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REVIEW ARTICLE

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Rapid actions of oestrogens and their receptors on memory acquisition and consolidation in females

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Increased attention has been paid in recent years to the ways in which oestrogens and oestrogen receptors rapidly affect learning and memory. These rapid effects occur within a timeframe that is too narrow for the classical genomic mode of action of oestrogen, thus suggesting nonclassical effects as underlying mechanisms. The present review examines recent developments in the study of the rapid effects of 17β-oestradiol and oestrogen receptor (ER) agonists on learning and memory tasks in female rodents, including social recognition, object recognition, object placement (spatial memory) and social learning. By comparing studies utilising systemic or intracranial treatments, as well as pre- and post-acquisition administration of oestradiol or ER agonists, the respective contributions of individual ERs within specific brain regions to various forms of learning and memory can be determined. The first part of this review explores the effects of systemic administration of 17β-oestradiol and ER agonists on memory when administered either pre- or post-acquisition. The second part not only focuses on the effects of pre- and post-acquisition infusions of 17β-oestradiol or ER agonists into the dorsal hippocampus on memory, but also discusses the contributions of other brain regions, including the medial amygdala, medial prefrontal cortex and paraventricular nucleus of the hypothalamus. The cellular mechanisms mediating the rapid effects of 17β-oestradiol on memory, including activation of intracellular signalling cascades and epigenetic processes, are discussed. Finally, the review concludes by comparing pre- and post-acquisition findings and effects of 17β-oestradiol and ER agonists in different brain regions.

KEYWORDS
cell signalling, nongenomic, object recognition, social learning, social recognition, spatial memory

1 | INTRODUCTION

It is well established that oestrogens affect learning and memory via both rapid "nonclassical" and longer-term "classical" mechanisms. "Classical" mechanisms involve lipid-soluble oestrogens binding to oestrogen receptors (ERs), ERα or ERβ, which then dimerise, forming complexes that act as transcription factors and bind to oestrogen response elements (EREs) on target genes.[1] These classical effects are typically evident between 4 and 48 hours post-administration.[1] By contrast, rapid nonclassical effects begin within minutes of administration and are the result of oestrogens binding to membrane-bound or neurotransmitter/growth factor receptor-associated ERα, ERβ, G protein-coupled ER1 (GPER1, previously GPR30) or Gq-coupled membrane ER (Gq-mER). These ERs trigger the activation of signalling cascades that affect cell function via local protein synthesis, post-translational protein modifications or downstream gene regulation by transcription factors and epigenetic processes.[2-8] Importantly, classical and nonclassical mechanisms are not mutually exclusive; activation of signalling cascades can affect non-ERE-regulated gene transcription and products of ERE-regulated genes can affect signalling cascades.[8,9] Behaviourally, classical or nonclassical effects of oestrogens can have different implications.[10-15] For example, oestrogens acting via classical

mechanisms in California mice reduce aggression, whereas nonclassical actions increase aggression.[14,15] Historically, most research on oestrogens has focused on classical effects. However, with novel discoveries revealing the depth and variety of rapid effects of oestrogens, nonclassical mechanisms are gaining greater attention,[16] particularly with respect to learning and memory.

Learning and memory involve time-dependent structural and functional changes at the synaptic level[17,18] that are associated with key phases of memory formation; early encoding during learning/acquisition (when information is gathered from the environment), consolidation (in which initially labile memories are gradually moved to a more fixed state during a 2-3 hours "consolidation window") and retrieval/recall of consolidated memories.[19] The encoding and subsequent consolidation of a new memory have been associated with changes in dendritic morphology and synaptic plasticity, including long-term potentiation (LTP) or depression (LTD). LTP involves increased synaptic responsiveness to stimulation (ie potentiation) following high frequency stimulation. Two main phases of LTP exist; early LTP (E-LTP), which is independent of gene transcription and translation, and late LTP (L-LTP), which requires both. These phases of LTP have been linked to early and late stages of consolidation respectively.[17,18] Oestrogens very rapidly affect membrane post-synaptic potentials,[20] LTP, LTD,[21] synapse morphology, dendritic spines[22,23] and neurotransmitter systems.[24] These cellular effects parallel rapid enhancement of learning and memory, directly affecting early stages of memory formation, from encoding to consolidation. Effects on declarative memory have been mostly investigated using rodent tasks that assess recognition of conspecifics, objects and object location. Although testing protocols differ somewhat among laboratories (ie total trial time, intertrial interval), those tasks make use of a training (also known as sample) phase in which subjects are exposed to two identical stimuli (objects or conspecifics) placed near the corners of a square arena or home cage, and a single test (also known as choice) trial in which one stimulus is moved to a new location (object placement) or is replaced with a novel stimulus (object or social recognition). Because rodents are drawn to novelty, subjects that remember the identity and location of the training stimuli should spend more time than chance, or a vehicle-treated control group, exploring the moved or novel stimuli.

To study the effects of oestrogens on specific phases of learning and memory, the timing of treatment and testing is critical. Administration of oestrogens or ER agonists/antagonists prior to learning (pre-acquisition) can be utilised to study how oestrogens affect acquisition. However, in most cases, pre-acquisition treatment will affect subsequent phases, especially consolidation, because the treatment and/or its downstream products/effects will remain active during this phase. Therefore, to study effects on acquisition, tasks are commonly designed such that testing occurs immediately after learning and/or before consolidation is complete[20,25-30] [Lymer JM, Sheppard PAS, Kuun T, et al. Estrogens and their receptors in the medial amygdala rapidly promote social recognition in female mice (unpublished)] or results from pre- and post-acquisition treatments are compared. If pre-acquisition, but not post-acquisition, treatment affects memory, this would suggest a treatment effect on acquisition but not consolidation. Post-acquisition treatments are typically used to study the rapid effects of oestrogens on memory consolidation.[7,31-39] These treatments can be timed to target early and later phases of consolidation.[7,32,33,40] In addition, when post-acquisition treatments given after the "consolidation window" fail to influence memory, then any effects on memory can be attributed to consolidation.[7,32,40] To ensure that treatment effects are specific to consolidation, testing must occur long after the consolidation window to ensure that active treatment does not also affect retrieval.[7,41,42] Finally, pre-testing treatments can be utilised to explore the involvement of oestrogens in the retrieval of consolidated memories. Such treatments must be given after the consolidation window has closed to ensure that effects are exclusive to retrieval processes.

ERα, ERβ and GPER1 all show high affinity for 17β-oestradiol, the most common, abundant, and biologically active oestrogen.[9] ERα and ERβ are found in multiple brain regions and are widely expressed in the brain.[43] Both receptors are located in the cortex, hippocampus, amygdala, bed nucleus of the stria terminalis, preoptic area, hypothalamus and several brainstem nuclei. In addition, ERβ is also found in areas of the basal ganglia, thalamus, paraventricular nucleus of the hypothalamus (PVN), ventral and anterior tegmental nucleus, and other brainstem nuclei.[9,43] In rats and mice, GPER1 is expressed in the hippocampus, cerebral cortex, striatum, a number of brainstem nuclei and the hypothalamus, including oxytocin and vasopressin neurones in the paraventricular and supraoptic nuclei.[44-46] Differences in expression intensity and locale, as well as mechanisms of action, suggest that the individual ER subtypes may mediate distinct behaviours and types of memory.[2,47]

In this review, we discuss current research into the rapid effects of oestrogens on learning and memory in rodents with a focus on the underlying neural mechanisms. In view of the paucity of studies in males, this review focuses on studies using female animals. In Part 1, we review rapid effects of systemic pre- and post-acquisition oestrogen treatments on memory. Part 2 discusses effects on memory and neural function of specific intracerebral infusions given pre- and post-acquisition. Within each part, pre-acquisition treatments are discussed first, followed by post-acquisition treatments. Finally, we conclude by considering implications of these findings for understanding rapid effects of oestrogens on memory formation.

2 | PART 1: RAPID EFFECTS OF OESTROGENS ON LEARNING AND MEMORY

2.1 | Pre-acquisition

Investigations using pre-acquisition treatments have demonstrated an important role for rapid mechanisms of oestrogens in the formation of new memories. In pioneering investigations, Victoria Luine and colleagues first demonstrated that ovariectomised rats receiving systemic treatment with 17β-oestradiol either 30 minutes before or immediately after investigation of novel objects showed improved memory for the identity and location of the objects 4 hours later.[7] In these studies, testing occurred temporally beyond the closure of the consolidation

window.[7,41,42] Oestrogens affect dendritic and synaptic plasticity even at times when memories are not fully consolidated.[20,23] Thus, the very rapid effects of oestrogens could enhance early memory formation prior to gene transcription- and protein synthesis-dependent late memory consolidation. Subsequent investigations showed that, when 17β-oestradiol was administered to ovariectomised mice 15 minutes before a task where acquisition and testing for the new memory were completed in 25 minutes, it facilitated social and object recognition, as well as object placement memory.[26] Similarly, ovariectomised mice showed enhanced social learning within 45 minutes of systemic pre-acquisition administration of 17β-oestradiol in an associative learning task in which a food preference is socially transmitted when a food flavour smelled on the breath of others is associated with the scent of CS_2, a product of digestion.[48] The four tasks used in these investigations were designed to be "difficult", such that mice would have limited learning opportunity (only two exposures to the conspecifics/objects or only one sniff of a flavored food on the breath of a demonstrator during acquisition) and control ovariectomised mice would show no learning at test. Moreover, testing in all tasks was conducted shortly (0-4 minutes) after acquisition, thus with minimal memory demand. Systemic treatment with 17β-oestradiol restored performance in social recognition, object recognition, object placement and social learning tasks.[26,48] These effects were observed within 40-45 minutes of oestradiol administration and thus are too rapid to be explained by classical ER mechanisms. The timing of these effects also suggests that rapid oestrogenic enhancement of performance in these tasks does not require later gene transcription and protein synthesis-dependent memory consolidation.

The rapid facilitating effects of 17β-oestradiol on learning, thus, spanned across four types of memories: socially acquired associative, as well as for items, conspecifics or locations.[47] The generality of these effects suggests potentially common neural mechanisms underlying the rapid facilitation of new memory formation by oestradiol. However, the results of studies investigating the role of ERα, ERβ and GPER1 in these tasks suggest otherwise. In the same "difficult" learning tasks where sesame oil-treated ovariectomised mice showed no memory, systemic treatments with the ERα agonist propyl pyrazole triol (PPT) and GPER1 agonist G-1 rapidly facilitated social, object and place recognition when acquisition and testing were completed within 40 minutes of treatment.[25,27] The ERβ agonist diarylpropionitrile (DPN) instead only rapidly facilitated new memory for object placement.[25] Different from other types of learning assessed, social learning was rapidly enhanced only by G-1, whereas the socially-acquired food preference was shortened by PPT and DPN when tested in an "easy" version of the task in which controls show strong social learning.[48] The opposing effects of GPER1 vs ERα or ERβ activation on social learning may explain why the socially-acquired food preference facilitated by G-1 lasted longer than that facilitated by 17β-oestradiol itself.[48] Thus, different types of learning may be differently affected by the rapid activation of 17β-oestradiol at various ERs. This notion is supported by discrepant patterns of behavioural results. First, the rapid effects of ERβ on early memory encoding are notably different from those of ERα and GPER1. Second, associative social learning is rapidly enhanced by selective activation of GPER1 but appears to be inhibited by activation of ERα or ERβ. The respective rapid effects of ER-specific agonists on the various types of learning suggest that oestrogens and ERs may differently enhance diverse types of memories that are mediated by different brain regions (reviewed further below). Additionally, the aforementioned studies utilised behavioural paradigms that were completed within 40 or 45 minutes of treatment administration. Hence, these studies suggest that enhancing effects of oestrogens and their ERs on memories can be observed before the completion of memory consolidation. These enhancing effects of pre-acquisition treatments on memories that were tested when they remained gene-transcription and protein-synthesis independent[17,18] may be directly mediated by effects of oestrogens on synaptic or dendritic plasticity that occur very rapidly.[22] These effects likely add to (and possibly interact with) rapid effects on memory consolidation, as indicated by studies using post-acquisition treatments in which testing was conducted well after the consolidation window (reviewed below).

2.2 | Post-acquisition

As described above, acute post-acquisition treatments allow the effects of oestrogen treatments on memory consolidation to be isolated from those on acquisition and retention. Such treatments are administered immediately after training to influence consolidation within the 2-3-hour window during which memories are formed. Effects of acute post-training oestrogen treatments on memory consolidation have been tested primarily in the two-trial object recognition and object placement/location tasks. The interval between training and testing varies by task and species, although it is sufficiently long for vehicle-treated subjects to show no preference for the moved or novel objects during testing.

Luine and colleagues provided the first evidence that post-training oestrogen treatment could enhance memory consolidation in these tasks by demonstrating that systemic injection of 17β-oestradiol, diethylstilbestrol or 16α-iodo-oestradiol immediately post-acquisition enhances the memory of ovariectomised rats in object recognition and object placement.[7] Importantly, no enhancement was observed when injections of 17β-oestradiol or diethylstilbestrol were delayed 2 hours post-acquisition, establishing the consolidation window in which oestrogens mediate memory formation. In subsequent years, several laboratories have similarly shown that systemic 17β-oestradiol injection given immediately after training to ovariectomised mice or rats enhances memory in object recognition[7,31,32,35,49-56] and object placement[7,35,40,49] at a wide range of doses (5-200 μg kg^{-1}). As in the Luine study, memory-enhancing effects were found only if 17β-oestradiol was administered immediately after training. When administered 1 hour after object recognition training[32] or 1.5 hours after object placement training,[40] 17β-oestradiol had no effect on memory. These findings demonstrate that 17β-oestradiol can specifically and rapidly enhance object recognition and spatial memory consolidation in ovariectomised females.

A few studies have used post-acquisition systemic injections of ER agonists to determine receptor mechanisms underlying the beneficial

effects of oestrogens on memory consolidation. These studies suggest a role for both ERα and ERβ, although their involvement varies among studies. For example, two studies report that post-training systemic DPN injection enhances object recognition in rats and mice.[32,54] However, whereas 0.1 mg kg^{-1} DPN enhanced object placement in mice,[49] 0.9 mg kg^{-1} DPN had no effect on object placement in rats,[42] suggesting potentially important influences of species and/or dose. A single study examining effects of PPT on object placement found that it enhanced memory in ovariectomised rats.[40] However, the effects of PPT on object recognition are inconsistent; 0.9 mg kg^{-1} PPT enhanced memory in rats[32] whereas 0.5 mg kg^{-1} PPT had no effect in mice.[56] As with DPN, these discrepant results suggest possible species or dose considerations. However, so few systemic studies have been conducted that it is difficult to draw firm conclusions. Presently, these data suggest that ERα and ERβ mediate the memory-enhancing effects of 17β-oestradiol, although the specific involvement of each ER may depend on several factors.

A particular disadvantage of systemic treatments in this regard is their lack of regional specificity. Thus, numerous studies have examined the rapid effects of 17β-oestradiol and ER agonists infused directly into brain regions that mediate memory function. This work is addressed below.

3 | PART 2: BRAIN MECHANISMS MEDIATING THE RAPID EFFECTS OF OESTROGENS ON LEARNING AND MEMORY

3.1 | Pre-acquisition

Considered to be necessary for spatial learning and memory, and also to be involved in object discrimination or social recognition,[57] the dorsal hippocampus has been implicated in rapid oestrogen-induced learning enhancements, both in the presence and absence of contextual spatial cues.[20,30,58] Within 40 minutes of systemic administration, 17β-oestradiol, PPT or G-1 increased dendritic spine density in the CA1 region of the hippocampus.[25-27] Similarly, bath application of 17β-oestradiol or PPT for 20-30 minutes caused an increase in immature dendritic spines in dorsal hippocampal CA1 neurones,[20] suggesting an involvement of the dorsal hippocampus with respect to the rapid effects of oestrogens on learning. We review below the results of studies on the rapid effects of pre-acquisition dorsal hippocampal infusion of 17β-oestradiol or ER agonists on three types of memory. In each study, treatment was infused 15 minutes prior to two 5-minute acquisition phases followed by a 5-minute test administered 5 minutes after acquisition. In these tasks, memory demand was minimal and the effects were observed within 40 minutes of treatment, before the closure of the consolidation window. We further review studies that have begun to investigate the involvement of other brain regions in rapid oestrogen facilitation of learning.

Dorsal hippocampal infusion of 17β-oestradiol, PPT or G-1 facilitated learning in various tasks.[20,30] In ovariectomised mice, dorsal hippocampal infusion of 17β-oestradiol 15 minutes before the acquisition phases of social recognition, object recognition and object placement tasks facilitated memory at test in paradigms where control animals do not typically learn.[20] Membrane-bound ERs may be one site of oestrogenic action because bovine serum albumin conjugated 17β-oestradiol (BSA-E_2), which does not cross the cell membrane, facilitated social and object recognition.[28] Dorsal hippocampal infusion of PPT facilitated object recognition, social recognition and object placement, whereas DPN facilitated only object placement.[20] Although dorsal hippocampal infusion of G-1 did not affect object placement, it facilitated social and object recognition, in both the home cage and in a Y-apparatus designed to minimise spatial cues.[30] Similar to effects on gene transcription- and protein synthesis-dependent memory consolidation (see below), these rapid, pre-acquisition effects depend upon activity of the extracellular signal-regulated kinase (ERK) pathway because pre-acquisition inhibition of ERK1/2 activation in the dorsal hippocampus blocked the rapid oestrogenic facilitation of social recognition in ovariectomised mice.[29]

Another region of interest in the rapid effects of oestrogens on learning is the medial nucleus of the amygdala (medial amygdala), which has been consistently implicated in sociosexual behaviours and social recognition in rodents[59-63] and shows robust expression of ERα and ERβ and limited expression of GPER1.[43,44] Intra-medial amygdala administration of 17β-oestradiol, or agonists for ERα, ERβ and GPER1, prior to acquisition in a 40-minute task facilitated social recognition [Lymer JM, Sheppard PAS, Kuun T, et al. Estrogens and their receptors in the medial amygdala rapidly promote social recognition in female mice (unpublished)]. Thus, in the medial amygdala, all three ERs mediate social recognition, which differs from the dorsal hippocampus where ERβ activation did not affect social recognition. Furthermore, the dose of PPT required to facilitate social recognition in the medial amygdala was 2-3× higher than in the dorsal hippocampus, suggesting that ERα may play a lesser role in the medial amygdala. Thus, the three ERs may play different roles in different brain regions.

Recently, it has been shown that pre-acquisition infusion of 17β-oestradiol into the PVN rapidly facilitates social recognition within 40 minutes of treatment (P. Paletta, S. Howard, K. Ali and E. Choleris, unpublished observations). Among other neurotransmitters, the PVN produces oxytocin (OT), which is necessary for social recognition *via* action on the OT receptor (OTR) in the medial amygdala.[64,65] ERβ and GPER1 regulate OT production and release in the PVN and, as noted above, in the medial amygdala, all three ERs rapidly facilitate social recognition. This suggests that oestrogens may rapidly promote social recognition through interaction with the OT/OTR system in the PVN and in the medial amygdala.[66,67] Whether these effects are specific to social recognition or generalise to other types of learning remains to be investigated. Similarly, whether oestrogens enhance social recognition in the dorsal hippocampus independently or by interacting with the PVN/medial amygdala remains to be determined.

3.2 | Post-acquisition

As with pre-acquisition infusions, post-acquisition infusions administered directly into brain regions associated with memory formation have provided more specific information than systemic injections

about the neural bases underlying rapid oestrogenic regulation of memory. To date, most studies have focused on the dorsal hippocampus of ovariectomised females. This work has begun to provide a detailed picture of the molecular mechanisms underlying the effects of 17β-oestradiol in the dorsal hippocampus on memory consolidation, which has been reviewed in detail elsewhere[68,69] and is summarised briefly below. Recent data suggesting that oestrogenic regulation of other brain regions may also contribute to memory consolidation will be discussed as well.

The memory-enhancing effects of dorsal hippocampal oestradiol infusion were first demonstrated in 2008, when it was shown that a bilateral infusion of 5 μg of 17β-oestradiol into the dorsal hippocampus of ovariectomised mice given immediately, but not 3 hours, post-training facilitated memory consolidation in object recognition.[33] Subsequently then, numerous other mouse studies have replicated this finding[33,36-39,56,70,71] and extended it to object placement.[37,39] In ovariectomised mice, the memory-enhancing effects of 17β-oestradiol depend on rapid activation of numerous cell-signalling cascades in the dorsal hippocampus. Of prime importance is phosphorylation of ERK, which can be activated in the dorsal hippocampus within 5 minutes by dorsal hippocampal infusion of 17β-oestradiol or BSA-E_2. Post-training dorsal hippocampal infusion of an ERK phosphorylation inhibitor prevents 17β-oestradiol from enhancing object recognition[33,36,38,70] and object placement[39] memory consolidation in ovariectomised mice, demonstrating the necessity of ERK activation for the mnemonic effects of oestradiol. Upstream signalling molecules that activate ERK are also regulated by 17β-oestradiol and are required for the effects of 17β-oestradiol on memory in mice. These include protein kinase A, phosphatidylinositol 3-kinase (PI3K) and Akt. Post-training dorsal hippocampal infusion of inhibitors of these kinases prevent 17β-oestradiol from phosphorylating ERK and enhancing memory consolidation[34,38,53] in ovariectomised mice, suggesting that ERK serves as a common signalling molecule for oestrogenic activation of several upstream kinases.

Extracellular signal-regulated kinase phosphorylation has numerous downstream effects, including phosphorylation of the transcription factor cyclic AMP response element binding protein (CREB). 17β-oestradiol facilitates this phosphorylation in cultured rat hippocampal neurones,[72] although the necessity of CREB phosphorylation for memory enhancement by oestrogens remains untested. ERK also activates other cell signalling cascades including the mammalian target of rapamycin (mTOR) pathway, which is important for local protein synthesis in the hippocampus.[73] In the dorsal hippocampus of ovariectomised mice, 17β-oestradiol activates mTOR signalling in a manner dependent on both ERK and PI3K signalling, and this activation is necessary for 17β-oestradiol to enhance object recognition memory consolidation.[38] Because mTOR signalling promotes local protein synthesis, this finding suggests a role for rapid cell signalling in oestrogen-induced spinogenesis. Indeed, dorsal hippocampal 17β-oestradiol infusion increases CA1 dendritic spine density in ovariectomised mice within 2 hours, and activation of ERK or mTOR signalling in the dorsal hippocampus is necessary for this effect.[74] Thus, the rapid effects of 17β-oestradiol on hippocampal cell signalling can mediate both memory consolidation and key elements of neuronal morphology that likely contribute to memory consolidation.

In addition to cell signalling, ERK phosphorylation may affect hippocampal functioning by influencing epigenetic mechanisms that regulate access to DNA such as histone acetylation and DNA methylation. Histone acetylation and DNA methylation regulate memory formation in multiple brain regions including the hippocampus.[75-81] Within the nucleosome, DNA is tightly wrapped around four core histone proteins (H2A, H2B, H3, H4). Acetylation of histone tails by histone acetyltransferases facilitates gene transcription, whereas removal of acetyl groups by histone deacetylases (HDACs) decreases transcription. ERK facilitates the acetylation of H3 in the dorsal hippocampus, which is associated with enhanced memory consolidation.[82] Accordingly, 17β-oestradiol infused into the dorsal hippocampus also significantly increases H3 acetylation in ovariectomised mice, most likely by decreasing levels of HDAC2 and HDAC3.[36,83] This increased acetylation is necessary for 17β-oestradiol to enhance object recognition memory consolidation in mice.[70] Moreover, dorsal hippocampal infusion of an ERK phosphorylation inhibitor prevents 17β-oestradiol from increasing H3 acetylation in the dorsal hippocampus of ovariectomised mice, indicating that ERK activation, and the resulting H3 acetylation, are necessary for 17β-oestradiol to enhance memory.[36,70,83] Additional work has identified the brain derived neurotrophic factor (*Bdnf*) gene as a specific target of 17β-oestradiol-induced histone acetylation. In young and middle-aged ovariectomised mice, 17β-oestradiol increased H3 acetylation of *Bdnf* promoters II and IV, which was accompanied by increases of BDNF and pro-BDNF protein.[83] Both proteins are key neurotrophic factors associated with synaptic plasticity and long-term memory.[84,85]

17β-oestradiol also affects DNA methylation, although there is no indication that this effect is associated with ERK. DNA methylation involves the addition of methyl groups to cytosines in promoter sequences by DNA methyltransferases (DNMTs). Methylation typically suppresses gene expression, whereas demethylation typically facilitates gene expression, although the functional effects of methylation depend on the genes affected. For example, DNA methylation can facilitate hippocampal memory by both methylation of memory suppressing genes and demethylation of memory promoting genes.[80,81] In ovariectomised mice, 17β-oestradiol increases mRNA for the de novo methyltransferases DNMT3A and DNMT3B, but not the maintenance methyltransferase DNMT1, in the dorsal hippocampus 45 minutes after dorsal hippocampal infusion.[36] Protein levels of DNMT3B are increased 4 hours after 17β-oestradiol infusion,[36] suggesting a role for de novo DNA methylation in 17β-oestradiol-induced memory enhancement. The fact that post-training dorsal hippocampal infusion of a DNA methylation inhibitor prevented 17β-oestradiol from enhancing object recognition memory consolidation provides support for this notion.[36]

The rapid molecular effects of 17β-oestradiol described above likely involve multiple ERs. The involvement of cell-signalling pathways suggests an essential role for nonclassical mechanisms. Indeed, BSA-E_2 mimics the effects of 17β-oestradiol on both ERK phosphorylation[33,86] and object recognition[33] and these effects are not entirely blocked in ovariectomised mice by the nonspecific ER antagonist ICI

182 780. These data suggest that activation of plasma membrane receptors is sufficient to enhance memory consolidation.[33] However, the specific receptors involved are not completely understood. Interestingly, post-training dorsal hippocampal infusion of PPT or DPN in ovariectomised mice enhances object recognition and object placement memory consolidation in a manner that is dependent on dorsal hippocampal ERK phosphorylation and identical to 17β-oestradiol,[37] suggesting nonclassical effects of ERα and ERβ. Indeed, 17β-oestradiol causes ERβ to translocate to the plasma membrane[87] and increases the distribution of ERβ to dendritic spines and shafts in the hippocampus.[88] This translocation may facilitate interactions between the ER and neurotransmitter receptors. For example, dorsal hippocampal infusion of NMDA or mGluR1a antagonists in ovariectomised mice block the memory-enhancing effects of 17β-oestradiol in object recognition and object placement.[37,53] Similarly, mGluR1a antagonism in the dorsal hippocampus of ovariectomised mice also prevents PPT and DPN from enhancing memory consolidation in both tasks.[37] Moreover, ERα, ERβ, mGluR1 and ERK are localised to the plasma membrane in the dorsal hippocampus of ovariectomised mice, suggesting that ERα and ERβ physically interact with mGluR1 at the membrane to mediate the rapid memory-enhancing properties of 17β-oestradiol.[37]

The importance of membrane-associated events for oestrogenic regulation of memory consolidation would further suggest involvement of the transmembrane oestrogen receptor, GPER1. GPER1 is present within hippocampal neurones[46,89] and activates similar pathways as classical ER receptors, such as ERK and Akt, in vitro.[90] However, this receptor does not appear to be involved in the in vivo effects of 17β-oestradiol on memory consolidation in ovariectomised mice. Post-training dorsal hippocampal infusion of G-1 in ovariectomised mice enhances object recognition and object placement memory consolidation and, accordingly, the GPER1 antagonist G-15 impairs memory in both tasks.[39] However, G-1 does not increase phosphorylation of ERK, PI3K or Akt, but rather phosphorylates c-jun N-terminal kinase (JNK), which is not activated by 17β-oestradiol in ovariectomised mice.[39] This finding is supported by other studies showing that G-1 does not block Akt phosphorylation, unlike 17β-oestradiol.[38,89,91] Post-training dorsal hippocampal infusion of a JNK inhibitor blocks the memory-enhancing effects of G-1, but not 17β-oestradiol, in ovariectomised mice, whereas ERK inhibition blocks the effects of 17β-oestradiol, but not G-1.[39] These data suggest that G-1 and 17β-oestradiol enhance memory via different cell-signalling mechanisms. Interestingly, post-training dorsal hippocampal infusion of G-15 does not prevent 17β-oestradiol from enhancing consolidation in both object tasks,[39] suggesting that GPER is not involved in the memory-enhancing effects of 17β-oestradiol in the dorsal hippocampus of mice. This effect is curious for a supposed ER, and future studies will need to address how GPER regulation promotes memory formation.

Although much attention has been paid to oestrogenic regulation of the hippocampus, effects of oestrogens in other brain regions may be involved in memory consolidation. The medial prefrontal cortex (mPFC) is important for memory consolidation,[92,93] and systemic injection of 17β-oestradiol in ovariectomised rats increases mPFC dendritic spine density. Recently, dorsal hippocampal infusion of 17β-oestradiol was shown to increase dendritic spine density in the mPFC of ovariectomised mice within 2 hours of infusion.[74] Moreover, activation of ERK or mTOR signalling in the dorsal hippocampus was necessary for this effect,[74] suggesting an interaction between the hippocampus and mPFC in female mice that could be essential for memory consolidation. Effects of mPFC infusions of 17β-oestradiol have not been published, although preliminary data from ovariectomised mice suggest that immediate post-training infusion into the prelimbic/infralimbic area enhance both object recognition and object placement memory (J. J. Tuscher and K. M. Frick, unpublished observations). As such, the mPFC may be a key player in the oestrogenic regulation of memory consolidation. Temporal lobe cortices may also be a key player because immediate post-training infusion of 17β-oestradiol into the perirhinal cortex/entorhinal cortex enhances object recognition in ovariectomised rats[94] using a task similar to those described above. However, using a delayed nonmatching-to-sample task of object recognition, the same investigators found that perirhinal/entorhinal infusion of 17β-oestradiol impairs object recognition,[95] suggesting potential task-specific or brain region-specific effects of 17β-oestradiol on memory consolidation. These few studies indicate the potential key involvement of nonhippocampal brain regions in the memory-enhancing effects of oestradiol that should be revealed by future investigations.

4 | CONCLUSIONS

In discussing the rapid effects of oestrogens on memory in females and our current understanding of the brain regions involved, we have described studies that have followed different approaches to this area of investigation. In one approach, treatments were

TABLE 1 General summary of the effects of pre-acquisition oestrogen treatments on object recognition, object placement and social recognition tasks

	Object recognition		Object placement		Social recognition	
Treatment	Systemic	DH	Systemic	DH	Systemic	DH
Oestradiol	↑	↑	↑	↑	↑	↑
PPT (ERα)	↑	↑	↑	↑	↑	↑
DPN (ERβ)	--/--	--/?	↑	↑	↓	--/?
G-1 (GPER1)	↑	↑	↑	--/?	↑	↑

DH, dorsal hippocampal infusion; DPN, diarylpropionitrile; G-1, G protein-coupled ER1 agonist; PPT, propyl pyrazole triol; ↑, memory facilitated; ↓, memory blocked; –/–, no facilitation/no inhibition of memory; –/?, no facilitation of memory/memory-inhibiting effects not investigated.

TABLE 2 General summary of the effects of post-acquisition oestrogen treatments on memory consolidation in the object recognition and object placement tasks

	Object recognition		Object placement	
Treatment	Systemic	DH	Systemic	DH
Oestradiol, immediate	↑	↑	↑	↑
Oestradiol, delayed	–	–	–	?
PPT (ERα)	↑,–	↑	↑	↑
DPN (ERβ)	↑	↑	↑,–	↑
G-1 (GPER1)	?	↑	?	↑

DH, dorsal hippocampal infusion; DPN, diarylpropionitrile; G-1, G protein-coupled ER1 agonist; PPT, propyl pyrazole triol; ↑, memory facilitated; –, no facilitation of memory; ?, effect on memory not investigated.

administered shortly before acquisition and mice were tested before the closure of the memory consolidation window. In another approach, treatments were administered immediately after acquisition and their effects were tested well after the closure of the consolidation window. The comparison of these two approaches reveals similarities and differences that shed light on the mechanisms through which oestrogens rapidly regulate memory formation. Differences in results include the discrepant effects of GPER1, ERα and ERβ agonists on object recognition and object placement. Pre-acquisition intrahippocampal treatment with PPT and G-1 enhanced social recognition, object recognition and object placement, whereas DPN only enhanced object placement.[20,30] By contrast, post-acquisition PPT, DPN and G-1 treatment all enhanced memory in object recognition and object placement tasks[37,39] (Tables 1 and 2). These discrepant patterns of results suggest that ERβ may be more involved in later gene-transcription and protein synthesis-dependent memory consolidation than early gene-transcription and protein synthesis-independent memory consolidation.[18] The mechanisms of these different effects remain unknown, although they may be related to differential actions of pre- and post-synaptically expressed receptors. Even though GPER1, ERα, and ERβ in the dorsal hippocampus are found both pre- and post-synaptically,[91,96,97] DPN, but not PPT or G-1, increased presynaptic glutamate release in the CA1 region of female rats.[21] These presynaptic actions of ERβ may be more effective at enhancing late memory consolidation, whereas rapid ER postsynaptic actions may enhance both early and later stages of memory consolidation. L-LTP and later stages of memory consolidation require gene transcription and protein synthesis,[17,18] and this agrees with findings that post-acquisition oestrogenic treatments that produce enhanced memory several hours later are mediated by epigenetic regulation of transcription of memory enhancing genes.[83-97] Pre-acquisition treatments that affect performance before the closure of the consolidation window instead may only be mediated by effects upon early stages of memory encoding/consolidation, when E-LTP and memories are still independent of gene transcription.[18] Although speculative at this point, this idea is worth pursuing in further research.

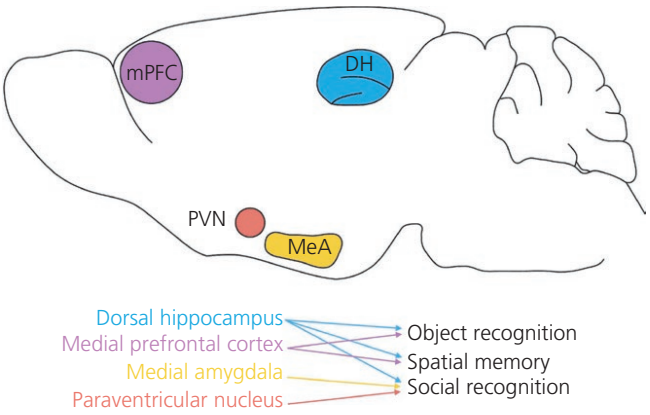

FIGURE 1 Summary of brain regions known to be involved in the rapid effects of 17β-oestradiol and oestrogen receptor (ER) agonists on object recognition, spatial memory or social recognition. Oestrogenic effects in the dorsal hippocampus (DH) affect object recognition, spatial memory or social recognition, whereas actions in the medial prefrontal cortex (mPFC) have only been shown to affect object recognition and spatial memory. Activation of ERs in the medial amygdala (MeA) or paraventricular nucleus (PVN) facilitates social recognition

So far, most research on brain regions involved in mediating rapid memory-enhancing effects of oestrogens and their receptors in females has focused on (and highlighted the importance of) the dorsal hippocampus. More recent research has begun to identify other brain regions that may also be involved, and these different regions may be specifically involved in mediating certain types of memories (Figure 1). For example, oestrogens in the medial amygdala may specifically mediate social recognition and the perirhinal cortex may help mediate object recognition. Both regions have reciprocal connections with the hippocampus, suggesting they may integrate memory-specific information with hippocampal processing of memory. Similar to the hippocampus, the mPFC instead may mediate most learning effects, enabling memory consolidation in concert with the hippocampus. Mechanisms of these actions remain largely unexplored, although they may show interesting region-specific differences. For example, rapid enhancement of dendritic spines in the hippocampus appears to be mediated predominantly by ERα and GPER1,[20] whereas ERβ appears to play a predominant role in cortical neurones.[22]

In conclusion, although a depiction of the mechanisms underlying oestrogenic enhancement of memory formation in females is slowly materialising, there remains much to be explored, including the intricacies of the action of oestrogens on cell signalling pathways, spine and synapse dynamics, and neurotransmission, potential differences in the rapid effects of oestrogens between males and females, and the networks of brain regions regulating the rapid effects of oestrogen on learning and memory. The future promises interesting developments in the field.

CONFLICT OF INTERESTS

The authors declare that they have are no conflicts of interest.

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