HHS Public Access

Author manuscript

Curr Opin Behav Sci. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Curr Opin Behav Sci. 2018 October ; 23: 65–74. doi:10.1016/j.cobeha.2018.03.011.

Estradiol and hippocampal memory in female and male rodents

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Abstract

Estrogens influence nearly every aspect of hippocampal function, including memory formation. Although this research has traditionally focused on ovariectomized females, more recent work is providing insights into the ways in which estrogens regulate hippocampal function in both sexes. This review provides an overview of estrogenic regulation of hippocampal function in female and male rodents, with a particular emphasis on memory formation. Where applicable, we discuss the involvement of specific estrogen receptors and molecular mechanisms that mediate these effects. The review concludes by suggesting gaps in the literature that need to be filled to provide greater insights into potential sex differences in the effects of estrogens on hippocampal function.

Keywords

estrogen; hippocampus; sex differences; consolidation; ERK; estrogen receptors

Introduction

In the past three decades, increasing attention has been paid to the effects of the potent estrogen 17β-estradiol (E_2) on the hippocampus. This research has provided important insights into estrogenic facilitation of hippocampal synaptic plasticity and memory formation in female rats and mice. Much less is known about how E_2 regulates hippocampal memory in males, despite high levels of estrogen receptor (ER) expression and E_2 levels in the male hippocampus. This review synthesizes key studies examining effects of exogenous E_2 on hippocampal learning and memory in female and male rodents. Molecular mechanisms underlying the memory-enhancing effects of E_2 on hippocampal memory consolidation will also be described. The review concludes by considering gaps in the literature that should be filled to better understand how E_2 regulates hippocampal learning and memory in both sexes. Due to the short format of this article, we refer readers to other

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Conflict of interest statement

The authors have no conflicts to declare.

Guest editors: Jill Becker, Natalie Tronson, Carrie Ferrario

recent reviews (e.g., [1–8]) for more detailed information on sex differences in hippocampal memory, and effects of E_2 on hippocampal morphology, physiology, and memory.

Estrogens and the hippocampus

The most well-studied ERs, ERα, ERβ, and G-protein-coupled ER (GPER), are located throughout the rodent hippocampus [9,10]. The structurally homologous ERα and ERβ are intracellular receptors that act in the nucleus as transcription factors to mediate slower classical (aka, "genomic") effects of estrogens, and at the plasma membrane where they interact with neurotransmitter and growth factor receptors to trigger rapid non-classical (aka, "non-genomic") effects on cell signaling and gene transcription. GPER is a membrane ER that mediates rapid G-protein-stimulated cell signaling. In both sexes, these receptors are widely distributed throughout hippocampal neurons, appearing within nuclei, dendritic spines, dendrites, axons, and axon terminals, as well as in astrocytes [11–••14]. ER localization to extranuclear sites, particularly dendritic spines [11–••14], positions them to mediate the rapid effects of estrogens on processes like cell signaling, local protein synthesis, and dendritic spinogenesis.

In females, numerous aspects of hippocampal morphology and physiology are regulated by E_2, including CA1 dendritic spine density, neurogenesis, cell signaling, epigenetic processes, gene transcription, protein translation, and synaptic plasticity (see [1,3,15–19] for reviews). For example, CA1 spine density in female rats is elevated during the proestrus phase of the estrous cycle, when estrogen levels are most elevated, relative to the estrus phase, in which estrogen levels are low [20]. Bilateral ovariectomy in rats and mice reduces CA1 spine density [20], an effect that can be reversed within 30 minutes by systemic injection or dorsal hippocampal infusion of E_2 [21, ••22]. These effects can be mediated by ERα or ERβ, or GPER [•23,24], and depend on rapid activation of extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR) cell signaling in the dorsal hippocampus [••22]. The mTOR pathway is activated by upstream signaling kinases including phosphoinositide 3-kinase (PI3K) and ERK, and triggers rapid local protein translation within dendrites leading to spine remodeling [25]. Both ERK and mTOR signaling are necessary for hippocampal synaptic plasticity and memory formation in male rodents [25], and for E_2-induced memory consolidation in ovariectomized mice [26]. Thus, the fact that inhibitors of ERK and mTOR phosphorylation prevent E_2 from increasing CA1 spine density suggests a key role for rapid local protein synthesis in E_2-induced spinogenesis. However, as will be described later, E_2-induced ERK phosphorylation also promotes epigenetic processes, potentially implicating gene transcription as well.

Effects of E_2 on hippocampal dendritic spine density in males are similar to those in females. *In vivo*, bilateral gonadectomy in male rats reduces CA1 spine density, and this effect is reversed within 30 minutes of systemic testosterone or E_2 injection [••27]. Likewise, *ex vivo* studies using hippocampal slices from gonadally-intact males, report that E_2 increases CA1 spinogenesis within 2 hours of bath application. This effect depends on activation of ERα, but not ERβ [28,29]; a role for GPER has not yet been determined. In hippocampal slices, E_2-induced spinogenesis depends on activation of cell-signaling kinases including protein kinase A (PKA), protein kinase C (PKC), phosphoinositide 3-kinase

(PI3K), ERK, calcium calmodulin kinase II (CaMKII), LIM kinase (LIMK), and calcineurin, but not c-Jun N-terminal kinase (JNK) [30]. Inhibition of PKA, PKC, PI3K, ERK, and CaMKII also prevent E_2 from enhancing long-term potentiation (LTP) in these slices [30], suggesting a role for these signaling kinases in E_2-induced spinogenesis and synaptic plasticity.

Consistent with its effects on CA1 dendritic spines in females and males, E_2 significantly enhances hippocampal synaptic plasticity, including NMDA-dependent LTP. In both sexes, exogenous E_2 increases baseline EPSP amplitude, reduces LTP threshold, and increases LTP amplitude [19,31,32, ••101]. The LTP enhancement has been shown to depend on ERβ in adult males and females [32,33]. However, more recent work suggests important sex differences in the pre- and post-synaptic mechanisms involved in synaptic potentiation. In females, excitatory synapses are potentiated via pre-synaptic increases in glutamate release probability that are mediated by ERβ and post-synaptic increases in glutamate sensitivity that are mediated by GPER [••101]. In males, however, glutamate release probability is regulated pre-synaptically by ERα, whereas ERβ is involved post-synaptically in glutamate sensitivity [••101]. Thus, although ERβ plays a role in mediating synaptic potentiation in both sexes, the nature of its effects differs between the sexes. E_2-induced LTP enhancement also involves actin polymerization. Actin polymerization, which promotes cytoskeletal shape and stabilization, is regulated by the RhoA/RhoA kinase (ROCK) signaling pathway. E_2 activates this pathway in hippocampal slices from intact male rats, and reverses ovariectomy-induced reductions in RhoA levels and actin polymerization [32]. In hippocampal slices from male rats, latrunculin A, a toxin that disrupts assembly of actin filaments, blocks E_2-induced LTP [32], suggesting that actin polymerization is critical for estrogenic regulation of hippocampal plasticity. Recent preliminary data from our laboratory support this assertion, as latrunculin A prevents E_2 from enhancing memory consolidation in ovariectomized mice [34].

Collectively, evidence to date implicates E_2 as an important modulator of hippocampal function. E_2 regulates many of the morphological, biochemical, and physiological aspects of hippocampal function thought to underlie learning and memory processes, so it is perhaps not surprising that E_2 also regulates memory formation. Although a thorough review of this literature is beyond the scope of this review, the sections below will provide an overview of the effects of exogenous E_2 on hippocampal learning and memory in females and males, and discuss the molecular mechanisms through which E_2 regulates hippocampal memory consolidation in females.

Effects of pre-training E_2 treatment on hippocampal learning and memory

The preponderance of hormones and cognition research has examined effects of exogenous E_2 on hippocampal memory in young adult (2-3 months old) ovariectomized females. Most studies have administered E_2 for some period prior to and/or during training, either chronically (e.g., via implanted silastic capsules or pellets) or acutely (e.g., via systemic injection or intracranial infusion). Similar studies have been conducted in gonadally-intact and castrated males, but these are far less numerous. Data from both sexes will be summarized below, including information about specific ER involvement where known. As

with all pharmacological treatments, effects of E_2 on memory depend on many factors, including dose, route of administration, timing and duration of administration, task difficulty, duration of handling prior to treatment, age at treatment, and duration of gonadectomy prior to treatment [1]. Nevertheless, the balance of studies in both sexes indicates that acute or chronic E_2 treatment prior to training is beneficial for hippocampally-mediated spatial and non-spatial learning and memory (see Table 1 for a schematic summary of pre-training studies in both sexes).

In ovariectomized rats and mice, spatial memory assessed via the radial arm maze, Morris water maze, and T-maze tasks is generally enhanced by chronic E_2 [35–50]. Improvements have been observed in both spatial reference memory (long-term memory for trial-independent information) and spatial working memory (short-term memory for trial-dependent information). Depending on the task and treatment, effects in females can be mediated by any ER. For example, spatial working memory in a delayed non-match-to-position (DNMTP) T-maze task is facilitated in ovariectomized rats by agonists of ERα, ERβ, or GPER administered via mini osmotic pumps for two weeks prior to training [50]. Studies using ER knockout (KO) mice report that E_2 improves spatial memory and inhibitory avoidance in female ERαKO mice [51], but has no effect or impairs spatial and object recognition learning and memory in ERβKO mice [33,52], suggesting a primary role for ERβ in the memory-enhancing effects of E_2. However, more recent work found that viral vector-mediated delivery of ERα to the hippocampus of female ERαKO mice improved spatial memory [53], suggesting a role for ERα in spatial memory formation as well. Although effects of E_2 in GPER KO mice have not been tested, chronic systemic administration of a GPER antagonist to ovariectomized rats impairs spatial working memory in a DNMTP task and blocks the memory-enhancing effects of chronic E_2, suggesting that GPER mediates effects of E_2 on spatial memory in rats [54]. Consistent with the effects of E_2 and ER manipulations on spatial memory, E_2 also promotes the use of hippocampal-dependent spatial learning strategies in ovariectomized rats, an effect that depends on hippocampal ERα and ERβ [•55,56].

Similar memory-enhancing effects of pre-training E_2 have been reported in castrated or gonadally-intact male rats and mice, as acute or chronic treatment with various forms of estradiol improve spatial reference and working memory in the radial arm maze, T-maze, and Barnes maze, and in passive avoidance [46,57–61]. In contrast to the relative wealth of ER-specific information in females, nearly nothing is known about which ERs mediate the effects of E_2 on spatial memory in males. One study reported that infusion of an ERα agonist into the dorsal hippocampus of gonadally-intact male rats 30-35 minutes before training impaired spatial reference memory in the Morris water maze [62], suggesting that ERα may not be involved in the memory-enhancing effects of E_2 in males. However, no studies to date have examined the role of ERα in other forms of memory or the role of other ERs in memory among castrated or intact males. Thus, this is an area ripe for future investigation.

Various tests of non-spatial hippocampal memory are also facilitated by pre-training administration of E_2. In females, including object recognition, social recognition, social learning of food preferences, and trace eye-blink conditioning [63–68]. In ovariectomized

mice, acute E_2 administered within 45 minutes before training facilitates object recognition and social recognition, as well as the object placement test of spatial memory [63,69–•71]. All three ERs are involved in these effects, as suggested by the memory-enhancing effects of pre-training dorsal hippocampal infusion of ER agonists, although the role of any specific receptor depends on the type of memory and test difficulty. For example, in one series of studies, pre-training administration of an ERα agonist facilitated object recognition, social recognition, and object placement, whereas an ERβ agonist facilitated only object placement and a GPER agonist enhanced only social and object recognition [6, ••65, •71]. Whether pre-training E_2 treatment might regulate the memory of males in these tasks remains to be investigated. However, an interesting sex difference has been reported in contextual fear generalization among gonadally-intact rats, such that fear generalization was enhanced in females relative to males [72]. This increase in females appears to be mediated by E_2, as contextual fear generalization was increased in ovariectomized female rats treated with estradiol benzoate-filled silastic capsules relative to rats treated with vehicle-filled capsules [73]. Interestingly, this E_2-induced fear generalization in ovariectomized females resulted from regulation of retrieval, rather than acquisition or consolidation, and depended on ERβ [73], but not membrane-associated ERs [•74]. Consistent with the sex difference observed in gonadally-intact rats, chronic pre-training exposure of gonadectomized male rats to testosterone or E_2 prevented fear generalization in males, as did acute treatment 24 hours prior to retrieval [•75]. Effects of pre-retrieval E_2 were mimicked by acute injection of ERα or ERβ agonists, suggesting a role for both receptors in males that differs from the singular involvement of ERβ in ovariectomized females [•75]. Together, these fear generalization-*reducing* effects of E_2 in males directly contrast with the fear generalization-*inducing* effects of E_2 in females, suggesting important sex differences in the role of E_2 in mediating fear memory.

Together findings from pre-training studies suggest that E_2 can facilitate hippocampally-mediated spatial and non-spatial learning and memory in both male and female rodents. These effects depend in part on activation of various ERs, although the specific ERs involved in each sex and type of memory may differ. Of note, however, relatively few studies have investigated effects of pre-training E_2 on learning and memory in males, or have investigated the relative contributions of different ERs to learning and memory in males, so sex comparisons are difficult to draw. Nevertheless, the data thus far support a generally beneficial effect of pre-training E_2 on learning and memory in both sexes.

Effects of post-training E_2 treatment on hippocampal memory: Elucidating molecular mechanisms underlying estrogenic memory enhancement

Although the findings of pre-training studies suggest that E_2 regulates hippocampal memory formation, the presence of E_2 during both acquisition and consolidation prevents identification of the neural mechanisms through which E_2 specifically influences memory formation. In recent years, numerous labs have used immediate post-training administration of acute exogenous E_2 to assess effects of E_2 on memory consolidation in ovariectomized rodents. In addition to pinpointing effects of E_2 specifically on consolidation, these post-training treatments avoid potential confounds during acquisition resulting from E_2 effects on

motivation or sensorimotor functions [76]. Furthermore, because the consolidation process is confined to a limited time after training, post-training studies allow elucidation of the molecular and cellular mechanisms underlying estrogenic regulation of memory formation. This section will first describe the effects of post-training E_2 on memory consolidation in females, and then summarize the receptor and intracellular mechanisms on which this consolidation depends. The section ends with a discussion of how post-training E_2 treatment affects memory consolidation in males. See Table 2 for a schematic summary of post-training studies in both sexes.

Systemic injection or dorsal hippocampal infusion of E_2 immediately after training in spatial memory and object recognition tasks enhances memory consolidation consistently across tasks, laboratories, and species. In the Morris water maze, systemic injection or dorsal hippocampal infusion of E_2 immediately, but not two hours, post-training enhances spatial reference memory formation in ovariectomized rats and mice [77–79]. Similarly, post-training dorsal hippocampal infusion of E_2 immediately after Morris water maze training enhances spatial reference memory in intact male rats [80]. It is unclear what molecular mechanisms drive these enhancements, but effects in both sexes involve activation of the cholinergic system [77, 80]. Spatial memory is also enhanced by post-training E_2 in the object placement task. Using delays at which vehicle-treated subjects show no preference for the moved object, several laboratories have shown that systemic or dorsal hippocampal administration of E_2 given immediately, but not 1.5 hours, after training enhances spatial memory consolidation (e.g., [69,••81–85]).

Object recognition memory consolidation, another type of memory dependent on hippocampal function [86–88], can be tested using a similar experimental approach and apparatus as the object placement task. As with object placement, systemic or dorsal hippocampal administration of E_2 immediately, but not 1.5-3 hours, after training enhances object recognition memory consolidation in ovariectomized rats and mice [21,26,69,79,••81,82,84,89–92]. Interestingly, we recently showed that blocking the synthesis of E_2 within the dorsal hippocampus of ovariectomized mice immediately after training prevents consolidation in both the object recognition and object placement tasks [•93], demonstrating the importance of hippocampally-synthesized E_2 to memory consolidation in females. Collectively, the consolidation-enhancing effects of exogenous E_2 have been so consistent across and within laboratories that we have exploited these tasks as tools to understand the molecular basis of E_2-induced memory enhancement. The information gleaned from these studies thus far will be summarized below (see [15,94] for a more detailed discussion).

Given the rapid nature of estrogenic facilitation of memory consolidation, we reasoned that the memory-enhancing effects of post-training E_2 were mediated by rapid non-classical effects of ERs (see Figure 1 for a diagrammatic illustration of these effects in ovariectomized mice). As such, we explored the involvement of cell-signaling cascades known to regulate memory formation and found that rapid activation of PKA, PI3K, ERK, and mTOR signaling within 5 minutes of infusion was necessary for post-training dorsal hippocampally-infused E_2 to enhance object recognition memory consolidation in ovariectomized mice [26,90,95,96]. The estrogenic regulation of mTOR by ERK and PI3K

was particularly intriguing because mTOR signaling triggers local protein synthesis in dendrites, which could play a role in E_2's effects on hippocampal spinogenesis. Indeed, inhibitors of ERK or mTOR phosphorylation prevent E_2 from increasing CA1 dendritic spine density in ovariectomized mice [••22], linking E_2-induced cell signaling to both spinogenesis and memory formation. Downstream from ERK, E_2 causes rapid epigenetic changes in the dorsal hippocampus that are necessary for memory consolidation. For example, dorsal hippocampal infusion of E_2 triggers ERK-dependent acetylation of the H3 histone protein in the hippocampus within 30 minutes [92]. Moreover, dorsal hippocampal infusion of a histone acetyltransferase inhibitor prevents E_2 from enhancing object recognition memory consolidation [97], suggesting an essential role for H3 acetylation. Although the specific genes acetylated remain largely unknown, E_2 increases H3 acetylation of specific promoters of the gene for brain derived neurotrophic factor (BDNF) [98], a memory-promoting neurotrophin.

Cell signaling is triggered by receptor binding, typically at ion channels and G protein-coupled receptors. Evidence that cell signaling is necessary for E_2 to regulate hippocampal dendritic spine density [••22,29,30] suggests the involvement of ERs in at least some of the aforementioned effects. Systemic injection of ERα and ERβ agonists in ovariectomized rats and mice typically enhance memory consolidation in the object placement and object recognition tasks, although the effects can be dose-dependent [84,85,89]. Dorsal hippocampal infusion of an ERα agonist enhances object recognition and object placement in ovariectomized mice of both the C57BL/6 and Swiss strains [82,91], but an ERβ agonist enhances consolidation in both tasks only in C57BL/6 mice [82], suggesting potential strain differences in ER involvement. In C57BL/6 mice, the ability of E_2 and agonists of ERα and ERβ to facilitate memory consolidation and ERK phosphorylation is dependent on activation of metabotropic glutamate receptor 1a (mGluR1a), and additional data showed that ERα, ERβ, and mGluR1a interact at the plasma membrane [82]. As such, these findings support non-classical actions of ERα and ERβ in which they interact with neurotransmitter receptors to rapidly trigger cell signaling. More recently, post-training infusion of ER antagonists into the dorsal hippocampus of ovariectomized C57BL/6 mice showed that ERβ antagonism blocked memory formation in both object recognition and object placement, whereas ERα antagonism blocked only object placement [•99]. Together, both agonist and antagonist data support a role for ERβ in both object recognition and spatial memory in ovariectomized C57BL/6 mice. It is curious, however, that ERα agonism enhanced memory in both tasks, whereas antagonism blocked only spatial memory. This discrepancy could be related to drug dose, or could suggest that ERα is sufficient, but not necessary to facilitate object recognition memory consolidation in females. Given the paucity of studies addressing this issue, more data will be needed to evaluate this speculative conclusion.

In ovariectomized mice, post-training dorsal hippocampal infusion of a GPER agonist enhances, whereas a GPER antagonist impairs, consolidation in the object recognition and object placement tasks [••81], suggesting that activation of GPER may also mediate the memory-enhancing effects of E_2. Our preliminary data indicates that dorsal hippocampal GPER activation also increases CA1 dendritic spine density in ovariectomized mice within 40 minutes of infusion [34]. Curiously, however, the effects of GPER activation on consolidation are not mediated by ERK [••81], as are the effects of E_2 and agonists of ERα

and ERβ [82,90]. Rather, the effects of GPER activation are mediated by c-Jun N-terminal kinase (JNK; Figure 1) [••81]. Moreover, GPER antagonism does not prevent E_2 from facilitating memory consolidation in either task, nor does inhibition of JNK signaling [••81]. These data suggest the intriguing possibility that GPER acts independently of E_2 to regulate memory consolidation in the dorsal hippocampus of ovariectomized mice. The fact that GPER antagonism prevents chronic systemic E_2 from enhancing spatial working memory in a T-maze DNMTP task in ovariectomized rats [54] suggests that GPER may play a greater role in acquisition than consolidation. However, these two studies differed in many important regards, so additional study is needed to resolve these discrepancies.

In contrast to the relative wealth of data on the effects of post-training E_2 treatment on memory consolidation in females, very little is known about such effect in males. One recent of castrated rats found that post-training systemic injection of E_2 or testosterone enhanced memory consolidation in the object placement task [••27]. Consistent with this finding, preliminary data from our laboratory directly comparing the effects in males and females of post-training dorsal hippocampal E_2 infusion on object recognition and object placement memory show that E_2 enhances memory in both tasks in castrated and intact male mice in a manner similar to ovariectomized females [100]. These data suggest the absence of sex differences in the effects of exogenous E_2 on memory consolidation in these tasks, and that the effects of exogenous E_2 on consolidation do not depend on the presence of the testes. Interestingly, however, post-training infusion of an aromatase inhibitor into the dorsal hippocampus blocks memory consolidation in castrated, but not intact, males [100]. Thus, endogenous E_2 appears essential for memory consolidation in gonadectomized male and females, but not intact males, suggesting that testicular-derived E_2 or androgens may be sufficient to regulate memory in males.

Interestingly, whereas E_2 in females increased ERK and Akt levels as in previous studies, no increase in ERK was detected in intact males [100]. Also, in intact and castrated males, an inhibitor of ERK phosphorylation did not prevent E_2 from enhancing consolidation in the object recognition and object placement tasks, unlike previous studies in females [100]. These data suggest that ERK activation is not necessary for E_2 to enhance memory as in females, and indicates a potentially important sex differences in the molecular mechanisms through which E_2 regulates memory consolidation. Although it is unknown at present what cell-signaling pathways might regulate memory consolidation in males, our data indicate that E_2 increases phosphorylation of the transcription factor CREB in the dorsal hippocampus of castrated males [100]. Thus, efforts are currently underway to identify the upstream signaling pathway(s) that may play a role in E_2-induced memory consolidation in males.

Sex-specific molecular mechanisms have been observed previously in E_2-induced facilitation of hippocampal glutamatergic neurotransmission, where glutamate release probability is mediated pre-synaptically by ERβ in females and ERα in males, and post-synaptic glutamate sensitivity is mediated by GPER in females and ERβ in males [••101]. In this study and our preliminary data [100], the end result—memory enhancement or synaptic potentiation—is similar in males and females. However, the sexes differ in the molecular mechanisms that mediate these effects. As such, more studies are needed to directly compare

the molecular mechanisms underlying hippocampal function in both sexes to determine the nature and scope of potential sex differences. Such differences could have significant implications for the design of future drug treatments aimed at influencing cognitive function in neurodegenerative and psychiatric diseases.

Conclusions

In this abridged *Current Opinion* format, we have provided a simplified overview of the effects of E_2 on hippocampal memory in females and males. Although the evidence generally suggests that E_2 can benefit the formation of memories mediated by the hippocampus, a few caveats should be considered. We know far more about the effects of E_2 on memory in ovariectomized females than in males, despite evidence that the male hippocampus responds to exogenous E_2. For example, E_2 rapidly regulates CA1 dendritic spine density in male hippocampal cultures by triggering activation of numerous cell-signaling cascades [30], including some that our laboratory has demonstrated are essential for E_2 to enhance memory consolidation in ovariectomized mice. But as described above, males and females may use different molecular mechanisms to mediate the effects of E_2 on memory, so these mechanisms must be examined in both males and females. Indeed, we know very little about potential sex differences in the mnemonic response to E_2 because so few studies have directly compared the effects of E_2 on memory in females and males. Typically, studies have been conducted using one sex, and therefore, estimations of possible sex differences require apples-to-oranges comparisons among studies in which many aspects of experimental design may differ, including behavioral protocols and E_2 formulation, dose, and/or route of administration. Thus, to allow for more accurate assessment of putative sex differences in estrogenic regulation of hippocampal memory, many more studies are needed that directly compare the effects of E_2 on memory in males and females within the same study using the same experimental conditions.

Even within ovariectomized females, however, we still know relatively little about how E_2 facilitates memory formation. We have learned a great deal in recent years about the receptor, cell-signaling, and epigenetic mechanisms necessary for E_2 to facilitate memory consolidation in ovariectomized mice, but much more remains unknown, including how these mechanisms interact within cells, in which cell populations these mechanisms are activated (e.g., pyramidal neurons, interneurons, granule cells, glia), and how E_2-induced alterations in the hippocampus may affect the activity of interconnected brain regions such as the prefrontal cortex. As such, much more remains to be done.

Finally, whereas nearly all studies examining effects of estrogens on memory have been conducted using ovariectomized females, which facilitates more control over E_2 levels than is possible using naturally cycling females, there is no standard convention regarding the gonadal status of males. Studies of exogenous E_2 administration have been conducted in both gonadally-intact and castrated males, which complicates interpretation of results given that castrated males are deprived of endogenous circulating E_2 derived from aromatization of testosterone in the testes. The studies conducted to date have generally failed to consider gonadal status in their interpretations, and to our knowledge, only our preliminary study [100] has directly compared the effects of E_2 on hippocampal memory in castrated and intact

males. Thus, more studies directly comparing effects of E_2 on memory in castrated and intact males are necessary to determine the extent to which gonadally-derived sex steroid hormones may interact with exogenous E_2 to influence memory formation.

Although the past three decades have seen a dramatic increase in research on the effects of E_2 on hippocampal memory in females and males, this work is just the beginning of what is likely to be a very complicated neuroendocrinological story. With increased awareness of putative sex differences and the relative roles of gonadal vs. brain-derived E_2, the field is poised to make significant breakthroughs in better understanding how this vital hormone regulates cognition.

Acknowledgments

The University of Wisconsin-Milwaukee supported the writing of this manuscript. Empirical work from our laboratory described herein was supported by the National Institutes of Health (R01AG022525, R01MH107886, R03MH065460), the American Federation for Aging Research, the Ellison Medical Foundation, University of Wisconsin-Milwaukee Research Growth Initiative Awards (101×240 and 101×334), the University of Wisconsin-Milwaukee, and Yale University.

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•of special interest

••of outstanding interest

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- Estradiol (E_2) enhances many forms of hippocampal learning and memory
- In females, rapid E_2 effects are mediated by mechanisms including cell signaling
- Much less is known about how E_2 regulates hippocampal function in males
- E_2 may enhance memory in females and males via distinct molecular mechanisms
- Future studies should include more direct comparisons between the sexes

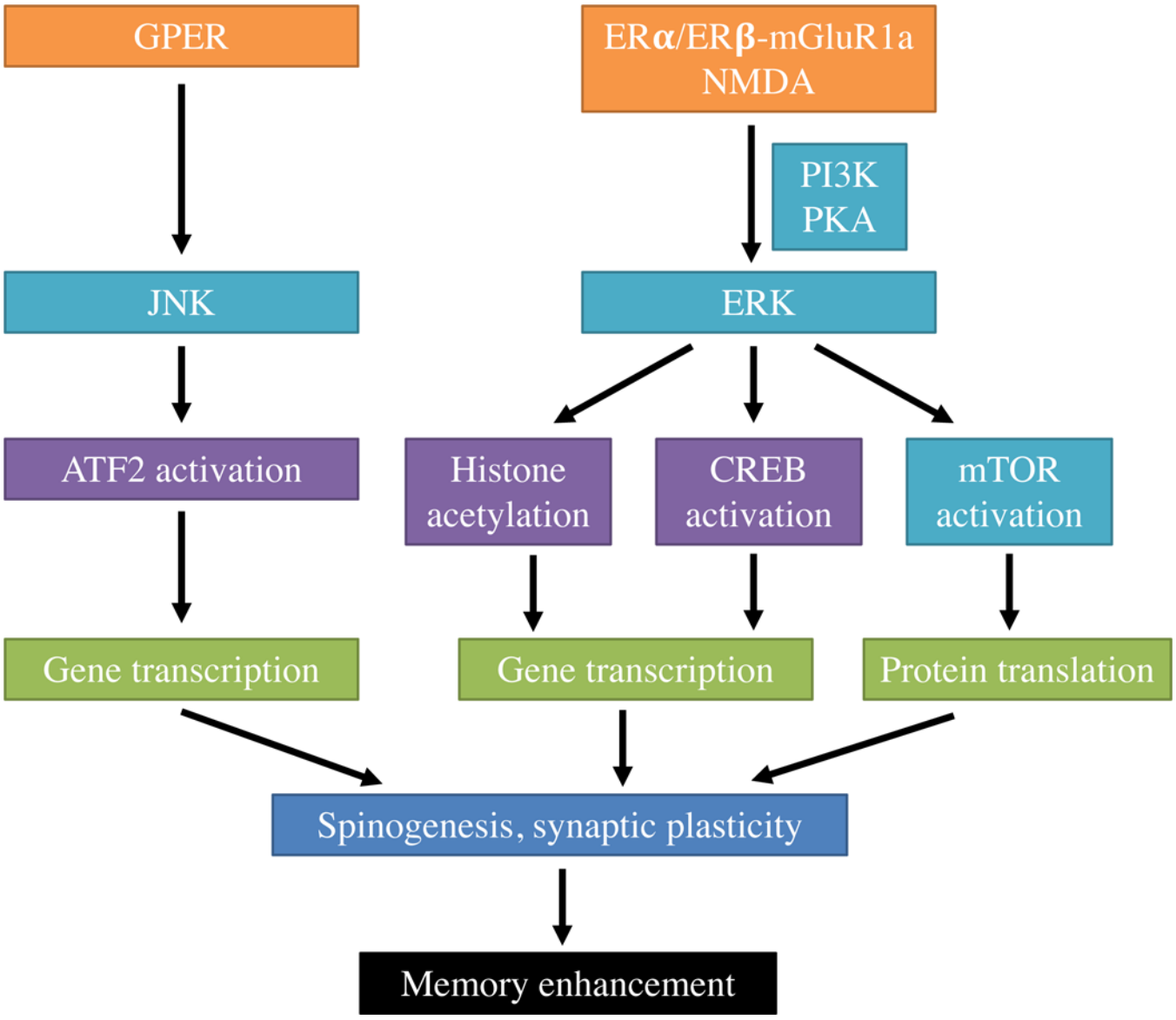

Figure 1.

Schematic illustration of the receptors molecular mechanisms identified to date through which E_2 facilitates object recognition memory consolidation in ovariectomized mice. ERα or ERβ interact with glutamate receptors (NMDA, mGluR1a) to trigger ERK signaling, which promotes H3 acetylation, CREB phosphorylation, and activation of mTOR signaling, leading to gene transcription, protein synthesis, increased CA1 dendritic spine density and synaptic plasticity, and memory enhancement. Activation of GPER also enhances memory, but via activation of JNK signaling. Preliminary work from our lab suggests that GPER activation also increases CA1 spine density. See text for references to empirical work supporting this model. Receptors are indicated in the figure in orange, cell-signaling molecules in teal, transcription factors or epigenetic events in purple, gene transcription and

protein translation in green, spinogenesis and synaptic plasticity in blue, and memory enhancement in black.

Table 1

Effects on memory of exogenous pre-training E_2 treatment and involvement of specific estrogen receptors

	Female		Male	
	E_2	**ERs involved**	**E_2**	**ERs involved**
Spatial Memory	↑	α, β, GPER	↑	?
Object Recognition	↑	α, GPER	?	?
Social Recognition	↑	α, β, GPER	?	?
Fear Generalization	No effect	n/a	↓	?

Table 2

Effects on memory of exogenous post-training E_2 treatment, and involvement of specific estrogen receptors and key molecules

	Female			Male		
	E_2	**ERs involved**	**Key molecule**	**E_2**	**ERs involved**	**Key molecule**
Object Recognition	↑	α, β	ERK	↑	?	CREB?
		GPER	JNK			
Object Placement	↑	α, β	ERK	↑	?	CREB?
		GPER	JNK			