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Review article

Mechanisms underlying the rapid effects of estradiol and progesterone on hippocampal memory consolidation in female rodents

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ABSTRACT

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Although rapid effects of 17β-estradiol (E_2) and progesterone on cellular functions have been observed for several decades, a proliferation of data in recent years has demonstrated the importance of these actions to cognition. In particular, an emerging literature has demonstrated that these hormones promote the consolidation of spatial and object recognition memories in rodents via rapid activation of numerous cellular events including cell signaling, histone modifications, and local protein translation in the hippocampus. This article provides an overview of the evidence demonstrating that E_2 and progesterone enhance hippocampal memory consolidation in female rodents, and then discusses numerous molecular mechanisms thus far shown to mediate the beneficial effects of these hormones on memory formation.

1. Introduction

One of the most exciting developments in behavioral neuroendocrinology has been the realization that sex steroid hormones, including 17β-estradiol (E_2) and progesterone, can act rapidly to regulate cellular and behavioral function. Although this idea seems new, its origins date back as far as the late 1960s, when E_2 was found to regulate electrical activity in the hippocampus and amygdala (Terasawa and Timiras, 1968). Additional findings from the late 1970s demonstrated that E_2 could rapidly alter the firing of neurons in the hypothalamus and pituitary (Dufy et al., 1979; Kelly et al., 1977), and later work indicated effects on physiology of the hippocampus, cerebellum, amygdala, and striatum (Arnauld et al., 1981; Nabekura et al., 1986; Smith et al., 1987; Teyler et al., 1980). Much recent research has focused on rapid effects of E_2 and progesterone on functioning of the hippocampus, a brain region that is rich in estrogen and progesterone receptors and is, therefore, quite responsive to both estrogens and progestogens. The hippocampus mediates the formation of many types of memories, including those involving spatial, relational, contextual, and object recognition information (Cohen and Stackman, 2015; Eichenbaum, 2017; Olton et al., 1979; Squire, 1992), and its dysfunction is implicated in cognitive deficits in normal aging, neurodegenerative diseases (e.g., Alzheimer's), and various mental illnesses (e.g., depression, schizophrenia) (Aisen et al., 2017; Burke and Barnes, 2010; de Toledo-Morrell et al., 2000; deToledo-Morrell et al., 2007; Kessler et al., 2005; Marks et al., 2017; Yassa et al., 2011). Of the sex steroid hormones, E_2 has received the lion's share of attention for its classical and rapid effects on the hippocampus in both females and males, but a small literature suggests that progesterone can rapidly influence hippocampal function in females as well. As such, this article will focus on the rapid effects of E_2 and progesterone on memory consolidation in females, and the underlying molecular mechanisms thus far identified that mediate these effects. Because a comprehensive discussion of the rapid effects of these hormones on hippocampal function in both sexes is beyond the scope of this article, we refer readers to other recent reviews for additional information (e.g., (Frick et al., 2015; Koss and Frick, 2017)).

Before discussing the rapid effects of hormones on hippocampal memory, we should take a moment to consider why these effects are important. Sex steroid hormones are probably best known for their long-term effects on form and function; for example, their organizational effects on the brain that produce feminine or masculine behaviors in adulthood or cyclic effects on ovulation and mating receptivity (Beach et al., 1969; Blaustein, 2008). In contrast to these effects whose impacts are not evident until hours to days later, rapid actions of sex steroid hormones occur in a matter of seconds to minutes (e.g., (Boulware et al., 2013; Gu et al., 1999; Gu and Moss, 1996; Wade and Dorsa, 2003; Yokomaku et al., 2003)). As discussed in more detail below, the actions of sex steroid hormones are broadly categorized into two types: those that involve binding of a hormone-hormone receptor complex to the DNA (classical) and those that do not (non-classical). Because non-classical effects involve activation of membrane receptors and signaling kinases that alter neuronal excitability within just a few

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minutes (e.g. (Boulware et al., 2005)), these effects are thought to occur more rapidly than classical effects. However, E_2, for example, alters epigenetic processes in the nucleus within just 30 min via a process that involves cell signaling, so some rapid non-classical effects can also influence nuclear gene expression. Why might rapid effects be particularly important for behaviors such as learning and memory? The cellular changes that occur during a learning event and lead to the formation of a memory occur within seconds of stimulus presentation. These alterations include the opening and closing of ion channels and activation of G-proteins and cell signaling kinases that alter neuronal excitability in ways that produce the long-term potentiation or long-term depression that support memory formation or suppression (Sweatt, 2016; Weeber and Sweatt, 2002). As such, rapid actions afford sex steroid hormones the ability to modulate the learning-induced alterations in neuronal excitability that lead to memory consolidation. These rapid effects may be mediated, at least in part, by sex steroid hormones synthesized within the hippocampus and other brain regions, where they function in many ways like neurotransmitters (Balthazart and Ball, 2006; Balthazart et al., 2018). Indeed, rapid alterations in E_2 levels have been reported in the female mouse hippocampus in response to object learning (Tuscher et al., 2016b) and in the male zebra finch forebrain in response to song playback or social interactions with females (Remage-Healey et al., 2008), suggesting that stimuli such as object exposure, song, or social interactions may trigger E_2 production as a means of facilitating memory formation.

The sections below will provide an overview of the rapid non-classical molecular mechanisms thus far shown to underlie the effects of E_2 and progesterone on memory consolidation in female rodents. The distribution of estrogen and progesterone receptors within the hippocampus will first be described, followed by a brief review of the effects of E_2 and progesterone on memory consolidation in ovariectomized rodents. Following this background material, the cell signaling and receptor mechanisms necessary for E_2 and progesterone to enhance memory consolidation will be discussed. Females will be the focus of this review because far more is known about these mechanisms in females, although data are beginning to emerge in males as well (Koss and Frick, 2016; Oberlander and Woolley, 2017).

2. Estrogen and progesterone receptors in the hippocampus

Like other steroid hormones, estrogens and progesterone exert classical effects on cellular functions via so-called “nuclear” receptors in the cytoplasm that dimerize upon steroid binding and translocate to the nucleus, where they complex with transcriptional co-regulators at estrogen or progesterone response elements on DNA to stimulate gene transcription (Walters, 1985) (Fig. 1). The resulting hormone response element-dependent alterations in gene transcription and protein translation are thought to require hours for full effect (McEwen et al., 1979). The estrogen receptors (ERs) ERα and ERβ mediate the classical hormone response element-dependent effects of estrogens, whereas the progesterone receptor (PR) isoforms PR-A and PR-B mediate the classical effects of progesterone. In the rat and mouse hippocampus, nuclear ERα and PR labeling is sparse and limited to inhibitory interneurons and pyramidal cells, respectively, whereas ERβ immunoreactivity is not found in the nuclei of either cell type (Milner et al., 2005; Milner et al., 2001; Mitterling et al., 2010; Waters et al., 2008). Immunolabeling for ERα, ERβ, and PR is far more abundant in extranuclear sites throughout the rat and mouse hippocampus. In both species, ERα and ERβ are found in axons, axon terminals, dendrites, and dendritic spines of pyramidal neurons, as well as in granule cells and astrocytes located near pyramidal cells (Milner et al., 2005, 2001; Mitra et al., 2003; Mitterling et al., 2010; Waters et al., 2008). PRs have a similar distribution but are not found in granule cells (Mitterling et al., 2010). Both ERs and PRs are located throughout dendritic spines, often prominently located near the post-synaptic density. In mice, ERβ is more often found on or near the plasma membrane of cell bodies and dendrites than ERα and PRs (Mitterling et al., 2010). The positioning of ERβ at the membrane appears to be driven by estradiol, as data from a mouse hippocampus-derived cell line showed that ERβ, but not ERα, translocates to the plasma membrane as a monomer 5 min after E_2 exposure but prior to the activation of cell signaling, suggesting that this translocation precedes, and likely triggers, cell signaling (Sheldahl et al., 2008). Indeed, the extranuclear positioning of ERs and PRs in dendritic spines and axon terminals, combined with scant nuclear localization, suggests a primary role for these receptors in the rapid non-classical effects of estrogens and progesterone.

Non-classical effects of hormones on cellular function occur independently of hormone response elements in the nucleus (Fig. 1). The rapid non-classical mechanisms of ER and PR action influence neuronal excitability via effects on, for example, ion channels, G-proteins, and cell signaling kinases. These non-classical effects can be mediated by intracellular ERs or PRs at or near the membrane or by membrane-bound ERs and PRs. For estrogens, identified membrane receptors include G protein-coupled ER (GPER), Gq-ER, and ER-X; of these, the most well characterized is GPER (Barton et al., 2018). Like classical ERs, GPER is found throughout the hippocampus in both astrocytes and pyramidal neurons, where it is localized to membranes of axons, axon terminals, cell bodies (but not the nucleus), dendrites, and dendritic spines (Waters et al., 2015). Two classes of membrane receptors exist for progesterone, membrane PRs (mPRs α-ε) and progesterone membrane receptor components (PGMRC1 and PGMRC2) (Singh et al., 2013). Although ultrastructural analysis of mPR and PGMRC localization in the hippocampus has not been conducted, both classes of PR are found in the hippocampus (Meffre et al., 2013; Thomas, 2008). Progesterone can also directly regulate the actions of inhibitory GABA-A receptors via binding of metabolites like allopregnanolone to the steroid binding site on this receptor (Schumacher and Guennoun, 2009). Because GABA is the major inhibitory neurotransmitter in the central nervous system and its receptors are the ubiquitously expressed throughout the brain, this neurosteroid function of progestins affords an additional opportunity for these hormones to rapidly affect neuronal excitability.

Non-classical effects of E_2 and progesterone are observed within minutes of exposure. For example, E_2 potentiates kainate currents in dissociated hippocampal CA1 pyramidal neurons within 10 min of application, an effect dependent on G-protein-coupled cAMP-dependent phosphorylation, but not on nuclear estrogen receptors (Gu et al., 1999; Gu and Moss, 1996). Within 5–10 min of application, E_2 also activates numerous cell signaling cascades in the hippocampus, including extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase (PI3K) in dissociated rat hippocampal cultures and in the dorsal hippocampus of ovariectomized mice and gonadally-intact male rats in vivo (Fernandez et al., 2008; Kuroki et al., 2000; Yokomaku et al., 2003). Progesterone also increases ERK activation within 5 min in both rat primary hippocampal neurons and in the dorsal hippocampus of ovariectomized mice in vivo (Fortress et al., 2015; Nilsen and Brinton, 2003; Orr et al., 2012). Studies using a variety of approaches, including BSA-conjugated hormones and classical ER or PR antagonists suggest that these effects are mediated by membrane ERs and PRs (Fernandez et al., 2008; Fortress et al., 2015; Kuroki et al., 2000; Yokomaku et al., 2003). As will be discussed below, these rapid effects on cell signaling are instrumental for the memory-enhancing effects of both E_2 and progesterone.

3. Hormonal regulation of memory consolidation

The effects of E_2 and progesterone on memory consolidation have been detailed comprehensively in previous articles (K.S.J. Ervin et al., 2015; Luine, 2015; Sheppard et al., 2018; Tuscher et al., 2015), so will be reviewed only briefly here. Before discussing these studies, we will consider briefly behavioral tasks most commonly used to test these effects and provide an overview of effects of E_2 and progesterone on

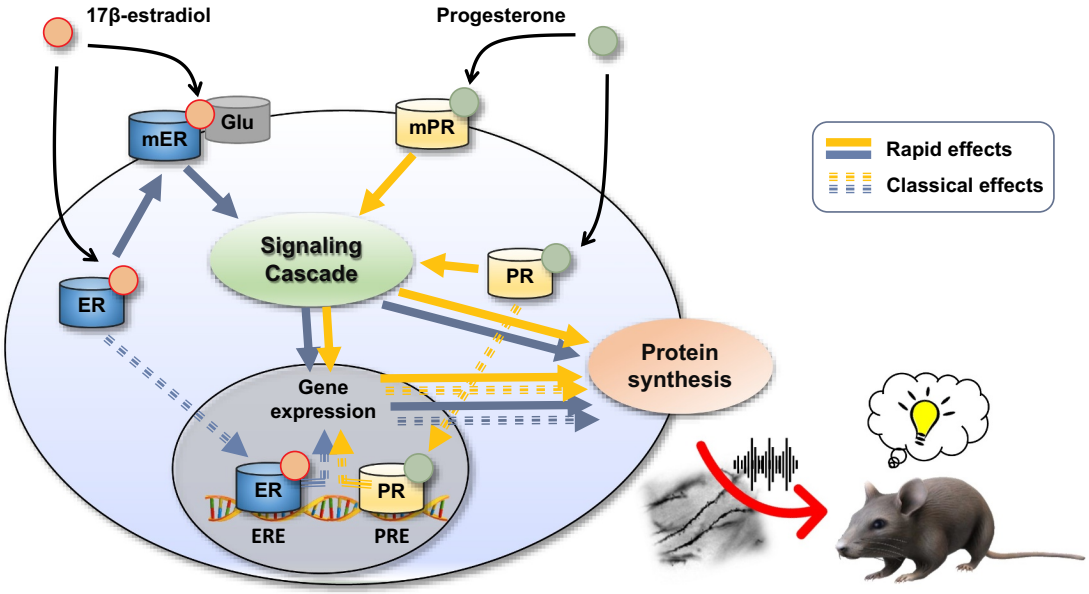

Fig. 1. Simplified schematic illustration of classical and rapid (non-classical) mechanisms underlying the effects of 17β-estradiol (E_2) and progesterone on memory consolidation in female rodents. Classical effects are mediated by the binding of an E_2-ER or progesterone-PR complex to a hormone response element (ERE or PRE) on DNA, leading to gene transcription and protein synthesis. The impact of classical effects are typically evident within hours to days. Rapid non-classical effects occur independently of hormone response elements and occur within seconds to minutes. E_2 and progesterone rapidly affect cell signaling by binding to membrane-bound receptors (mER, mPR) and/or glutamate receptors to activate cell-signaling cascades, or by binding to intracellular ERs that translocate to the plasma membrane and interact with glutamate receptors to activate signaling cascades. These rapid cell-signaling alterations trigger local mTOR-mediated protein synthesis to regulate neuronal excitability and CA1 spine density, and ultimately, memory consolidation. Although both classical and rapid effects can alter gene transcription, rapid effects occur independently of hormone response elements in the nucleus, in contrast to hormone response element-dependent classical effects. Abbreviations: ER, estrogen receptor; ERE, estrogen response element; PR, progesterone receptor; PRE, progesterone response element; Glu, glutamate receptor.

these tasks in female rats and mice.

There are many ways to measure hippocampal memory consolidation in rodents. To isolate consolidation from other memory processes such as acquisition and retention, most investigators have used one-trial learning tasks in which experimental manipulations are administered immediately after the training trial and memory is tested at some point afterwards (e.g., 1–48 h). Examples of such tasks are contextual fear conditioning and avoidance tasks (e.g., passive and active avoidance). However, these particular tasks are perhaps not ideal for studies of estrogenic regulation of memory because the footshock used as a motivating stimulus can rapidly increase levels of corticosterone in mice (Matthews et al., 2008), and acute corticosterone given immediately after contextual fear conditioning training can impair contextual fear conditioning in ovariectomized rats (Kashefi and Rashidy-Pour, 2014). Moreover, acute interactions between corticosterone and E_2 that influence contextual fear memory and spatial strategy selection have been documented in ovariectomized rats and naturally cycling mice (Kashefi and Rashidy-Pour, 2014; ter Horst et al., 2013), suggesting that aversively-motivated one-trial learning tasks might not be the best choice for studying effects of E_2 on memory consolidation. Other tasks whose training requires multiple trials (e.g., spatial Morris water maze) have been modified to study effects of E_2 and progesterone on memory consolidation (Gresack and Frick, 2006; Harburger et al., 2008; Packard and Teather, 1997a, 1997b), but these also have drawbacks, as the stress of water immersion blocks the beneficial effects of E_2 on CA1 spine density and spatial memory (Frick et al., 2004), and multiple training trials provide less temporal precision than one-trial tasks. As such, most investigators studying rapid effects of E_2 and progesterone on memory in rodents have used object recognition and object placement (a.k.a., object location) tasks to assess consolidation of memory for the identity and location of objects, or social recognition tasks to measure consolidation of memory for the identity of conspecifics (K.S.J. Ervin et al., 2015; Luine, 2015; Sheppard et al., 2018; Tuscher et al., 2015). In particular, object recognition and object placement tasks involve no extrinsically motivating stimuli that may confound performance and interact with exogenously administered hormones, such as footshock, water immersion, or nutrient restriction, and so are particularly well suited to examine the effects of E_2 on hippocampal memory consolidation. In addition, both tasks can easily be conducted on the same animals, ideally with the order of testing counterbalanced within experimental groups. Because effects of estrogens on social recognition are reviewed elsewhere in this volume, the sections below will focus on object recognition and object placement.

An important aspect of the use of object recognition and object placement tasks in assessing memory consolidation is the administration of hormones immediately *after* training. Our own studies use water-soluble forms of estradiol and progesterone that are metabolized within 24 h (Pitha et al., 1986; Pitha and Pitha, 1985), so are not active by the time of testing 24–48 h later. Because consolidation occurs within 1–3 h of training in these tasks (Fernandez et al., 2008; Frye et al., 2007; Orr et al., 2009; Walf et al., 2006), this post-training design permits effects of hormone administration on consolidation to be assessed in the absence of confounding influences of motivation, anxiety, and sensorimotor abilities on acquisition and retention (Frick et al., 2010).

Both object tasks involve one or more habituation trials in which subjects investigate an empty testing arena. Habituation is followed by a training trial in which subjects explore two identical objects for either a set period (e.g., 5 or 10 min) or until they have accumulated a set amount of object exploration (e.g., 30 s) (Fig. 2). We favor the latter in post-training memory consolidation experiments because it assures that all subjects experience the same amount of object exploration prior to drug treatment. After training and drug administration, memory is tested by either replacing one training object with a new object (object recognition) or by moving one training object to a new location in the arena (object placement) (Fig. 2). We find that ovariectomized mice treated with vehicle fail to remember the identity and location of the training objects 48 and 24 h, respectively, after training, so we use these

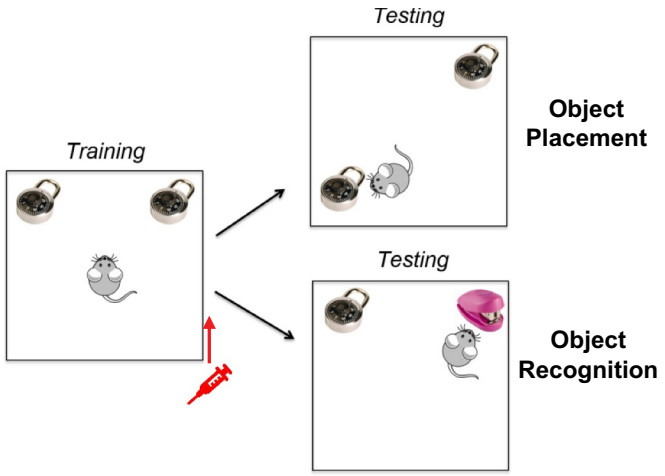

Fig. 2. Illustration of typical object recognition and object placement testing protocols. Labs that use these tasks to test effects of E_2 or progesterone on memory have used two objects placed in a square arena. During training, mice explore two identical objects for 3–5 min or until they have accumulated 30 s of object exploration. In post-training studies, hormones are administered immediately after training, or in some cases, delayed 1–3 h after training. Memory is then tested at some delay later by presenting mice with one novel and one familiar object (object recognition) or moving one familiar object to a new location in the arena (object placement). Because mice tend to prefer novelty, mice that remember the identity and location of the familiar object will spend more time exploring the novel or moved object.

delays to test the memory-enhancing effects of E_2 and progesterone (Boulware et al., 2013; Fortress et al., 2015; Kim et al., 2016). Because rodents tend to prefer novelty, those who remember the identity or location of the training objects will spend more time exploring the novel and moved objects than chance and/or than vehicle-treated subjects.

Nearly two dozen studies published by multiple labs have demonstrated that a single post-training treatment with E_2 administered immediately after training enhances memory consolidation in the object recognition and object placement tasks in ovariectomized rodents. The enhancement in young adult females has been observed after subcutaneous injection in rats (Frye et al., 2007; Inagaki et al., 2010; Luine et al., 2003; Walf et al., 2006), intraperitoneal injection in mice (Frick et al., 2010; Gresack and Frick, 2004, 2006; Gresack et al., 2007a, 2007b; Harburger et al., 2009; Lewis et al., 2008a; Pereira et al., 2014; Walf et al., 2008), and intracranial infusion into the dorsal hippocampus or dorsal third ventricle in mice (Boulware et al., 2013; Fernandez et al., 2008; Fortress et al., 2013a; Frick et al., 2010; Kim et al., 2016; Tuscher et al., 2016b; Zhao et al., 2012; Zhao et al., 2010). Similar enhancements have also been observed after post-training intraperitoneal injection or dorsal hippocampal infusion of E_2 in ovariectomized middle-aged rats and mice (Fan et al., 2010; Fortress et al., 2014; Gresack et al., 2007a; Walf and Frye, 2008), although ovariectomized aged mice do not respond to a single treatment with E_2 (Fan et al., 2010; Gresack et al., 2007a, 2007b). Nevertheless, the E_2-induced enhancement in object recognition and object placement tasks observed across labs, species, aged, training protocols, and routes of administration suggest that the ability of E_2 to facilitate object recognition and spatial memory consolidation is quite reliable. It is important to note that memory consolidation in young females is not enhanced when E_2 administration is delayed 1–3 h after training (Fernandez et al., 2008; Frye et al., 2007; Walf et al., 2006), suggesting an effect specific to the consolidation phase of memory formation.

Far fewer studies have examined effects of progesterone on memory consolidation, but these also consistently indicate that post-training administration of this hormone enhances memory consolidation. In young ovariectomized rats and mice, immediate post-training systemic injection of progesterone enhances memory in the object recognition and object placement tasks (Frye et al., 2007; Frye et al., 2013, 2009; Frye and Walf, 2008; Harburger et al., 2008, 2009; Walf et al., 2006). Similar effects are observed in young ovariectomized mice after immediate, but not delayed, dorsal hippocampal infusion (Fortress et al., 2015; Orr et al., 2009; Orr et al., 2012). Intraperitoneal or subcutaneous injections of progesterone also enhance memory in the object recognition task among middle-aged ovariectomized mice (Frye and Walf, 2008; Lewis et al., 2008b), and interestingly, enhance memory in both the object recognition and object placement tasks in aged ovariectomized mice (Frye and Walf, 2010; Lewis et al., 2008b). The latter finding suggests that the aged brain may be more sensitive to post-training administration of progesterone than E_2. It should be noted that the timing of treatment appears to be particularly important for progesterone, at least in aging rats, as acute or chronic progesterone given systemically prior to training impairs or has no effect on spatial memory in middle-aged and aged rats (Bimonte-Nelson et al., 2004; Sato et al., 2004).

Very few studies have examined effects of post-training co-administration of E_2 plus progesterone, but most also suggest a beneficial effect on memory consolidation throughout the female lifespan. In two studies of young ovariectomized rats, subcutaneous injections of E_2 and progesterone enhanced consolidation in the object recognition and object placement tasks, but not if delayed 1 or 1.5 h, respectively, after training (Frye et al., 2007; Walf et al., 2006). Intraperitoneal injections of water soluble E_2 and progesterone also enhanced object recognition memory consolidation in young ovariectomized mice, but this effect depended on the dose of progesterone administered (Harburger et al., 2009).

As discussed above, the object recognition and object placement tasks are excellent tools for studying the rapid effects of E_2 and progesterone on memory consolidation because the single learning trial and rapid consolidation allows for relatively precise identification of the molecular mechanisms underlying hormone-induced consolidation. Moreover, the reliability of the memory-enhancing effects observed after post-training administration of either hormone or both in combination supports the potential generalizability of the findings across labs and/or memory paradigms. Having established that post-training treatments of E_2 and progesterone enhance memory consolidation in these tasks, we could then ask *how* they do so. The next section describes the molecular mechanisms underlying the beneficial effects of these hormones on object recognition and spatial memory consolidation.

4. Mechanisms underlying estradiol-induced memory enhancement

4.1. Cell signaling: ERK and related kinases

Because of its important role in memory consolidation, ERK became an early focus of our quest to pinpoint the molecular mechanisms through which E_2 facilitates memory consolidation. Activation of ERK signaling in the hippocampus is necessary for the consolidation of spatial, contextual, and object memories, as illustrated by studies showing that blocking hippocampal ERK phosphorylation impairs

memory consolidation (Atkins et al., 1998; Blum et al., 1999; Kelly et al., 2003). E_2 also increases hippocampal ERK phosphorylation both in vitro and in vivo (Kuroki et al., 2000; Nilsen and Brinton, 2003; Yokomaku et al., 2003), so it seemed reasonable to hypothesize that ERK phosphorylation might be necessary for E_2 to enhance memory consolidation. Indeed, we found this to be the case. In the dorsal hippocampus of young ovariectomized mice, E_2 increases phosphorylation of the p42 isoform of ERK within 60 min of an intraperitoneal injection and 5 min of a dorsal hippocampal infusion (Boulware et al., 2013; Fernandez et al., 2008; Fortress et al., 2013a; Kim et al., 2016; Lewis et al., 2008a). Importantly, infusion of the ERK phosphorylation inhibitor U0126 into the dorsal hippocampus prevents this increase and blocks the memory-enhancing effects of E_2 in both the object recognition and object placement tasks, demonstrating that ERK phosphorylation is necessary for E_2's effects on memory consolidation (Boulware et al., 2013; Fernandez et al., 2008; Fortress et al., 2013a; Zhao et al., 2010). ERK is also necessary for E_2 to enhance object recognition memory consolidation in middle-aged ovariectomized mice, although the timing is a bit slower, in that E_2 increases p42 ERK phosphorylation 15, not 5, minutes after dorsal hippocampal infusion (Fan et al., 2010). Interestingly, a post-training infusion of E_2 into the dorsal hippocampus does not increase ERK phosphorylation or enhance object recognition memory consolidation in aged ovariectomized mice (Fan et al., 2010), suggesting that the aged female brain loses its ability to trigger ERK signaling in response to a single E_2 infusion.

Upstream from ERK, we have shown that activation of protein kinase A (PKA), PI3K, and NMDA receptors are necessary for E_2 to increase p42 ERK phosphorylation and enhance object recognition memory consolidation in young ovariectomized mice (Fortress et al., 2013a; Lewis et al., 2008a). Downstream from ERK, multiple processes are involved in E_2's effects on memory. One process involves hormone response element-independent gene expression (Fig. 3). We and others have shown that E_2 alters the expression of numerous genes in the hippocampus of female rodents of various ages (Aenlle and Foster, 2010; Aenlle et al., 2009; Pechenino and Frick, 2009). For example, 1 h after intraperitoneal injection in young ovariectomized mice, E_2 increased mRNA and protein levels of synaptic proteins (SNAP-25, Actn-4, tubulin-β) and the heat shock protein Hsp70-1, but decreased levels of the insulin-like growth factor binding protein 2 (IGFBP-2) (Pechenino and Frick, 2009). Interestingly, another microarray study showed that estradiol benzoate treatment in middle-aged ovariectomized mice reversed an age-related increase in histone deacetylase 2 (HDAC2) expression (Aenlle et al., 2009). HDAC enzymes, along with histone acetyltransferase (HAT) enzymes, regulate the post-translational epigenetic process called histone acetylation, in which acetyl groups are added to or subtracted from the tails of the four core histone proteins around which DNA is wrapped in the nucleosome. Histone acetylation relaxes the bonds between the DNA and histones, causing a permissive state that allows transcription factors to access DNA and promote gene transcription. HDAC enzymes, including HDAC2 and HDAC3, remove acetyl groups from histone tails, thereby creating a repressive state that reduces gene transcription. Expression of HDAC2 and HDAC3 impairs various forms of hippocampal memory including spatial memory, object recognition, and contextual fear conditioning (Guan et al., 2009; McQuown et al., 2011). Thus, the E_2-induced reduction in HDAC2 expression in middle-aged mice (Aenlle et al., 2009) provides a possible mechanism for E_2 to increase gene expression.

Connections among E_2, histone acetylation, and ERK activation come from studies of young ovariectomized mice in which dorsal hippocampal infusion of E_2 increased histone acetyltransferase activity and acetylation of the histone core protein H3 (but not other core histones) within 30 min and decreased dorsal hippocampal HDAC2 protein levels by 4 h (Zhao et al., 2012, 2010). Hippocampal learning increases H3 acetylation in a manner dependent on ERK phosphorylation (Chwang et al., 2006; Levenson et al., 2004), and H3 acetylation is necessary for object recognition memory consolidation (Zhao et al., 2012). Accordingly, the E_2-induced increase in H3 acetylation is also dependent on ERK phosphorylation (Zhao et al., 2010), suggesting that histone acetylation is necessary for E_2 to enhance memory consolidation. We examined this issue using the HAT inhibitor garcinol, which prevents HAT enzymes from acetylating histones and represses gene transcription (Balasubramanyam et al., 2004). Indeed, dorsal hippocampal infusion of garcinol prevented E_2 from enhancing object recognition memory consolidation in young ovariectomized mice (Zhao et al., 2012), demonstrating an essential role for H3 acetylation in the memory-enhancing effects of E_2 in females. Other data implicate another epigenetic process, DNA methylation, in E_2's effects on memory consolidation in young ovariectomized females (Zhao et al., 2010). Although DNA methylation is not directly tied to ERK activation, these data suggest that multiple epigenetic processes regulate the effects of E_2 on memory formation.

Local protein translation is another important downstream effect of ERK that regulates E_2's effects on memory. A hallmark of E_2's effects on the hippocampus is its ability to increase the density of dendritic spines on CA1 pyramidal neurons (e.g., (Woolley and McEwen, 1992, 1993)). Spines are thought to increase excitatory input to neurons, as more than 90% of excitatory synapses form on spines (Nimchinsky et al., 2002). Dendritic spines are formed in response to neural activity and bear the NMDA and AMPA receptors necessary for the long-term potentiation (LTP) and related forms of synaptic plasticity necessary for memory (Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999). Accordingly, learning in spatial and recognition tasks is associated with

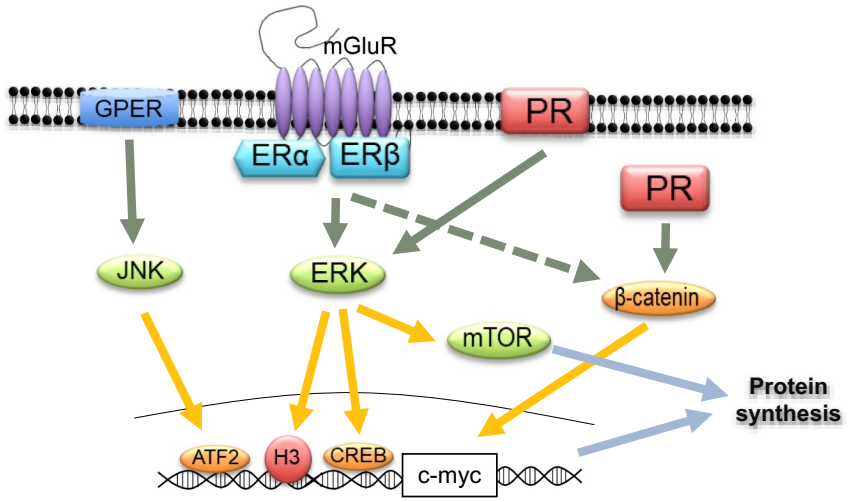

Fig. 3. A diagrammatic representation of rapid molecular effects mediated by E_2 and progesterone receptors, emphasizing common mechanisms between the two hormones. ERK phosphorylation is necessary for ERα and ERβ (interacting at the membrane with mGluR1a) and membrane PRs to enhance memory consolidation in the object recognition and object placement tasks. Downstream from ERK, mTOR-mediated protein synthesis is also essential for the memory-enhancing effects of E_2 and progesterone, and for E_2's facilitation of CA1 dendritic spine density. ERK is also involved in E_2's effects on gene transcription through H3 acetylation and CREB phosphorylation. Neither membrane-associated GPER nor intracellular PRs mediate memory consolidation via ERK. Whereas GPER's effects depend on JNK, intracellular PR's effects may involve Wnt/β-catenin signaling. Wnt/β-catenin signaling also appears to play a role in the memory-enhancing effects of E_2, although the ERs involved are unknown.

increased hippocampal spine density, suggesting that new spines may underlie hippocampal memory formation (Moser et al., 1994; O'Malley et al., 2000; Wallace et al., 2006). In vivo, E_2 increases CA1 spine density within 30 min (Inagaki et al., 2012; Phan et al., 2015; Tuscher et al., 2016a), indicating a rapid effect that requires local protein synthesis within dendrites. A cell signaling pathway likely involved in this E_2-induced protein synthesis is mammalian target of rapamycin (mTOR), which is activated by ERK and regulates local protein synthesis at synapses by phosphorylating two key elements of the translational initiation machinery, p70 ribosomal S6 kinase (S6K) and eIF4E-binding proteins (4E-BPs) (Hoeffer and Klann, 2010; Kelleher III et al., 2004; Tsokas et al., 2005). In response to neural activity, activation of either ERK or mTOR signaling leads to new protein synthesis, increased synaptic plasticity, and memory formation (Hoeffer and Klann, 2010; Kelleher III et al., 2004; Myskiw et al., 2008; Tsokas et al., 2005). Inhibitors that prevent phosphorylation of ERK (e.g., U0126) or mTOR (e.g., rapamycin) block these effects, suggesting critical roles for ERK and mTOR phosphorylation in dendritic spinogenesis and memory consolidation. Given E_2's effects on CA1 spine density and memory consolidation, we thought that mTOR might be essential. We first examined mTOR's involvement in the memory-enhancing effects of E_2 in ovariectomized mice. We found that dorsal hippocampal infusion of E_2 increased the phosphorylation of the downstream mTOR effectors S6K and 4E-BP1 in the dorsal hippocampus within 5 min (Fortress et al., 2013a). This activation was necessary for E_2 to enhance object recognition memory consolidation, as E_2's beneficial effects in the object recognition task were blocked by the mTOR inhibitor rapamycin (Fortress et al., 2013a). Linking this finding with underlying morphological substrates of this memory enhancement, we more recently found that infusion of E_2 into the dorsal hippocampus of ovariectomized mice increases dorsal CA1 spine density 30 min and 2 h later (Tuscher et al., 2016a). As mentioned above, such a rapid increase in CA1 spinogenesis has been observed by others (Inagaki et al., 2012; Phan et al., 2015), so we asked whether ERK or mTOR signaling might be involved. Using dorsal hippocampal infusions of U0126 and rapamycin, we found that phosphorylation of ERK or mTOR in the dorsal hippocampus was necessary for E_2 to increase CA1 dendritic spines 2 h later (Tuscher et al., 2016a). Although in vitro studies have shown that numerous cell signaling cascades, including ERK, are necessary for E_2 to increase CA1 spine density in male hippocampal slices (Hasegawa et al., 2015; Hojo et al., 2015), our findings were the first to demonstrate in vivo that rapid activation of cell signaling cascades is necessary for E_2 to increase dendritic spinogenesis in the female hippocampus. Although this work does not provide a direct link between E_2's effects on spines and memory formation, the combination of the spine data and our behavioral findings strongly suggest that E_2 enhances memory consolidation via rapid activation of ERK and mTOR, which then trigger local protein synthesis to increase CA1 spine density and synaptic plasticity.

Although ERK and mTOR appear to have a primary role in E_2's effects on hippocampal spinogenesis and memory consolidation, many other signaling pathways are likely involved. For example, activation of ERK, PI3K, PKA, protein kinase C (PKC), LIM kinase (LIMK), and calcium calmodulin kinase II (CaMKII) is necessary for E_2 to increase CA1 spine density in hippocampal slices from male rats (Hasegawa et al., 2015; Hojo et al., 2015). Of these, LIMK, which is activated by upstream signaling cascades including the RhoA/RhoA kinase (ROCK) pathway, regulates the actin cytoskeleton. The cytoskeleton of dendritic spines consists primarily of filamentous actin, or F-actin (Harris and Kater, 1994; Krucker et al., 2000). F-actin is stabilized by actin binding proteins like profilin, which promote the addition of monomeric G-actin to F-actin (Rust, 2015; Spence and Soderling, 2015). Actin depolymerizing proteins, like cofilin, sever actin filaments and play a key role in spine remodeling (Rust, 2015; Spence and Soderling, 2015). Cofilin is a constitutively active protein that is inactivated by LIMK-induced phosphorylation. During LTP induction, activated cofilin destabilizes actin filaments to promote spine growth and insertion of AMPA receptors into the post-synaptic density (Bosch et al., 2014; Gu et al., 2010; Rust, 2015). During LTP maintenance, however, cofilin phosphorylation permits the elongation of F-actin and stabilization of newly inserted AMPA receptors and the spine cytoskeleton (Bosch et al., 2014; Gu et al., 2010; Krucker et al., 2000; Rust, 2015). Given E_2's role in promoting synaptic plasticity and LTP, a role for cofilin-mediated actin polymerization seems likely.

In hippocampal slices from male rats, E_2 increases cofilin phosphorylation, actin polymerization, and promotes LTP, suggesting that E_2-induced actin polymerization facilitates synaptic plasticity (Kramár et al., 2009). Accordingly, treatment with latrunculin A, a toxin that binds actin monomers, thereby blocking F-actin assembly, prevents E_2 from promoting LTP (Kramár et al., 2009). In slices from mature adult ovariectomized rats, E_2 reverses ovariectomy-induced reductions in RhoA levels and actin polymerization (Kramár et al., 2009). In mouse hippocampus or hippocampal cell lines, E_2 increases cofilin phosphorylation, an effect that is mimicked by in vivo ERα and ERβ agonists and blocked by ERα and ERβ antagonists (Zhao et al., 2017). Similarly, a GPER antagonist decreases hippocampal cofilin phosphorylation and CA1 dendritic spine density (Xing et al., 2018). Together, these data suggest that actin polymerization may play an important role in E_2's effects on memory. One study examined this relationship in ovariectomized rats treated chronically with cholesterol or E_2. Dorsal hippocampal infusion of latrunculin A given 15 min before object placement training dose-dependently impaired memory in both groups, suggesting that E_2 could not prevent the detrimental effects of latrunculin A (Nelson et al., 2012). Chronic E_2 also did not increase hippocampal cofilin phosphorylation (Nelson et al., 2012). However, preliminary data from our laboratory indicates that acute infusion of E_2 or the GPER agonist G-1 into the dorsal hippocampus of ovariectomized mice increases cofilin phosphorylation within 5 and 15 min and increases CA1 dendritic spines within 40 min (Kim et al., 2017). Moreover, the ability of G-1 to enhance both object recognition and object placement memory consolidation is blocked by dorsal hippocampal infusion of latrunculin A (Kim et al., 2017), suggesting that actin polymerization is necessary for GPER to facilitate memory formation. As discussed below, GPER and E_2 appear to act independently to regulate memory consolidation, so it is currently unclear whether this finding relates to E_2's effects on memory. Studies investigating the involvement of actin polymerization in E_2-induced hippocampal spinogenesis and memory consolidation are currently underway.

4.2. Receptor mechanisms

As mentioned above, E_2 may rapidly act to influence hippocampal function and memory consolidation via non-classical effects on ERα, ERβ, or GPER. Non-classical effects of E_2 on hippocampal memory consolidation were first indicated a decade ago in studies of young ovariectomized mice. This work found that the enhancing effects of post-training dorsal hippocampal E_2 on object recognition memory consolidation were mimicked by dorsal hippocampal infusion of a form of E_2 conjugated to bovine serum albumin (BSA-E_2). The large size of the BSA protein prevents E_2 from penetrating the cell membrane, and thus, any effects of BSA-E_2 can be attributed to actions at the membrane. Post-training dorsal hippocampal infusion of BSA-E_2 increased dorsal hippocampal p42 ERK phosphorylation and enhanced object recognition memory consolidation in ovariectomized mice (Fernandez et al., 2008). BSA-E_2's effects on memory were blocked by U0126, but not by the nuclear ERα/β antagonist ICI 182,780 (Fernandez et al., 2008), supporting a role for rapid non-classical ER signaling, but not classical ER-mediated gene transcription, in the memory-enhancing effects of E_2.

Which ERs may mediate these rapid non-classical effects of E_2 on memory consolidation? The most likely candidates are ERα and ERβ acting at or near the cell membrane, because agonists of these ERs very closely mimic E_2's effects on hippocampal ERK signaling and memory

consolidation in ovariectomized mice. Specifically, post-training dorsal hippocampal infusion of the ERα agonist propyl pyrazole triol (PPT) or ERβ agonist diarylpropionitrile (DPN) increases dorsal hippocampal p42 ERK phosphorylation and enhances consolidation in both the object recognition and object placement tasks in a manner similar to E_2 (Boulware et al., 2013; Pereira et al., 2014). Effects of E_2 and both agonists were blocked by dorsal hippocampal infusion of an antagonist for metabotropic glutamate receptor 1a (mGluR1a), suggesting that ERα and ERβ must interact at the membrane with mGluR1a to facilitate memory formation (Boulware et al., 2013) (Fig. 3). These membrane interactions were supported by sucrose fractionation and immunoprecipitation data, implicating membrane-associated effects of ERα and ERβ in the rapid actions of E_2 on cell signaling and memory consolidation (Boulware et al., 2013). More recently, post-training dorsal hippocampal infusion of ERα and ERβ antagonists were shown to impair object recognition and object placement in ovariectomized mice (Kim and Frick, 2017), providing additional evidence for a role of both receptors in mediating the rapid effects of E_2 on memory consolidation.

The role of GPER in mediating the memory-enhancing effects of E_2 is more complicated. Numerous studies demonstrate that pre-training treatment with the GPER agonist G-1 enhances, whereas the antagonist G-15 impairs, working memory, object recognition, object placement, social recognition, and social learning in ovariectomized rats and mice (K.S. Ervin et al., 2015; Gabor et al., 2015; Hammond et al., 2009, 2012; Lymer et al., 2017). Moreover, G15-laden hippocampal implants block spatial learning and memory in adult male zebra finches, suggesting a general role of GPER in hippocampal learning across species (Bailey et al., 2017). Effects on object and social recognition in rodents were observed within 40 min of a single systemic injection or dorsal hippocampal infusion (K.S. Ervin et al., 2015; Gabor et al., 2015; Lymer et al., 2017), suggesting rapid transcriptionally-independent effects of GPER activation on memory. Similarly, post-training dorsal hippocampal infusion of G-1 enhances, whereas G-15 impairs, the consolidation of both object recognition and object placement memories in ovariectomzied mice (Kim et al., 2016). However, we found that dorsal hippocampal infusion of G-1 did not increase p42 ERK phosphorylation in the dorsal hippocampus like E_2 and agonists of ERα and ERβ; instead, it increased the phosphorylation of c-Jun N-terminal kinase (JNK) (Kim et al., 2016), a MAP kinase that activates a largely distinct set of transcription factors from ERK. Dorsal hippocampal infusion of the JNK inhibitor SP600125, but not U0126, blocked the ability of G-1 to increase JNK phosphorylation and enhance memory (Kim et al., 2016), demonstrating that activation of JNK, but not ERK, is necessary for G-1 to regulate memory consolidation. Interestingly, E_2 did not increase JNK phosphorylation, nor did G-15 or SP600125 block the memory-enhancing effects of E_2 (Kim et al., 2016), suggesting that E_2 and GPER act independently to regulate memory formation in the dorsal hippocampus of ovariectomized mice (Fig. 3). However, more work must done to determine if this finding generalizes to other forms of memory or species, and to reconcile these results with other data showing that bath application of G-1 increases ERK phosphorylation in hippocampal slices from ovariectomized mice (Kumar et al., 2015).

5. Mechanisms underlying progesterone-induced memory enhancement

5.1. Cell signaling and receptor mechanisms

Like E_2, ERK was an early focus of our studies with progesterone because of data showing that either E_2 or progesterone increased ERK phosphorylation in primary cultures of dissociated embryonic hippocampal neurons (Nilsen and Brinton, 2002, 2003). In addition, systemic injection of progesterone increases hippocampal ERK phosphorylation in young ovariectomized rats 24 h later (Guerra-Ariaza et al., 2009). Thus, we first examined progesterone's effects on dorsal hippocampal ERK phosphorylation. Dorsal hippocampal infusion of progesterone in young ovariectomized mice had a biphasic effect on dorsal hippocampal p42 ERK, such that phosphorylation was increased after 5 min, decreased after 15 min, and unaltered after 30 min relative to mice receiving vehicle (Fortress et al., 2015; Orr et al., 2012). Phosphorylation of p44 ERK was unaltered after 5 min, decreased after 15 min, and then unaltered again after 30 min (Orr et al., 2012). These data illustrate the rapid nature of progesterone's effects on ERK activation, and its biphasic effect on p42 ERK is reminiscent of its biphasic effects on E_2-induced CA1 dendritic spine density, where progesterone initially increases, but then decreases, spine density (Woolley and McEwen, 1993). However, it is important to note that the observed spine changes occurred in the order of hours, not minutes. Nevertheless, the rapid actions of progesterone on ERK phosphorylation may be integral for progesterone's numerous effects in the hippocampus. For example, progesterone's neuroprotective effects against ischemic damage in male rats are dependent on ERK phosphorylation (Cai et al., 2008), as is its ability to promote the proliferation and survival of new neurons in the rodent dentate gyrus (Liu et al., 2009; Zhang et al., 2010). Consistent with these effects, we found that dorsal hippocampal infusion of U0126 prevented post-training progesterone treatment from enhancing object recognition memory consolidation in ovariectomized mice (Orr et al., 2012), suggesting that the ability of progesterone to regulate memory consolidation depends on dorsal hippocampal ERK phosphorylation. Interestingly, we also found that dorsal hippocampal progesterone infusion activated mTOR signaling in the dorsal hippocampus of ovariectomzied mice (Fortress et al., 2015; Orr et al., 2012), indicating that progesterone and E_2 generate similar downstream effects of ERK activation. As with E_2, dorsal hippocampal infusion of rapamycin blocked the memory-enhancing effects of progesterone in ovariecomized mice (Orr et al., 2012), demonstrating that activation of both ERK and mTOR are necessary for progesterone to regulate object recognition memory consolidation in female mice.

Given these findings, we suspected that membrane PRs may mediate progesterone's effects on cell signaling and memory consolidation. As with E_2, we tested effects of a BSA-conjugated P (BSA-P) to determine the extent to which membrane-associated actions were involved. In young ovariectomized mice, post-training dorsal hippocampal infusion of BSA-P enhanced object recognition memory consolidation in a manner dependent on activation of ERK, but not intracellular PRs (Fortress et al., 2015). The latter was tested using dorsal hippocampal infusion of the intracellular PR antagonist RU486. Accordingly, BSA-P also significantly increased phosphorylation of p42 ERK and the downstream mTOR effectors S6K and 4E-BP1, effects that were blocked again by ERK inhibition but not intracellular PR antagonism (Fortress et al., 2015). Collectively, these data suggest that progesterone in the dorsal hippocampus of female mice can rapidly facilitate memory consolidation via binding to membrane PRs and activation of ERK and mTOR signaling (Fig. 3).

However, these findings do not preclude an additional role for intracellular PRs in memory consolidation. In fact, we also found that dorsal hippocampal infusion of the intracellular PR agonist R5020 enhanced object recognition memory consolidation in ovariectomized females (Fortress et al., 2015). This effect was blocked by RU486, but not U0126. Moreover, R5020 did not increase p42 ERK, S6K, or 4E-BP1 phosphorylation (Fortress et al., 2015). Together, these results suggest that R5020 influences object recognition memory consolidation in the dorsal hippocampus via an intracellular mechanism distinct from ERK signaling. That mechanism may involve rapid actions of progesterone on canonical Wnt/β-catenin signaling. Within 5 min of dorsal hippocampal infusion, R5020 increased levels of the canonical Wnt ligand Wnt7a, total β-catenin, and the canonical Wnt target c-myc (Fortress et al., 2015). All of these increases were blocked by RU486 (Fortress et al., 2015), suggesting a role for intracellular PRs (Fig. 3). How these PRs might trigger canonical Wnt signaling is not yet known, nor is the necessity of Wnt signaling for the memory-enhancing effects of R5020. However, combined with the BSA-P data, these findings reveal that

both intracellular and membrane PRs can rapidly affect hippocampal cell signaling in ways that influence memory consolidation.

6. Conclusions

In the past two decades, E_2 and progesterone have become well established as key regulators of memory consolidation in female rodents. Important advances have been made during this time by applying lessons learned from in vitro studies of rapid hormone effects on cell signaling and receptor mechanisms to in vivo experiments testing the necessity of those effects for hormonal regulation of memory consolidation. Thus far, the data suggest numerous commonalities between E_2 and progesterone. For example, both hormones enhance memory consolidation in young and middle-aged female rodents, although aged females seem to be more responsive to progesterone. Both hormones can influence memory consolidation via membrane-associated or intracellular receptors, or some combination thereof, and require activation of ERK and mTOR signaling to facilitate memory (Fig. 3). E_2 and progesterone may also share a common mechanism in canonical Wnt/β-catenin signaling, which is triggered by intracellular PRs and which our preliminary data suggest is necessary for E_2 to enhance memory consolidation in female mice (Taxier et al., 2017). Wnt/β-catenin signaling is essential for normal hippocampal development and regulates hippocampal plasticity in adulthood (Ciani and Salinas, 2005; Tabatadze et al., 2014). In male rodents, object training or spatial learning activates Wnt/β-catenin signaling in the dorsal hippocampus (Fortress et al., 2013b; Tabatadze et al., 2012), and this activation is necessary for intact object recognition and object placement memory consolidation (Fortress et al., 2013b). Thus, the emerging role of Wnt/β-catenin signaling in memory formation makes this signaling pathway an interesting potential point of convergence between E_2 and progesterone to be studied in future work.

Although we have learned much, the rapid actions of E_2 and progesterone on memory consolidation are likely considerably more complicated than those presented above, involving interactions among numerous receptors, signaling molecules, and post-translational modifications. Moreover, studies to date have focused largely on the hippocampus, but other interconnected brain regions, like adjacent temporal lobe cortices and the prefrontal cortex, surely play critical roles that remain unexplored. Effects on memory consolidation of the dynamic interplay between E_2 and progesterone during the natural cycle, and of hippocampally synthesized estrogens and progestogens, also remain poorly understood. As such, there remain many interesting and important questions to be addressed in the coming decades. This future work should provide exciting new insights into the rapid actions of E_2 and progesterone on memory formation.

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