcription factors and non-classically by interacting at the membrane with neurotransmitter receptors to stimulate cell signaling [63–65]. Although both classical and rapid mechanisms influence gene transcription, the genes influenced by both processes are unlikely to be identical. Of the identified ERs, intracellular ERα and ERβ, as well as the membrane ER termed G protein-coupled estrogen receptor (GPER), are localized throughout the hippocampus in dendrites, dendritic spines, axons, and terminals [66–68], where they are poised to mediate rapid non-classical effects of estrogens. Given that E_2-induced memory consolidation is a relatively fast process lasting between 1 and 3 h after treatment [69,70], these findings render the hippocampus an ideal brain region in which to study the rapid effects of E_2 on memory consolidation.

Memory consolidation can be examined using treatments administered prior to training (pre-training) or immediately after training

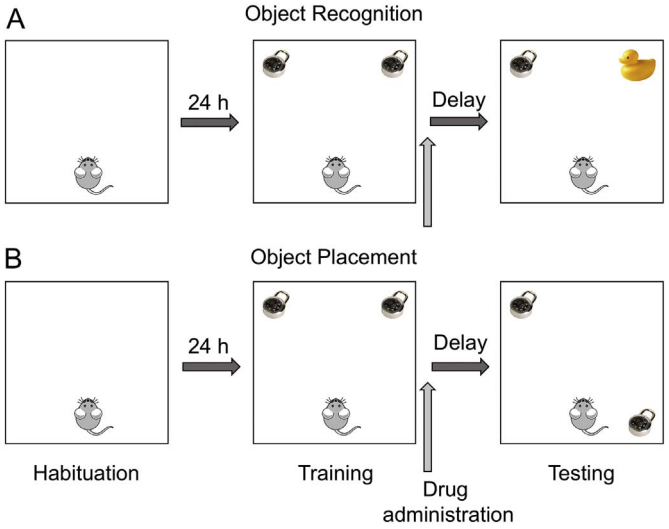

Fig. 1. Schematic of the object recognition and object placement tasks. Both tasks begin with a habituation phase in which subjects explore an empty box, typically once or twice for 5 min each. During the training phase, subjects explore two identical objects placed near the corners of the box. Training ends after a fixed amount of time (e.g., 5 min) or after subjects have accumulated 30 s of object exploration. Drugs are administered immediately post-training to assess effects on memory consolidation. After a delay (e.g., 24–48 h), the testing phase occurs, during which one training object is replaced with a new object (A) or moved to a new location (B). Testing ends after a fixed duration or after 30 s of object exploration.

(post-training). Numerous studies have shown that pre-training administration of E_2 or ER agonists given systemically or directly into the hippocampus can rapidly enhance various forms of hippocampus-mediated memories including spatial, object, and social memories [57,70–73]. However, the timing of such treatments makes it difficult to tease apart effects on acquisition vs. consolidation and performance vs. memory. Thus, to pinpoint effects of E_2 specifically on consolidation, several laboratories, including our own, have used immediate post-training treatments.

We have primarily used two object-based one-trial learning tasks: object recognition and object placement (aka., object location) (Fig. 1). Both tasks take advantage of rodent's natural proclivity to explore novelty. In both tasks, subjects are habituated within the testing apparatus, which is an empty white square arena (e.g., for 5 min/day for 1 or 2 days), after which they are then given the opportunity to explore two identical objects. In some protocols, subjects are given a total of 5 min to explore the objects, but our laboratory prefers for subjects to remain in the box until they have accumulated 30 s exploring the objects to ensure that all animals accrue the same amount of object exploration [74,75]. Immediately after training, pharmacological treatments (e.g., intracranial infusions, systemic injections, oral gavage) are administered, after which subjects are returned to their home cages. After a delay (24 or 48 h for object recognition and 4 or 24 h for object placement in our laboratory), subjects are returned to the box and again allowed to explore two objects. In object recognition, one object is identical to training and the other is a novel object. If subjects remember the identity of the familiar object, then they should spend more time than chance (15 s) exploring the novel object. In object placement, one of the training objects is moved to a different corner of the box. If subjects remember the locations of the training objects, then they should spend more time than chance with the moved object. Thus, the key difference between these two tasks involves the nature of the memory expressed during testing: "what" the object is in object recognition versus "where" the object is in object placement. As described in more detail elsewhere [69,74,76], these tasks are advantageous to study the molecular mechanisms underlying memory consolidation because they involve one-trial learning and rapid consolidation (within 3 h). They also use the same general procedure and apparatus to test multiple types of hippocampal memory and do not require potentially confounding motivational stimuli (e.g., aversive or appetitive) to encourage exploratory behavior.

We and others have shown consistently that E_2 significantly enhances hippocampal-dependent spatial and object recognition memory consolidation in young male and female mice and rats. A comprehensive discussion of these effects is beyond the scope of this review, but they have been detailed recently in numerous reviews to which we refer the reader [36,70,74,77,78]. These studies employ acute systemic injections or infusions delivered into the dorsal hippocampus or dorsal third ventricle immediately or within 1–3 h after behavioral training to pinpoint effects of E_2 on the consolidation phase of memory formation (see [69,70] for further discussion of this post-training rationale). This work has shown that E_2 administered immediately, but not 1–3 h, after training enhances memory as measured in the Morris water maze, object recognition, and object placement tasks. Most of these studies used ovariectomized mice and rats as subjects, although similar effects have been reported in gonadally-intact males (e.g., [31]). The consistency of E_2's ability to enhance memory consolidation across various labs and species, in both sexes, and in behavioral tasks tapping into different types of memory, makes the post-training paradigm an excellent tool for probing the molecular mechanisms through which E_2 regulates hippocampal memory formation. Thus, the sections below describe the current state of knowledge about the molecules and molecular processes necessary for post-training E_2 treatment to enhance memory consolidation.

2.2. *Cell-signaling and receptor mechanisms mediating E_2's effects on memory in females*

Nearly ten years ago, our laboratory discovered that phosphorylation of the mitogen activated protein (MAP) kinase called extracellular signal-regulated kinase (ERK) was necessary for E_2 to enhance object recognition memory in ovariectomized female mice [59,62]. We have since extended this finding to object placement (spatial memory) as well [79–86]. Systemic injection (0.2 mg/kg) or dorsal hippocampal infusion (5 μg bilaterally) of E_2 increased phosphorylation of the p42 isoform of ERK within 60 or 5 min, respectively, and dorsal hippocampal inhibition of ERK phosphorylation prevented E_2 from enhancing object recognition memory consolidation [59,83]. These findings demonstrated for the first time that the memory-enhancing effects of E_2 depended on phosphorylation (i.e., activation) of a cell-signaling kinase. Dorsal hippocampal ERK phosphorylation is also necessary for dorsal hippocampal infusion of 5 μg E_2 to enhance object recognition memory consolidation in middle-aged ovariectomized mice [62]. However, 5 μg E_2 has no effect on object recognition or ERK phosphorylation in aged ovariectomized mice [62], suggesting a loss of responsiveness to E_2 in the hippocampus after middle age in female mice. In subsequent work with young and middle-aged ovariectomized mice, we have shown that the beneficial effects of E_2 on memory consolidation are mediated in the dorsal hippocampus by complex interactions among cell-signaling pathways and receptors for estrogens and glutamate neurotransmission. For example, upstream from ERK, we found that the ability of E_2 to activate p42-ERK and enhance memory consolidation in young ovariectomized mice depended on activation of protein kinase A (PKA), phosphatidylinositol 3-kinase (PI3K), *N*-methyl-D-aspartate (NMDA) receptors [83,84], and interactions between metabotropic glutamate receptor 1a (mGluR1a) and ERα or ERβ [79] (Fig. 2, left). Similarly in middle-aged ovariectomized mice, the ability of E_2 to enhance object recognition memory consolidation depended on PI3K-induced activation of ERK [62]. Unpublished work from our laboratory suggests that activation of canonical Wnt/β-catenin signaling in the dorsal hippocampus of young ovariectomized mice is also necessary for E_2 to enhance object recognition and object placement memory consolidation (Taxier and Frick, unpublished observations;

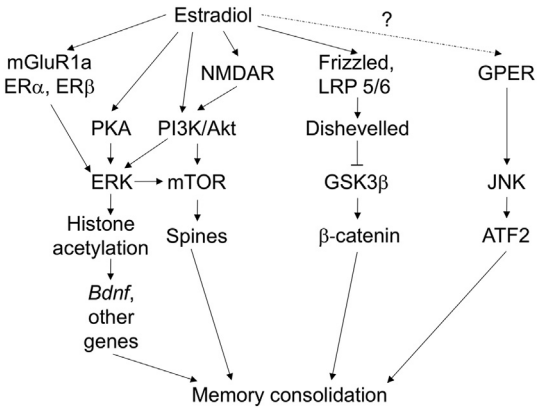

Fig. 2. Schematic illustration of the putative molecular mechanisms underlying estrogenic regulation of memory consolidation in female mice. Published work indicates that E_2 enhances memory consolidation in ovariectomized female mice by rapidly activating ERK via ERα/β-mGluR1a interactions, NMDA receptors, and activation of PI3K/Akt and PKA [79,83,84]. ERK phosphorylation triggers activation of mTOR signaling and CA1 dendritic spinogenesis [56,83], as well as histone H3 acetylation of *Bdnf* and transcription of multiple other genes [81]. These alterations presumably lead to enhanced memory consolidation. Unpublished data suggest that E_2 also enhances memory consolidation by activating canonical Wnt/β-catenin signaling, presumably via activation of the Frizzled receptor-LRP5/6 complex and recruitment of dishevelled, which dephosphorylates glycogen synthase kinase 3β (GSK3β) and allows the transcription factor β-catenin to translocate into the nucleus and promote gene transcription [85]. The mechanisms through which E_2 may interact with NMDA and Frizzled receptors are unknown. Other published findings indicate that activation of GPER enhances object recognition and spatial memory consolidation by activating JNK and the transcription factor ATF2, although the data suggest that E_2 does not play a role in the effects of GPER on memory consolidation [86].

Fig. 2, center; [85]), but it is currently unclear if estrogenic regulation of this signaling pathway is associated with ERK or upstream signaling.

Bilateral infusions of agonists for ERα, ERβ, or GPER into the dorsal hippocampus of young ovariectomized mice mimic the beneficial effects of E_2 on object recognition and object placement [79,86], suggesting that activation of any of the ERs can enhance memory consolidation. However, the signaling kinases used by these receptors to influence memory differ. Whereas ERα and ERβ regulate memory via ERK [79], GPER enhances memory in young ovariectomized mice by activating a different MAP kinase, c-Jun N-terminal kinase (JNK) [86] (Fig. 2, left). Indeed, our work showed that E_2 does not increase JNK phosphorylation, nor did infusion of a JNK inhibitor or GPER antagonist prevent E_2 from enhancing object recognition or object placement memory [86]. Thus, these data suggest the interesting possibility that GPER does not interact with E_2 to regulate hippocampal memory. Instead, E_2 appears to act via ERα and ERβ to activate ERK and related kinases to influence memory formation.

Downstream from ERK, we have demonstrated multiple ways in which E_2 may rapidly regulate gene transcription and protein translation. In one line of research, we showed that epigenetic processes, such as histone acetylation and DNA methylation, were necessary for E_2 to enhance object recognition memory in young ovariectomized mice (see [87,88] for recent reviews). Within 30 min of a dorsal hippocampal infusion, E_2 significantly increased acetylation of histone H3 in the hippocampus in an ERK-dependent manner, and this acetylation was necessary for E_2 to enhance object recognition memory [89,90]. Subsequent work in young and middle-aged ovariectomized mice showed that E_2 rapidly (within 30 min) increased H3 acetylation of specific promoters of the gene for brain derived neurotrophic factor (*Bdnf*) [81], a neurotrophin that is both essential for hippocampal memory formation and is regulated by E_2[91–93]. Not only did E_2 increase H3 acetylation of *Bdnf* promoters II and IV in middle-aged females, but treatment also significantly increased levels of BDNF and Pro-BDNF proteins in the dorsal hippocampus [81]. Collectively, these data suggest that E_2 treatment triggers the activation of numerous cell-signaling cascades that converge on ERK to rapidly promote gene transcription and protein translation via epigenetic mechanisms including histone acetylation.

In addition to altering protein translation via gene transcription, E_2 can rapidly influence local protein synthesis by activating the mammalian target of rapamycin (mTOR) signaling pathway. mTOR mediates local protein synthesis within hippocampal dendrites and is necessary for hippocampal memory formation [94]. Because mTOR signaling is activated by both ERK and PI3K [94–96], we surmised that it may play a role in estrogenic regulation of memory formation. In young ovariectomized mice, we found that E_2 activated dorsal hippocampal mTOR signaling within 5 min of a bilateral dorsal hippocampal infusion, and that this activation was necessary for E_2 to enhance object recognition memory consolidation [83]. This finding was particularly intriguing because of previous reports from Drs. Victoria Luine, Maya Frankfurt, and colleagues that systemically-injected E_2 could increase dendritic spine density in the CA1 and medial prefrontal cortex of ovariectomized rats within just 30 min [54,55]. In young ovariectomized mice, several studies show a similarly rapid increase in CA1 dendritic spine density by systemic or dorsal hippocampal administration of E_2 or agonists of ERα and GPER [57,71,72,97]. The rapid timeframe in which E_2 and ER agonists increases spines in rats and mice suggested to us that local protein synthesis, such as that mediated by mTOR, could play a major role in E_2-induced spinogenesis. Therefore, in collaboration with Drs. Luine and Frankfurt, we examined in young ovariectomized mice whether rapid activation of ERK and/or mTOR contributed to E_2's effects on dendritic spines. We first found that a bilateral dorsal hippocampal infusion of E_2 significantly increased basal and apical spine density on CA1 dendrites within 30 min, and this effect lasted for two hours [56]. The effect was specific to the CA1, as infusions did not affect spine density in the dentate gyrus. Next, to examine whether ERK or mTOR activation was necessary for E_2 to increase dendritic spine density, we infused inhibitors of ERK or mTOR phosphorylation (U0126 and rapamycin, respectively) bilaterally into the dorsal hippocampus in conjunction with an infusion of E_2 into the dorsal third ventricle (this protocol allows us to deliver E_2 adjacent to the dorsal hippocampus without risking tissue damage from two successive infusions into the hippocampus). As we previously observed with memory consolidation [83], inhibition of ERK or mTOR phosphorylation prevented E_2 from increasing CA1 dendritic spine density 2 h after infusion [56] (Fig. 3A–C). These data demonstrate that rapid activation of ERK and mTOR signaling regulates E_2-induced spinogenesis in CA1. Indeed, these data provided the first in vivo evidence that E_2 influences dendritic morphology in females via activation of cell signaling. The findings are also consistent with in vitro data from adult male rat hippocampus and embryonic cortical rat cultures showing that E_2-induced spinogenesis depends on activation of ERK and other signaling cascades [32,58,98,99]. Current studies in our laboratory are investigating which ERs may mediate these effects, although previous work suggests the involvement of ERα and GPER [57]. Importantly, how might this rapid E_2-induced spinogenesis relate to E_2-induced memory consolidation? Numerous studies link increased spine density with enhanced memory and synaptic plasticity (e.g., [100–102]). Although evidence of a direct relationship between the two remains circumstantial, the fact that both E_2-induced memory consolidation and CA1 spinogenesis depend on ERK and mTOR phosphorylation provides evidence supporting the notion that E_2-induced spinogenesis underlies the enhanced memory consolidation. This relationship is also bolstered by timing, in that the increased spine density observed 30 min and 2 h after E_2 infusion occurs well within the 3-h time window in which E_2 enhances memory consolidation (e.g., [59,103,104]). In other work, a single injection of E_2 increased CA1 dendritic spine density in ovariectomized rats 24, 48, and 72 h later [105], suggesting that E_2-induced spine density increases may last through object placement and object recognition testing 24 and 48 h later, respectively. As such, the E_2 data lend support to the idea that rapid effects of E_2 on cell signaling trigger CA1 spinogenesis, which then provides a morphological substrate for

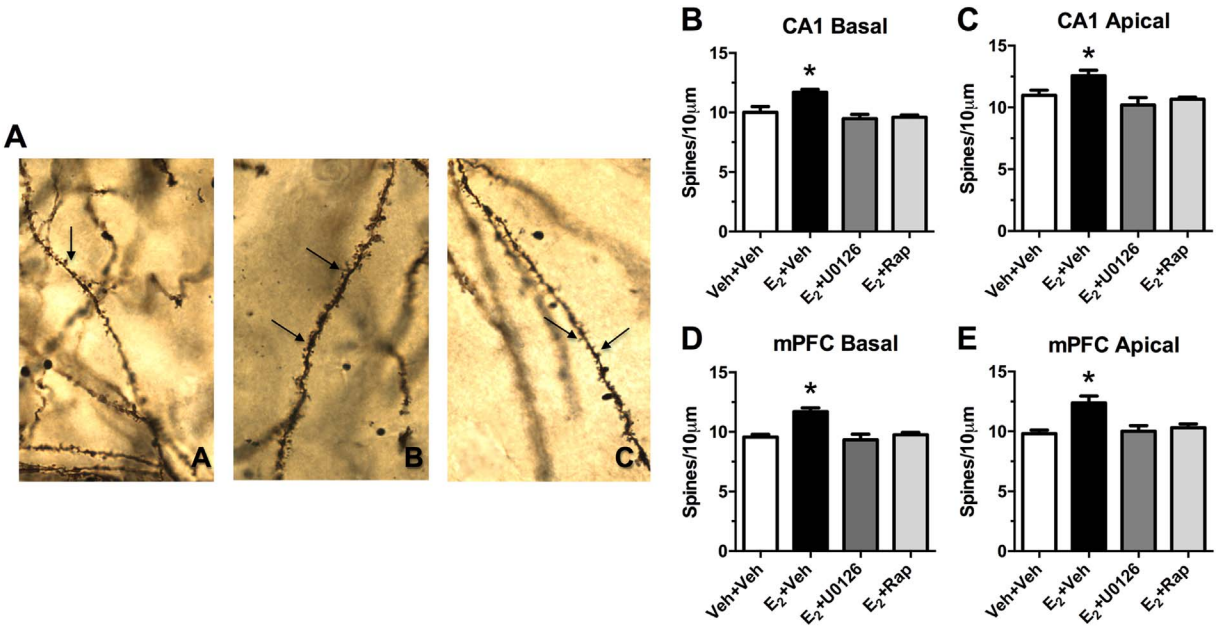

Fig. 3. Effects of E_2 on apical and basal dendritic spine density in hippocampal CA1 and the mPFC are dependent on activation of ERK or mTOR in the dorsal hippocampus. (A) Photomicrograph of Golgi-impregnated secondary basal dendrites of CA1 pyramidal cells (image A = vehicle + vehicle, image B = E_2 + vehicle, image C = E_2 + U0126). Arrows denote spines. Under oil 63 ×. (B–E) Two hours after an intracerebroventricular infusion of E_2, basal and apical spine density was significantly increased on pyramidal neurons in CA1 (A, B, C) and mPFC (D, E) relative to vehicle. These effects were blocked by dorsal hippocampal infusion of inhibitors of ERK (U0126) or mTOR (rapamycin) phosphorylation. Bars represent the mean ± SEM, $^*p < 0.05$ relative to all other groups.
Adapted from [56] with permission.

memory consolidation.

3. Interactions between the hippocampus and medial prefrontal cortex

Research on estrogens and cognition has been dominated by a primary focus on the hippocampus. However, accumulating evidence suggests that E_2 can influence various forms of learning and memory in other brain regions, such as the prefrontal cortex, striatum, amygdala, and perirhinal cortex (e.g., [106–108]). As mentioned above, systemic injections of E_2 increase dendritic spine density not only in the dorsal hippocampus, but also in the medial prefrontal cortex [54,55]. Both brain regions are essential for similar types of learning and memory, and accumulating evidence suggests a functional connection between the two [109–113]. Therefore, in our aforementioned spine density study, we examined the effects of dorsal hippocampal E_2 infusion on spine density in the medial prefrontal cortex. As a control for non-specific effects on brain regions not directly involved in learning and memory, we also examined the ventromedial hypothalamic nucleus as an estrogen-sensitive brain region involved in a different type of behavior (lordosis) [114]. Although dorsal hippocampal infusion of 5 μg E_2 had no effect on spine density in the hypothalamus, it increased basal dendritic spine density in the medial prefrontal cortex two hours later [56], suggesting that estrogenic regulation of dorsal hippocampal function influences dendritic morphology in the prefrontal cortex. To determine if the effects on cortical spinogenesis depended on rapid activation of ERK or mTOR signaling, as in the CA1, we examined spine density in the prefrontal cortex of mice infused with 10 μg E_2 into the dorsal third ventricle and inhibitors of ERK or mTOR phosphorylation into the dorsal hippocampus. Ventricular infusion of E_2 increased both basal and apical dendritic spine density in the medial prefrontal cortex [56]. As in the CA1, inhibitors of ERK or mTOR blocked this effect [56] (Fig. 3D–E), demonstrating that E_2-induced spinogenesis in the medial prefrontal cortex depends on ERK and mTOR activation in the dorsal hippocampus. These data suggest the intriguing possibility that the dorsal hippocampus and medial prefrontal cortex work in concert to mediate the memory-enhancing effects of E_2 in the dorsal hippocampus. Moreover, the results raise numerous questions about the role of E_2 in the medial prefrontal cortex in mediating memory consolidation. To address these issues, our laboratory has conducted preliminary work showing that bilateral infusion of E_2 into the medial prefrontal cortex enhances object recognition and object placement memory consolidation in ovariectomized mice (Tuscher and Frick, unpublished observations; [115]). Interestingly, our preliminary data also suggest that temporary post-training inactivation of the medial prefrontal cortex blocks the memory-enhancing effects of dorsal hippocampal E_2 infusion (Tuscher, Taxier, and Frick, unpublished observations; [116]). If confirmed, these data would support the notion that the dorsal hippocampus and medial prefrontal cortex interact to mediate the effects of E_2 on memory consolidation in females. Indeed, the data suggest a more circuit-level effect of E_2 on memory that may involve not only the medial prefrontal cortex but also other brain regions to which the hippocampus is connected, such as the basal forebrain, amygdala, entorhinal cortex, and perirhinal cortex. Recent work employing a contextual fear conditioning paradigm indicates that the development and maturation of engram cells in the prefrontal cortex of mice depends on input from several brain regions including the hippocampus, medial entorhinal cortex, and basolateral amygdala [113]. Thus, identifying the regions involved in the putative circuit involved in E_2's effects on memory is an area ripe for future investigation.

4. Role of hippocampally-synthesized estradiol

Estrogens are synthesized in multiple tissues through the body. The primary sources of estrogens in females are the ovaries, however, the brain also makes estrogens. The hippocampus contains all of the enzymes necessary to synthesize estrogens [117], and indeed, the concentration of E_2 in the hippocampus of male and female rats is higher than in plasma [33,34]. Although ovariectomy significantly decreases hippocampal E_2 levels, measureable levels remain present, and indeed, levels in ovariectomized females are comparable to intact females in diestrus [34]. That sufficient levels of E_2 remain after ovariectomy to

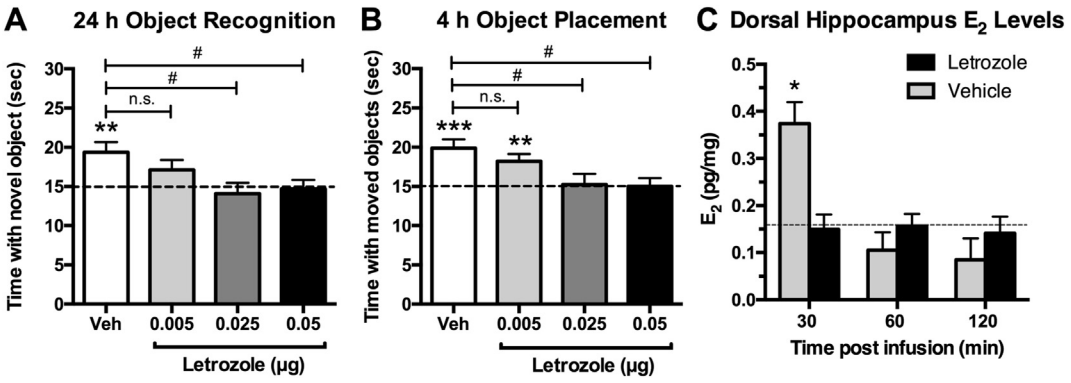

Fig. 4. Aromatase inhibition impairs memory consolidation and reduces hippocampal E_2 levels. (A, B) Mice receiving bilateral dorsal hippocampal infusion of 0.025 or 0.05 μg letrozole immediately after training were significantly impaired in both object recognition (A) and object placement (B) relative to chance (dashed line at 15 s, $^{**}p < 0.01$, $^{***}p < 0.001$) and to vehicle ($\#p < 0.05$), suggesting that these doses blocked memory consolidation. A 0.005 μg dose of letrozole had no effect on object placement and a minimal effect on object recognition. (C) Mice receiving bilateral dorsal hippocampal infusion of 0.025 μg letrozole had significantly lower dorsal hippocampal E_2 levels than vehicle-treated mice 30 min after infusion ($^{*}p < 0.05$ as measured by enzyme-linked immunosorbent assay (EIA)). E_2 levels in vehicle-treated mice dropped to the level of those in letrozole-treated mice by 60 min after training. Dashed horizontal line indicates the average background E_2 concentration as reported by EIA for control wells.
Adapted from [80] with permission.

compare to endogenous estrous cycle stages suggests that de novo hippocampal E_2 synthesis may contribute to memory formation. This idea was first tested in male song birds using hippocampal implants containing an inhibitor of aromatase, the enzyme that converts testosterone into E_2. In gonadally-intact male zebra finches, such pre-training aromatase inhibition blocks spatial memory formation [118,119]. This effect appears to depend at least in part on activation of GPER [119]. In addition, aromatase inhibition during fear extinction training impairs extinction recall in gonadally-intact male rats [120]. Interestingly, the hippocampus of female rats appears to be more sensitive to aromatase inhibition than that of males, as illustrated by data showing that systemic treatment with the aromatase inhibitor letrozole reduces CA1 spine density and LTP significantly more in females than in males [121–123]. Based on these collective data, we reasoned that aromatase inhibition might prevent memory consolidation in females. Ovariectomized mice received bilateral dorsal hippocampal infusion of letrozole immediately or three hours after training in the object recognition and object placement tasks. Infusion of letrozole immediately, but not two or three hours, after training dose-dependently blocked memory consolidation in both tasks [80] (Fig. 4A,B), suggesting that de novo hippocampal E_2 synthesis is necessary for females to form object recognition and spatial memories. A role for rapid E_2 synthesis was supported by data showing that E_2 levels were transiently elevated 30 min after object training, an effect that was blocked by letrozole [80] (Fig. 4C). Together, these data suggest that object training triggers local E_2 synthesis, which then binds to ERs and facilitates memory consolidation.

To study the role of ERs in mediating the effects of de novo E_2, we more recently infused ERα or ERβ antagonists into the dorsal hippocampus of ovariectomized mice and measured effects on memory. Inhibition of a single ER by an ER antagonist in ovariectomized subjects can provide indirect information about the role of individual ERs in the memory-enhancing effects of de novo hippocampal E_2 synthesis because any hippocampal E_2 in ovariectomized females would presumably be derived from de novo synthesis rather than the gonads. Preliminary data suggest that ERα antagonism blocked memory consolidation in the object placement, but not object recognition, task, whereas ERβ antagonism blocked consolidation of both types of memory (Kim and Frick, unpublished observations; [124]). These data suggest that the newly synthesized E_2 induced by object training mediates spatial memory via either ER, but regulates object recognition via ERβ. We should note that E_2 can be made in other non-gonadal tissues (e.g., adrenals, fat), however, the fact that aromatase inhibition in the hippocampus blocks spatial and object memory consolidation [80,118] strongly suggests that the learning-induced E_2 that influences memory consolidation is hippocampally derived. Nevertheless, although these findings support a primary role for de novo hippocampal E_2 synthesis in memory consolidation, considerably more work must be done to fully understand the extent to which hippocampal E_2 influences memory processes.

5. Sex differences in the molecular mechanisms regulating estradiol's effects on memory consolidation

Thus far, this review has focused exclusively on molecular mechanisms underlying estrogenic regulation of memory formation in females because the vast majority of work on this subject has been conducted in this sex. However, E_2 also regulates hippocampal function in males, and emerging data suggest interesting sex differences in the molecular mechanisms through which E_2 mediates memory consolidation in males and females. In both young males and females, gonadectomy has been reported to impair hippocampal memory (e.g., spatial reference memory, object recognition) and reduce CA1 dendritic spine density, and these effects can be reversed by E_2 or dihydrotestosterone [78,125–130]. Relatively few studies have examined the effects of E_2 on memory in males, but the balance suggests a beneficial effect on memory. For example, several studies of gonadectomized male rats report that chronic pre-training E_2 treatment reverses gonadectomy-induced deficits in spatial reference and working memory, as well as conditioned taste aversion and operant learning [127,131,132]. Relevant to the present discussion of consolidation, a single systemic post-training injection of E_2 given immediately after Morris water maze training enhanced spatial reference memory consolidation in gonadally-intact male rats [31]. Because more thorough reviews describing the effects of exogenous E_2 on hippocampal function in both sexes have been published previously [78,133,134], the section below will focus solely on information relevant to putative sex differences in the molecular mechanisms underlying estrogenic regulation of hippocampal memory consolidation.

As discussed above, the ability of E_2 to enhance memory consolidation in ovariectomized female mice depends on estrogen- and glutamate receptor-driven activation of numerous cell signaling pathways, including ERK, PI3K, PKA, and mTOR [59,62,83]. Moreover, the ability of E_2 to regulate dendritic spine density in the dorsal hippocampus and prefrontal cortex of ovariectomized females depends on ERK and mTOR activation in the dorsal hippocampus [115]. Similarly, Suguru Kawato's group has shown that bath application of E_2 to hippocampal slices from gonadally-intact adult males increases CA1

dendritic spine density within 2 h in a manner dependent on activation of ERK, PI3K, PKA, protein kinase C (PKC), and calcium calmodulin kinase II (CaMKII) [32,99,135–138]. Activation of these cell-signaling cascades is also necessary for E_2 to potentiate theta-burst-stimulated LTP in males [32]. Also in males, bath application of testosterone and the non-aromatizable androgen dihydrotestosterone produce similar effects on spine density and LTP as E_2, and these effects are blocked by inhibitors of ERK, PKA, PKC, LIM kinase (LIMK), and calcineurin [135,139]. Thus, these data indicate that both androgens and estrogens can regulate spine density and LTP in males. Interestingly, LIMK signaling also plays a role in E_2's ability to increase CA1 dendritic spine density and LTP in ovariectomized female rats [46], suggesting similar cell-signaling mechanisms underlying E_2's effects on spinogenesis and synaptic plasticity in males and females.

The overlap between cell-signaling mechanisms involved in spinogenesis and synaptic plasticity in females and males suggested to us that E_2 might employ similar cellular mechanisms to regulate memory in males and females. As such, we recently began to investigate the effects of E_2 on hippocampal cell signaling and memory consolidation in young male mice. We first needed to establish that E_2 could enhance memory consolidation in our behavioral paradigms. Our first experiments have used bilateral dorsal hippocampal infusions of 5 μg E_2 per hemisphere because this dose enhances spatial and object memory consolidation in female mice [59,62,79–86]. Ovariectomized female, castrated male, and sham castrated male mice received bilateral dorsal hippocampal infusions of 5 μg E_2 immediately after object recognition and object placement training. Preliminary data indicate that E_2 enhanced memory consolidation in both tasks in all groups (Koss and Frick, unpublished observations; [140,141]). These findings suggest two interesting points. First, that dorsal hippocampal infusion of E_2 enhances spatial and object memory consolidation in male mice, which is consistent with the beneficial effects of dorsal hippocampal E_2 infusion on spatial and object memory consolidation in ovariectomized female mice [59,79,80,86,142]. This effect in males is also consistent with a previous report that post-training dorsal hippocampal E_2 infusion enhances spatial memory consolidation in gonadally-intact male rats [31]. Effects of dorsal hippocampal E_2 infusion on middle-aged and aged males have yet to be examined as in females [62], so the ability of this treatment to reverse age-related memory decline in males is an open question for future investigation. The second point raised by these data is that E_2 appears to enhance memory consolidation in males regardless of gonadal status, suggesting that exogenous E_2 can regulate memory in the absence of circulating estrogens and/or androgens. Supporting a role for de novo hippocampal E_2 in males, our preliminary data also suggest that dorsal hippocampal infusion of letrozole blocks memory consolidation in castrated male mice, as it does in ovariectomized female mice [80], but not in sham castrated mice [141]. Other studies have shown that aromatase inhibition produces a much more robust reduction of LTP and CA1 dendritic spine density in ovariectomized and/or gonadally-intact female mice than in gonadally-intact male mice [121–123]. Although methodological differences (e.g., age, gonadal status, duration of letrozole treatment) make it somewhat difficult to directly compare these studies, the balance of data indicates that the testes may contribute to sex differences in the role of hippocampal E_2 in hippocampal function. Nevertheless, in vivo data in adult mice suggest that both hippocampally-synthesized E_2 and exogenous E_2 can positively regulate memory in males and females.

Interestingly, the biochemical mechanisms underlying the memory-enhancing effects of E_2 may differ between the sexes. Recall that the ability of E_2 to enhance object recognition and object placement memory consolidation in females depends on phosphorylation of ERK in the dorsal hippocampus [59,79]. Infusion of 5 μg E_2 in females results in a robust and reliable increase in p42 ERK phosphorylation within 5 min [59,79,86]. However, our pilot work shows no effect of 5 μg E_2 on p42 or p44 ERK in the dorsal hippocampus of males (Koss and Frick, unpublished observations; [140]). Moreover, blocking ERK phosphorylation in males does not prevent E_2 from enhancing memory in the object tasks as observed in females (Koss and Frick, unpublished observations; [141]). These preliminary findings indicate that E_2 regulates memory consolidation in males via a signaling mechanism different from ERK. This finding is contrary to in vitro reports showing that blocking ERK phosphorylation in gonadally-intact adult male mice and rats prevents E_2-induced LTP induction and CA1 dendritic spinogenesis [32,99,136], suggesting potentially important differences between the in vivo and in vitro preparations. We are currently trying to determine which signaling pathways are involved in E_2-induced memory consolidation in males. If supported by additional studies, this putative sex difference in underlying mechanism suggests potentially important sex differences in the way in which E_2 regulates memory.

There is some precedence for sex differences in the mechanisms through which E_2 regulates hippocampal function. For example, in hippocampal cultures from neonatal rats, E_2 interacts with mGluRs to increase ERK-dependent phosphorylation of cAMP response element binding (CREB) protein in females, but not in males [63]. Because mGluR1a activation is necessary for E_2 to increase ERK phosphorylation and enhance memory consolidation in adult females [79], the inability of E_2 to stimulate ERK-dependent CREB phosphorylation in neonatal males could provide insight into our observed sex difference in E_2-induced ERK activation. Sex differences in E_2-stimulated cell signaling may result from distinct effects of ERs on cell signaling in males and females. Alternatively, sex differences may result from differences in the specific ERs used in males and females to influence hippocampal function. This possibility is supported by a recent study showing similar potentiating effects of E_2 on glutamatergic synaptic transmission in male and female rats that were mediated by different ERs in each sex. In females, the probability of glutamate release depended on presynaptic activation of ERβ, whereas glutamate sensitivity was regulated post postsynaptically by GPER [35]. In males, glutamate release was mediated presynaptically by ERα, and glutamate sensitivity was regulated postsynaptically by ERβ [35]. These data suggest that different ERs act at different parts of the synapse in male and female rats to produce the same potentiating effects of E_2 on glutamatergic transmission. This phenomenon is reminiscent of our observation that E_2 produces similar memory-enhancing effects in male and female mice by apparently activating different cell-signaling pathways in each sex. Although we clearly must do more work to better understand how E_2 regulates memory consolidation in males and females, these preliminary observations suggest the presence of interesting, and potentially important, sex differences in the neural mechanisms underlying estrogenic mediation of memory.

6. Conclusions

This review has highlighted the molecular mechanisms thus far known to be essential for E_2 to enhance memory consolidation in females, and presented the intriguing possibility that these mechanisms may be different in males. Much of the literature on sex differences to date has focused on whether a sex difference is present in measureable outcomes, such as memory function, synaptic plasticity, or neuronal morphology. The advent of the new “sex as a biological variable” policy in the United States promises many more such reports in the future. The presence of observable sex differences leads to obvious next steps in trying to figure out the cause of these sex differences. However, we would caution against concluding that a variable is not affected by sex if no observable sex difference is present. As seen from our work and that from the Woolley laboratory [35,133], E_2 can produce similar effects on memory consolidation and synaptic transmission in both males and females, leading to the potential conclusion of no sex differences in response to E_2. However, these data belie the fact that the molecular mechanisms underlying these effects of E_2 (i.e., cell signaling and ER involvement) differ between the sexes. In both cases, the causes of these sex differences are currently unknown, but future work will

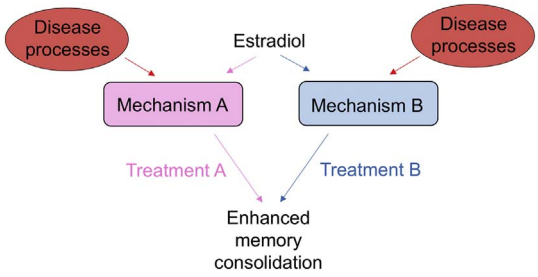

Fig. 5. Potential impact of sex differences in molecular mechanisms underlying estrogenic regulation of memory consolidation. If E_2 mediates memory consolidation in each sex via different molecular mechanisms (e.g., Mechanism A for females and Mechanism B for males), then different treatments (Treatment A for females and Treatment B for males) may be warranted during aging or in conditions such as Alzheimer's or depression for E_2 or related drugs to enhance memory formation. Different treatments may also be necessary if disease processes differentially affect Mechanisms A and B, resulting in sex differences in response to E_2.

undoubtedly address this question. Considerable possibilities abound, potentially involving genetic and epigenetic regulation of signaling kinases and ERs.

Why might it matter if males and females differ in their molecular responses to E_2 if the ultimate result of treatment (e.g., enhanced memory) is similar? We would argue that sex differences in molecular means to a phenotypic end could be vitally important to the development of new therapeutic drugs for neuropsychiatric and neurodegenerative diseases. If E_2 enhances memory consolidation via different mechanisms in males and females, then disease processes may differentially act upon those processes to alter the effects of E_2 on memory (Fig. 5). Even if disease processes have similar effects on the brain, using a one-size-fits-all strategy for the treatment of any condition makes no sense if the molecular mechanisms underlying the condition differ between men and women. If, as an exceedingly simplistic example, ERK phosphorylation is necessary for E_2 to enhance memory in women with Alzheimer's disease but not men with Alzheimer's disease, then drugs that potentiate ERK phosphorylation could improve memory in female, but not male, patients. Thus, the more we learn about putative sex differences in the molecular mechanisms underlying cognitive dysfunction in neuropsychiatric and neurodegenerative diseases, the more likely it seems that sex-specific approaches to new drug development will be needed. Such approaches could provide unique opportunities for the development of therapeutics that more effectively reduce cognitive dysfunction in both sexes than those in current use. This exciting possibility should be embraced with open arms by the research community, rather than with dread at having to consider another sex, as it may lead to improvements in human health that are not possible when considering only a single sex.

Conflicts of Interest

None

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