Memory and epigenetics: Influence of sex and estrogens

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Abstract

Memory dysfunction is a pervasive component of numerous central nervous system disorders, yet the finely-tuned processes governing memory formation and the mechanisms responsible memory persistence remains unclear. Epigenetic regulation of gene expression is a principal mechanism through which memories are maintained. Sex-steroid hormones, including 17β-estradiol (E_2), also regulate memory formation, as E_2's presence facilitates normal memory formation and its absence has deleterious effects on memory. This chapter will review ways in which endogenous sex-steroid hormones and exogenous E_2 regulate behavior by altering epigenetic signaling in the brain and explore ways in which sex-specific epigenetic signaling influences behavior.

Keywords

Chromatin; Epigenetics; Estradiol; Extracellular signal-regulated kinase; Hippocampus; Histone acetylation; Memory consolidation; Object recognition; Sex differences

Key points

- The cellular and molecular mechanisms through which sex steroid hormones like estrogens regulate neural function and memory remain unclear.
- Epigenetic modifications in the brain that regulate the transcription of genes associated with synaptic plasticity and memory formation differ by sex and are influenced by endogenous estrogen fluctuations and exogenous estrogen treatment.
- This chapter highlights findings to date indicating that sex and estrogens regulate the epigenome in post-mitotic neurons to regulate brain and memory function.

Introduction

Over three decades of research has demonstrated that sex steroid hormones like the potent estrogen 17β-estradiol (E_2) influence memory formation by rapidly altering the structure and function of brain regions that mediate cognition. Clinical studies investigating the estrogenic regulation of memory in the context of aging have demonstrated that ovarian hormone loss due to natural or surgical menopause impairs various aspects of cognitive function in women, including tests of verbal and spatial memory (Sherwin and Henry, 2008). Menopausal women are also at increased risk of developing Alzheimer's disease (AD) relative to men, even when accounting for women's longer life expectancies (Dye et al., 2012; Scheyer et al., 2018). A key role for menopausal estrogen loss in this increased risk is supported by data showing that longer lifetime estrogen exposure is associated with reduced likelihood of developing AD in women (Fox et al., 2013). The deleterious effects of menopause-related estrogen loss on cognition and risk of AD can be reduced by E_2 therapy (Conde et al., 2021), suggesting not only that E_2 loss at menopause contributes to memory dysfunction, but also that maintaining E_2 levels during the menopausal transition may help prevent or delay AD onset and reduce age-related cognitive decline. In premenopausal women, E_2 fluctuations across the month-long menstrual cycle impact certain aspects of cognitive function (Brinton et al., 2015). For example, women experiencing high E_2 levels during the midluteal phase of the cycle perform better in tests of verbal fluency, fine motor, and perceptual speed than women experiencing low E_2 levels during the menstrual phase (Hampson, 1990; Maki et al., 2002). Some evidence suggests that visual memory is also poorer during the menstrual phase (Le et al., 2020). However, high levels of E_2 do not always correlate with better cognitive function, as women with low E_2 levels perform best in tasks in which men traditionally outperform females (i.e., those related to spatial ability) (Hampson, 1990; Maki et al., 2002). Collectively, findings from human studies suggest that estrogen loss at menopause is associated with cognitive dysfunction, and that endogenous estrogen fluctuations in premenopausal women influence cognition.

Consistent with this work, rodent studies demonstrate that endogenous cycling and ovary removal (ovariectomy) influence neural function and memory (Taxier et al., 2020). Today's interest in the topic traces largely from seminal work published in the early 1990s demonstrating in female rats that the density of dendritic spines on pyramidal neurons in the CA1 region of the hippocampus is increased by estradiol (Gould et al., 1990; Woolley et al., 1990; Woolley and McEwen, 1992, 1993). Subsequent work found that synaptic plasticity, including long-term potentiation, is facilitated by E_2 in female rats (Foy et al., 1999). In the nearly four decades since this initial work, E_2 has been shown to enhance many types of learning and memory in adult males and females of various species including songbirds, rodents, nonhuman primates, and humans (Luine and Frankfurt, 2020; Ogawa et al., 2020; Taxier et al., 2020; Tuscher et al., 2015; Vahaba and Remage-Healey, 2018). However, our understanding of the cellular and molecular mechanisms through which sex steroid hormones like E_2 regulate neural and behavioral function throughout the lifespan remains rudimentary. A relatively scant but emerging literature suggests that E_2 influences memory via epigenetic modifications in the brain that promote gene transcription and de novo protein synthesis. As such, this chapter will highlight the ways in which sex and E_2 regulate the epigenome in post-mitotic neurons throughout adulthood to positively regulate brain and memory function.

Epigenetics and chromatin modifications: A primer

Epigenetic alterations influence gene expression by regulating accessibility to genes rather than changing the genetic code itself. DNA is tightly coiled around a core of eight histone (H) proteins (two each of H2A, H2B, H3, and H4) to form a nucleosome, which is linked via H1 linker histones to other nucleosomes that fold tightly onto each other, thereby giving rise to the highly compartmentalized and organized structure called chromatin. Gene transcription is controlled by post-translational epigenetic modifications to different 'levels' of chromatin which include methylation of individual cytosine residues on DNA (Fig. 1A), post-translational modifications to histone tails (Fig. 1B), and three dimensional (3D) conformational changes to chromatin within the nucleus (Fig. 2). Sex- and hormone-dependent regulation of epigenetic modifications to each level of chromatin organization have important implications for the brain and behavior which will be reviewed below.

At the simplest level, DNA can be modified by DNA methyltransferases (DNMTs) which covalently add methyl groups to cytosine residues predominantly within cytosine-guanine dinucleotides (CpG, where 'p' refers to their phosphodiester bond; Fig. 1A). DNA methylation typically represses transcriptional activity when it occurs within the promoter region of a gene, although this is not always the case (Chahrour et al., 2008). Methylation recruits corepressor complexes to the DNA, thereby inducing a repressive state by tightly packing heterochromatin which prevents binding of transcription factor complexes necessary for transcription initiation (Tsankova et al., 2007).

At the next level of complexity, individual nucleosome subunits can be epigenetically regulated by modifying their associated histone proteins (Fig. 1B). Histone modifications can alter how accessible DNA is to the transcriptional machinery required for regulating the expression of genes, including those relevant to neuroplasticity and cognition. Histones are primarily modified at the N-terminal portion of their tails that extends beyond the nucleosome. The histone tail can interact with regulatory proteins, as well as neighboring histones and the DNA itself (Marmorstein and Zhou, 2014; Tsankova et al., 2007). Tails can be altered in numerous ways, including acetylation, methylation, ubiquitination, phosphorylation, SUMOylation. Of these, acetylation is the most-well characterized in the neuroepigenetic literature. The positive charges of unmodified histone proteins confer a transcriptionally repressive state because they tightly interact with negatively charged DNA, making transcriptional machinery unable to bind

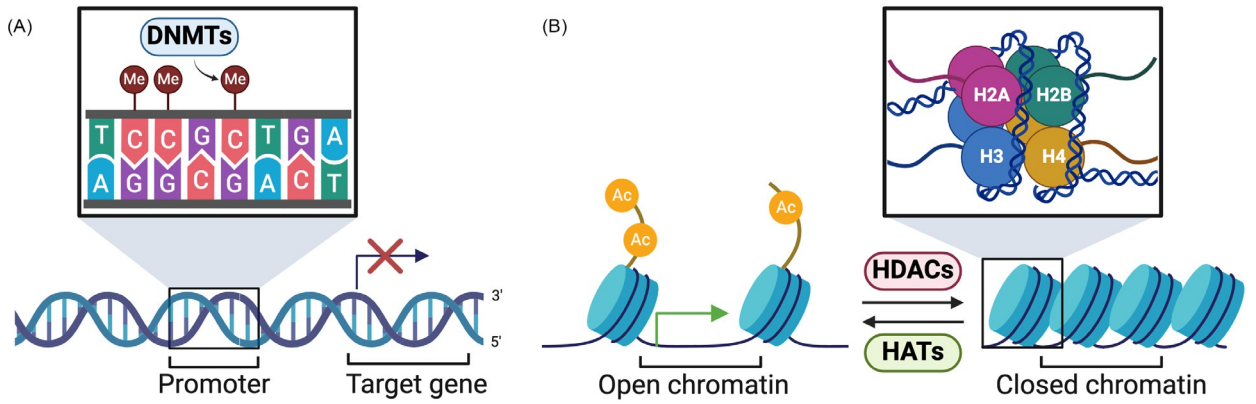

Fig. 1 Diagrammatic illustration of epigenetic modifications to DNA and histones. (A) DNA methylation is catalyzed by DNMT enzymes that covalently add methyl groups to cytosine residues of target genes which typically represses transcription, although this is not always the case. (B) The histone octamer consists of DNA coiled around two each of histones H2A, H2B, H3, and H4. Histone acetylation and deacetylation are mediated by HATs and HDACs, respectively. The N-terminal tails of histone proteins can become acetylated at specific lysine residues by HATs, which open the chromatin and increase accessibility to transcription factors. HDACs remove acetyl groups, thereby increasing chromatin compaction and decreasing transcription. Abbreviations: Me, methyl group; DNMTs, DNA methyltransferases; Ac, acetyl group; HAT, histone acetyltransferase; HDAC, histone deacetylase.

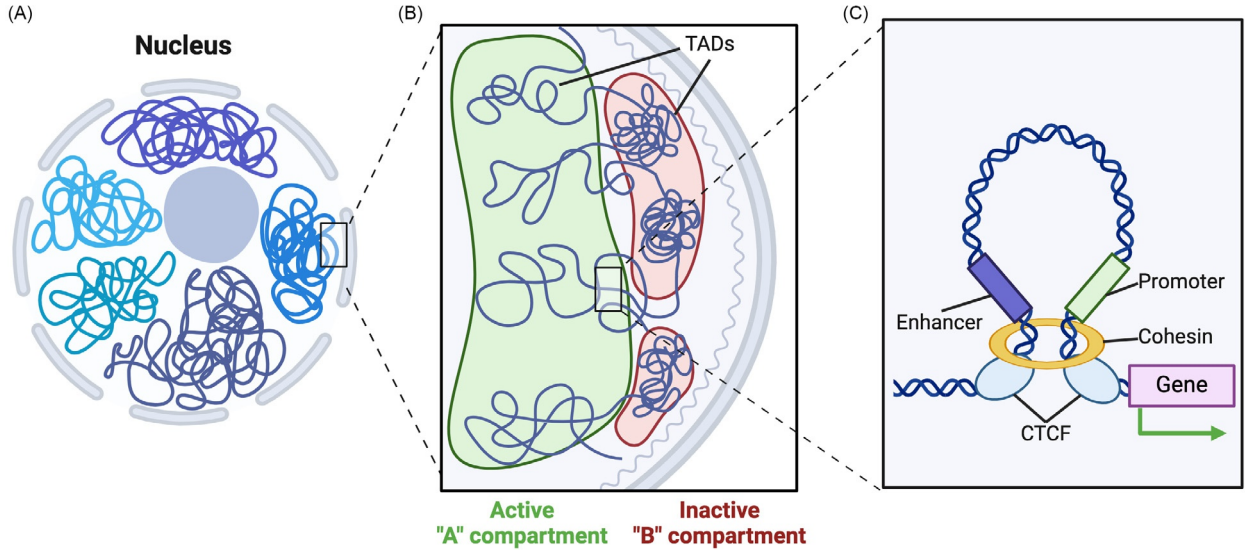

Fig. 2 Levels of chromatin organization within the nucleus. (A) Chromosomes of post-mitotic neurons are organized into chromosome territories within the nucleus. (B) Chromatin is further compartmentalized into transcriptionally active "A" compartments and transcriptionally inactive "B" compartments in the inner nucleus and nuclear periphery, respectively. Within "A" and "B" compartments, chromatin is further clustered into spatially distinct TADs. (C) Within individual TADs, gene expression is regulated by formation of chromatin loops which are maintained by the CTCF-cohesin protein complex. Chromatin looping brings distant enhancers closer to their target promoters, thereby regulating gene expression. Abbreviations: TAD, topologically associating domain; CTCF, CCCTC-binding factor.

(Bannister and Kouzarides, 2011). Histone acetylation is enzymatically controlled by histone acetyltransferases (HATs) and histone deacetylases (HDACs). In most cases, the addition of acetyl groups by HATs weakens the electrostatic affinity between histones and negatively charged DNA, effectively relaxing the chromatin structure and allowing transcription factors to access regulatory regions important for gene expression. Conversely, the removal of acetyl groups by HDACs restores the strong electrostatic affinity between histones and DNA, tightening chromatin structure and effectively repressing gene transcription (Burns and Gräff, 2021). In addition to histone post-translational modifications, histone variants are considered important epigenetic regulators of nucleosome stability because they replace canonical histone proteins in post-mitotic neurons with structurally and functionally distinct variants (Zovkic and Sweatt, 2015).

Gene expression can also be regulated by the 3D hierarchical organization of chromatin within the nucleus (Fig. 2A). Chromosomes of adult differentiated neurons occupy distinct territories within the nucleus giving rise to "A" and "B" compartments that allow for separation of transcriptionally active and inactive chromatin that is located in the inner nucleus and nuclear periphery, respectively (Fujita et al., 2022) (Fig. 2B). Chromatin within these distinct compartments is further organized into

topologically associating domains (TADs) which create chromatin loops that are held together by ring-shaped protein complex cohesin and the zinc-finger binding protein CCCTC-binding factor (CTCF) (Fig. 2C). The formation of chromatin loops brings distant enhancers physically closer to their target promoters which aids in gene transcription (Li et al., 2020). As such, the unique folding and compartmentalization of chromatin gives rise to its 3D conformation within the nucleus. This 3D chromatin remodeling has been implicated in experience-dependent changes in gene expression and cognition (Beagan et al., 2020; Marco et al., 2020; Rajarajan et al., 2016), although much remains to be learned about how 3D chromatin remodeling influences gene expression.

Epigenetic regulation of long-term memory formation

Learning and memory researchers have long been interested in how a brief stimulus can produce lasting effects on behavior. Although decades of study has demonstrated that memory formation requires de novo protein synthesis (Alberini and Kandel, 2014), it remains unclear how memories may persist a lifetime when their supporting proteins turn over in minutes to hours (Crick, 1984). Recent attention has turned to epigenetic changes because of their ability to stably regulate the accessibility of chromatin to transcription factors long after exposure to the initial stimulus (Burns and Gräff, 2021; Marshall and Bredy, 2016; Zovkic et al., 2013). This work has largely examined posttranslational modifications to histones and DNA at loci of memory-relevant genes in male rodents only. However, more recent work including both sexes indicates there are sex differences in epigenetic regulation of genes that regulate memory. As such, the next section will provide an overview of major histone modifications affecting memory and discuss sex differences in epigenetic modifications important for memory formation.

Sex differences in histone post-translational modifications related to memory formation

Histone acetylation

Histone acetylation acts as a transcriptional activator for genes important for memory formation. Histone acetylation in the hippocampus is associated with memory enhancement in a number of tasks including contextual fear conditioning in male rodents (Chwang et al., 2007; Vecsey et al., 2007), fear extinction in male rats (Lattal et al., 2007; Stafford et al., 2012), as well as object recognition in male mice (Korzus et al., 2004; Stefanko et al., 2009). Histone acetylation can occur in response to activation of signal transduction pathways, which is a mechanism that contributes to the precision and stability of a memory. One example is activation of the ERK/MAPK signaling pathway, which stimulates CREB binding protein (CBP), a transcriptional coactivator with intrinsic HAT activity (Vo and Goodman, 2001). Using the conditioned taste aversion paradigm, male mice that developed conditioned taste aversion exhibited increased phosphorylation of the p42 isoform of ERK and elevated HAT activity in the insular cortex 48 h later (Swank and Sweatt, 2001). Similarly, male rats displayed increased H3 acetylation in the hippocampus following contextual fear conditioning, an effect dependent on ERK signaling (Levenson et al., 2004). These findings suggest that rapid cell-signaling activation promotes histone acetylation, which in turn regulates gene transcription and memory.

Furthermore, preventing histone deacetylation with HDAC inhibitors can rescue memory impairments associated with numerous disorders that impair cognition (Gräff and Tsai, 2013). For example, the class I HDAC inhibitor sodium butyrate rescued fear and spatial learning deficits in transgenic male mice with massive forebrain neuronal loss (Fischer et al., 2007). Another seminal study found that male mice overexpressing HDAC2, but not HDAC1, had reduced contextual fear conditioning and impaired spatial memory in the Morris water maze, the former of which was reversed by the HDAC2 inhibitor suberoylanilide hydroxamic acid (SAHA) (Guan et al., 2009). Moreover, this work demonstrated that increased histone acetylation does not occur genome-wide, but rather targets the promoters of genes critical for memory formation. Specifically, the hippocampus of mice with HDAC2, but not HDAC1, conditional deletion had increased H3 and H4 acetylation of memory-relevant genes including *Bdnf*, *Egr1*, *Fos*, and *Creb*, which was accompanied by increased dendritic spine density on CA1 pyramidal neurons (Guan et al., 2009). Later work demonstrated that focal HDAC3 deletions within the male mouse hippocampus enhanced spatial memory in an object location task and increased histone acetylation of H4 lysine 8 (H4K8), which correlated with increased expression of the immediate early gene *c-Fos* in the CA1 (McQuown et al., 2011). Targeted epigenetic editing of the post-synaptic density protein 95 (PSD-95) promoter with an engineered DNA zinc-finger binding domain fused to a transactivator protein increased H3 acetylation in CA1 neurons and rescued spatial and object recognition memory deficits in aged and AβPPswe/PS-1 male mice (Bustos et al., 2017), suggesting that targeted epigenetic editing may be a viable approach for treating memory dysfunction in neurodegenerative disorders. Collectively, these early findings in male rodents were among the first to demonstrate that the opposing actions of histone acetylation and deacetylation are critical forces underlying synaptic plasticity and memory formation.

The relatively scant epigenetic work conducted in female rodents suggests a similarly important role for histone acetylation in hippocampus-dependent learning and memory. Adult female mice lacking the transcriptional co-activator CBP had impaired contextual fear, spatial navigation, and pattern recognition abilities, of which only contextual fear memory was reinstated following environmental enrichment (Lopez-Atalaya et al., 2011). Although previous findings indicate the presence of hormone-driven sex differences in histone acetylation patterns of the developing neonatal mouse brain (Tsai et al., 2009), relatively few studies have examined whether histone acetylation patterns underlie sex-specific behavioral phenotypes in adulthood. One early study found that p300/CBP-associated factor (PCAF) knockout mice had short-term memory deficits in spontaneous alteration, object

recognition, and acquisition of a daily changing platform position in the Morris water maze (Maurice et al., 2008), providing evidence that histone acetyltransferase activity is essential for memory formation in both sexes.

A more recent study investigated the sex-specific epigenetic regulation of cyclin-dependent protein kinase 5 (CDK5) in contextual fear memory retrieval and found that female, but not male, mice displayed reduced freezing responses 24 h after contextual fear conditioning (Sase et al., 2019). Although expression of *Bdnf* promoter IV was increased in both sexes, only males exhibited increased *Cdk5* mRNA and protein in CA1 following long-term fear memory retrieval. Accordingly, the *Cdk5* promoter in CA1 was enriched for the active histone modification H3 lysine 9/14 acetylation (H3K9/14 ac) in males only after contextual fear memory retrieval (Sase et al., 2019), indicating sex-specific epigenetic regulation of *Cdk5*. Interestingly, *Cdk5* expression did not differ between females in the proestrus and estrus phases of the estrous cycle (Sase et al., 2019), suggesting that the lack of retrieval-induced *Cdk5* expression was not due to circulating sex-steroid hormone levels. However, targeted epigenetic editing to acetylate H3K9/14 at the *Cdk5* promoter in CA1 had no effect on long-term memory in male mice but decreased freezing responses in females (Sase et al., 2019), indicating that the lack of expression and acetylation of *Cdk5* following fear memory retrieval may be an endogenous sex-specific mechanism that protects against memory impairments in females. To investigate this possibility, the investigators measured phosphorylation levels of tau, a major downstream target of CDK5, and found that targeted acetylation of *Cdk5* significantly increased phosphorylation of tau in CA1 following fear memory retrieval among females only (Sase et al., 2019). These findings indicate that CDK5 activation in the female, but not male, CA1 is restricted following fear conditioning to prevent activation of downstream targets of CDK5, including phosphorylated tau protein. Although this work suggests interesting sex differences in how histone acetylation influences fear memory, additional studies are needed to elucidate the mechanisms through which basal sex hormone levels, estrous cycle stages, and fear memory retrieval regulate epigenetic activation of CDK5 expression.

Histone methylation

Whereas histone acetylation is associated with a permissive transcriptional state, histone methylation can be transcriptionally permissive or repressive depending on the residue and number of sites methylated. The most commonly examined residue is lysine, which can be mono-(me), di-(me2), or tri-methylated (me3) (Ng et al., 2009). Methyl groups are added to lysine residues by histone lysine methyltransferases, which are specific to the residue they modify, and are removed by histone demethylases (Black et al., 2012). For example, unmethylated lysine 9 on H3 (H3K9) is converted to H3K9me1 and H3K9me2 by the G9a/G9a-like protein (GLP) methyltransferase, but only the MLL methyltransferase can convert H3K4 to H3K4me3 (Jarome and Lubin, 2013). H3K4me3 and H3K9me2, associated with transcriptional activation and repression, respectively, are both increased in the hippocampus following contextual fear conditioning in male mice (Gupta et al., 2010). Male mice deficient in MLL1 and MLL2 exhibit selective impairments in contextual fear memory formation, object recognition, and object placement memories, providing support that H3K4me3 modification is a transcriptionally permissive modification (Gupta et al., 2010; Kerimoglu et al., 2013). A subsequent study demonstrated that contextual fear conditioning increased both active H3K4me3 and repressive H3K9me2 modifications in the entorhinal cortex and CA1, and pharmacological inhibition of G9a/GLP H3K9me2-specific demethyltransferases impaired freezing responses in male rats (Gupta-Agarwal et al., 2012), indicating that learning induces both activation and silencing of genes in the hippocampus during memory consolidation. As with histone acetylation modifications, other work demonstrates that fear conditioning increased levels of the transcriptional repressive mark H3K9me2 in the lateral amygdala of male rats, and the learning-induced increase in H3K9me2 was dependent on GluN2B containing NMDA receptors and ERK signaling (Gupta-Agarwal et al., 2014).

A few studies have examined histone methylation in females, although not directly in relation to memory. One study investigating histone methylation patterns in cortical astrocytes from young adult and middle-aged female rats following stroke demonstrated that middle-aged females, who are more susceptible to ischemia-induced infarct, had reduced H3K4 methyltransferase activity and increased H3K9me3 enriched peaks of genes associated with cell migration, apoptosis, and DNA damage response (Chisholm et al., 2015). These data suggest a reduced transcriptional response in the cortex of middle-aged females following stroke relative to adult females.

Although most studies to date have examined individual histone post-translational modifications at a given gene promoter, an important facet of the histone code is that experience-dependent genes simultaneously contain both active and repressive marks. This allows a gene's expression to be easily switched between on and off states by regulating bivalent histone modifications which can include both active and repressive histone alterations on the same promoter or same histone tail (Carpenter et al., 2020). This notion of histone bivalency allows for a poised state of gene expression and raises questions about how various experiences elicit different epigenomic signatures between sexes. Although no studies to date have examined sex differences in histone bivalency with respect to memory formation, there appear to be sex-specific effects of cocaine on gene expression in brain regions important for drug seeking behavior. For example, expression of the activity-dependent transcription factor, nuclear receptor subfamily 4 group A member 1 (*Nr4a1*), is increased after cocaine exposure in the female, but not male, mouse striatum in the absence of changes in levels of H3K4me3, H3K27me3, and K4&K27 bivalency at the *Nr4a1* promoter (Fischer et al., 2022). This study raises the possibility of sex-specific histone bivalency for memory, which should be addressed in future work.

Histone ubiquitination

An underexplored facet of histone function is how different posttranslational modifications work together to regulate gene expression. Histone ubiquitination is perhaps the least explored histone modification in the brain and a role for this modification in regulating synaptic plasticity and memory formation remains poorly understood. However, emerging evidence suggests that histone ubiquitination may serve as a signal for downstream histone methylation, which together are critical for memory formation. Although histone ubiquitination is regulated by the ubiquitin proteasome system, which normally degrades proteins tagged with multiple ubiquitin modifiers, histones can acquire a single ubiquitin tag that is not degradation-specific (Jarome and Devulapalli, 2018). A recent study found that monoubiquitination of histone H2B at lysine 120 (H2BKubi120) is increased in hippocampal CA1 1 h, but not 24 h, following contextual fear conditioning in both male and female rats (Jarome et al., 2021), providing the first evidence that both sexes upregulate H2B ubiquitination in a learning-dependent manner. However, siRNA-mediated knockdown of the H2B ubiquitin ligase *Rnf20* in CA1 impaired long-term memory and hippocampal long-term potentiation, and prevented the learning-induced increase in H2BKubi120, in males only (Jarome et al., 2021). Surprisingly, *Rnf20* knockdown also prevented active H3K4me3, but not repressive H3K27me3, marks in the CA1 (Jarome et al., 2021), suggesting post-translational modulation crosstalk in which H2BKubi120 recruits H3K4me3 modification in a learning-dependent manner. Increasing the expression of *Rnf20* in neurons using CRISPR-dCas9 plasmids containing a double transcriptional transactivator domain under weak contextual fear training conditions enhanced fear memory in male rats and increased enrichment for both H2BubiK120 and H3K4me3 marks at the *cFos* promoter (Jarome et al., 2021), suggesting that H2BKubi120 modifications bidirectionally regulate fear memory formation in males. To date, this study is the first to define a clear role for histone ubiquitination in hippocampal memory formation, at least in males. Although no sex differences were observed in learning-induced H2BKubi120, further work is needed to determine if females need this histone modification to regulate H3 methylation dynamics and memory formation.

Histone phosphorylation

Histone phosphorylation has been associated with the activation of signaling kinases whose activity promotes memory formation; therefore, blocking histone phosphorylation could disrupt memory formation. Protein serine/threonine phosphatase 1 (PP1), which dephosphorylates proteins, has been implicated in hippocampal memory impairment and reduced plasticity in rodents (Genoux et al., 2002). Mice with inducible deficiency of forebrain PP1 demonstrated enhanced long-term memory in the object recognition, object placement, and Morris water maze tasks, which coincided with increased total phosphorylation of histone H3 on serine 10 (phospho-H3S10) in addition to increased phospho-H3S10 at the CREB promoter (Koshibu et al., 2009). In addition to its role in regulating histone acetylation, ERK/MAPK signaling can also mediate histone phosphorylation. Activation of the upstream ERK/MAPK regulators PKC and PKA increased phospho-H3S10 in the rat hippocampus (Chwang et al., 2006). Further, inhibition of ERK activation prevented phosphorylation of H3S10, suggesting that ERK signaling is necessary for H3S10 phosphorylation and contextual fear memory consolidation (Chwang et al., 2006). Notably, H3S10 and ERK1/2 phosphorylation are also increased in the hippocampus following retrieval of a fear memory (Besnard et al., 2014). Although site-specific dephosphorylation on histone tails has not been demonstrated to cause memory impairment, these studies collectively suggest that histone phosphorylation contributes to memory formation. To date, no studies have examined histone phosphorylation in females alone or in both sexes.

Sex differences in histone variant exchange related to memory formation

In addition to post-translational modifications to canonical histone proteins, replacing canonical histone proteins with functionally and structurally distinct variants can regulate synaptic plasticity and memory formation. In contrast to canonical histones, histone variants are replication-independent, which means they are transcribed and deposited into the nucleosome in a stimulus-dependent manner (Zovkic and Sweatt, 2015). Thus, histone variants are exceptionally well positioned to regulate neural plasticity (Maze et al., 2015). Among the many histone variants identified to date, the H2A variant H2A.Z appears to regulate memory in a sex-specific and hormone-dependent manner, as discussed below.

Zovkic et al. (2014) first demonstrated that contextual fear conditioning in male mice decreased the expression of the H2A.*Z*-encoding gene, *H2afz*, and levels of H2A.Z protein in the CA1 that coincided with increased methylation of the *H2afz* promoter. Chromatin immunoprecipitation analyses in male mice following contextual fear conditioning revealed that H2A.Z binding was reduced near the transcriptional start site of memory-promoting genes, including *Npas4*, *Egr1*, and *Arc*, expression of which were increased in CA1 (Zovkic et al., 2014). Conversely, H2A.Z binding was increased near the transcriptional start site of memory-repressor genes, including *Ppp3ca*, whose expression was decreased after contextual fear conditioning (Zovkic et al., 2014). Moreover, viral-mediated depletion of H2A.Z in CA1 increased freezing 24 h and 30 days later due to increased *Arc* and *Bdnf* exon IV expression (Zovkic et al., 2014). As such, these findings provided the first evidence that H2A.Z is a negative regulator of fear memory formation in male mice and indicate that H2A.Z localizes to both memory activating and suppressor genes in a stimulus-dependent manner.

Subsequent work suggests that males and females differ in their requirement for H2A.Z in aversive and non-aversive forms of long-term memory formation. Using an inducible-conditional H2A.Z knockout mouse (H2A.Z cKO) with selective loss of H2A.Z in

CaMKII-positive cells in CA1, Ramzan et al. (2020) demonstrated that male, but not female, H2A.Z cKO mice had enhanced 24-h contextual fear memory, suggesting sex-specific effects of H2A.Z on fear memory formation. For spatial memory, however, H2A.Z deletion in both sexes increased the amount of time spent with the novel object in an object-in-place spatial memory task (Ramzan et al., 2020), suggesting that the sex-specific effects of H2A.Z may depend on task or type of memory. Nevertheless, H2A.Z deletion had sex-specific effects on plasticity-related gene expression, such that *Arc*, *Gria4*, and *Grin1* expression in CA1 were increased in H2A.Z cKO males, whereas *Bdnf IV* and *Syt 1* expression were increased in H2A.Z cKO females following behavioral testing (Ramzan et al., 2020). The extent to which sex-steroid hormones regulate effects of H2A.Z on aversive and gene expression should be determined in subsequent work.

The mechanisms through which histone variants regulate gene expression mirror that of canonical histone proteins. Histone variants, including H2A.Z, contain tails that can acquire post-translational modifications. A recent study examined the effects on spatial and contextual fear memory formation of mimicking or preventing acetylation of H2A.Z in male and female mice (Reda et al., 2024). Commonly acetylated H2A.Z lysine sites were replaced with glutamine (KQ) to mimic acetylation or alanine (KA) to prevent acetylation, resulting in H2A.Z^{KQ} and H2A.Z^{KA} mutant mice. Spatial memory was assessed with an object location task using either subthreshold or standard training sessions; the subthreshold session consisted of a 5 min training phase in which control mice could not form a long-term memory, whereas the standard session consisted of a 10 min training session that produced intact memory 24 h later. In the subthreshold session, both male and female acetyl-mimic H2A.Z^{KQ} mutant mice spent more time with the moved object (Reda et al., 2024), suggesting that H2A.Z acetylation helps both sexes consolidate weak memories. In contrast, memory was not enhanced in H2A.Z^{KQ} male and female mice under standard training conditions (Reda et al., 2024), suggesting no benefit of H2A.Z acetylation under normal training conditions. However, acetyl-defective H2A.Z^{KA} male and female mice had impaired spatial memory under standard conditions, indicating that H2A.Z in its unmodified form negatively regulates spatial memory, which is consistent with previous work (Ramzan et al., 2020). For contextual fear conditioning, acetyl-defective H2A.Z^{KA} females, but not males, exhibited impaired fear memory assessed using a weak training protocol. Interestingly, however, H2A.Z^{KA} male mice displayed impaired contextual fear memory following a stronger training protocol (Reda et al., 2024). Collectively, this work suggests that sex, type of memory, and training strength influence the role of H2A.Z in regulating memory formation.

Histone variants accumulate in the aging brain (Maze et al., 2015; Stefanelli et al., 2018), which is important given the increased risks to women of age- and menopause-related memory dysfunction, including Alzheimer's disease. As such, there is considerable interest in targeting histone variants that negatively affect memory formation to prevent the memory dysfunction associated with aging and neurodegenerative disorders. For example, in a 5xFAD mouse model of AD, H2A.Z binding in the hippocampus is increased at memory-relevant genes among 5xFAD females, whereas overall H2A.Z binding is decreased in 5xFAD males (Creighton et al., 2023). Interestingly, viral-mediated H2A.Z depletion in the hippocampus of 5xFAD females, but not males, prevented memory impairments in object location and contextual fear tasks, suggesting that increasing H2A.Z binding may be a promising therapeutic avenue for treating memory decline in females.

Estrous cycle-dependent regulation of chromatin

The estrous cycle is the 4–5-day reproductive cycle for rodents and consists of four hormonally distinct phases: proestrus, estrus, metestrus and diestrus (Frick, 2015). Proestrus is characterized by high levels of estrogens and low levels of progesterone, whereas diestrus is associated with low levels of estrogens and high levels of progesterone. The proestrus and diestrus phases of the estrous cycle mimic the follicular and luteal phases of the human menstrual cycle, respectively. As such, the hormonally distinct proestrus and diestrus phases of the rodent estrous cycle represent distinctly opposing hormonal milieus in which investigators can study the effects of fluctuating hormone levels on behavior and epigenetic control of gene expression under naturally cycling contexts (Rocks et al., 2022a). In support of the seminal studies documenting changes in spine number and type during proestrus (Gould et al., 1990; Woolley et al., 1990; Woolley and McEwen, 1992, 1993), recent advances in sequencing methods support the notion of hormone-induced fluctuations in hippocampal chromatin accessibility and 3D chromatin organization throughout the rodent estrous cycle (Jaric et al., 2019; Kundakovic and Tickerhoof, 2024; Rocks et al., 2022a; Rocks and Kundakovic, 2023).

One recent landmark study was the first to identify sex hormone-induced epigenomic programming that occur over days of the natural reproductive cycle in post-mitotic neurons of female brain. They first demonstrated that adult female mice in diestrus, but not proestrus females or males, exhibited increased anxiety-like behavior in the open field, light-dark box, and elevated plus maze tasks (Jaric et al., 2019). To determine the extent to which chromatin reorganization may play a role in this anxiety-like phenotype, assay for transposase-accessible chromatin (ATAC-seq) was conducted on purified neuronal nuclei from ventral hippocampus. Chromatin accessibility differed by 32% in proestrus and diestrus females (Jaric et al., 2019), suggesting that chromatin undergoes significant reorganization across the few days of the estrous cycle. Moreover, the genes accessible during proestrus were predominantly involved in regulating synaptic transmission, membrane potential, and neurite organization (Jaric et al., 2019), suggesting that the genes expressed during proestrus may protect against anxiety-like behavior by facilitating synaptic plasticity. Interestingly, expression of the immediate early gene *Egr1* was also increased in proestrus, and proestrus-specific genes with *Egr1* binding sites included those involved in MAPK signaling, calcium signaling, and neurotrophin signaling (Jaric et al., 2019), all of which are crucial for neuroplasticity.

The high degree of chromatin reorganization observed throughout the estrous cycle prompted investigators to next examine the extent to which ovarian hormones regulate higher-order reorganization of 3D chromatin adult ventral hippocampal neurons. To this end, Rocks et al. (2022b) used an unbiased chromatin conformation capture (Hi-C) method to assay genome-wide chromatin interactions across estrous cycle and sex at three different levels of chromatin organization, including measuring active and inactive chromosome compartments, CTCF chromatin loops, and enhancer-promoter interactions. Their findings indicate that the compartmentalization of the X chromosome in proestrus females was more similar to that of males than diestrus females, as were inter-chromosomal interactions on the X chromosome and neuronal enhancer-promoter interactions, suggesting that elevated sex steroid hormone levels in female mice shift the interaction profile of the X chromosome towards that of males (Rocks et al., 2022b). Although the functional outcomes of these changes remain unclear, these data provide further support for the notion that gene expression is dynamically regulated in females across the estrous cycle (Jaric et al., 2019). Moreover, adult ovariectomized mice treated with a single subcutaneous injection of estradiol benzoate displayed changes in X chromosome compartmentalization, CTCF loops, and enhancer-promoter interactions that closely resembled the 3D organization of proestrus females (Rocks et al., 2022b), strongly suggesting that E_2 is the catalyst for changes to 3D genome reorganization in naturally cycling females.

Together, recent studies of 3D chromatin organization demonstrate that ovarian-derived sex steroid hormones are important epigenomic regulators that alter chromatin accessibility and higher-order 3D organization in adult post-mitotic neurons. Although the studies did not directly relate these changes to memory, their approach to examining how cyclic hormone fluctuations and exogenous estradiol influence complex chromatin organization and behavior is an important model for future studies.

Estrogenic regulation of epigenetic modifications and its effects on long-term memory

E_2 and hippocampal function

In both sexes, dorsal hippocampus (DH) infusion or systemic injection of E_2 facilitates consolidation of multiple hippocampus-dependent memories, including spatial, object recognition, fear, and social memories (Fleischer and Frick, 2023; Sheppard et al., 2019; Taxier et al., 2020). The E_2-induced enhancements in hippocampus-dependent memories are driven in part by E_2's rapid ability to increase total spine number and mushroom-type spines in the CA1 (Inagaki et al., 2012; Kim et al., 2019; Mukai et al., 2007; Tuscher et al., 2016). Although the canonical intracellular estrogen receptors (ERs), ERα and ERβ, are known for exerting their classical genomic effects in the nucleus (Bean et al., 2014), they are also abundantly expressed throughout all segments of hippocampal neurons, including axon terminals, dendrites, and dendritic spines (Milner et al., 2001, 2005), where they are positioned near the plasma membrane to interact with metabotropic glutamate receptors to rapidly activate intracellular signaling pathways on the order of seconds to minutes (Mitterling et al., 2010).

Rapid activation of cell-signaling cascades allows for acute modulation of cellular function in response to learning. E_2 infusion directly into the DH rapidly activates cell-signaling cascades including ERK/MAPK, PI3K, PKA, and mTOR within 5 min, and pharmacological inhibition of these kinases prevents E_2 from enhancing spatial and object recognition memory consolidation and spine density in ovariectomized female mice (Fan et al., 2010; Fernandez et al., 2008; Fortress et al., 2013; Tuscher et al., 2016). Among the cellular effects of E_2-induced cell signaling is regulation of gene expression in the nucleus through ultimate activation of transcription factors. The following sections will discuss work from our laboratory demonstrating the ways in which exogenous E_2 infusion to the DH of ovariectomized female mice regulates epigenetic modifications in the DH essential for memory consolidation, which are summarized in Fig. 3.

E_2, histone acetylation, and DNA methylation

As discussed above, several studies in the 2000s demonstrated that H3 acetylation levels in male mice were increased in the hippocampus by learning in the contextual fear conditioning and object recognition tasks (Korzus et al., 2004; Levenson et al., 2004; Stefanko et al., 2009). Moreover, evidence at the time indicated that learning-induced increases in H3 acetylation depended on phosphorylation of the p42 isoform of ERK in the hippocampus (Levenson et al., 2004). As such, our laboratory reasoned that E_2 might enhance object recognition memory by triggering ERK-mediated histone acetylation. Indeed, post-training DH infusion of E_2 enhanced object recognition memory and increased p42 ERK phosphorylation within 5 min, as well as increased levels of H3K14 and H3K9/14, but not H4, acetylation in the DH within 30 min. Moreover, DH infusion of the ERK phosphorylation inhibitor U0126 blocked E_2-induced increases in H3 acetylation levels 30 min later (Zhao et al., 2010), suggesting that ERK activation regulates E_2's effects on histone acetylation. Subsequent work demonstrated that DH infusion of the HAT inhibitor garcinol blocked E_2-induced enhancements in object recognition memory, as well as H3K9/14, but not H2BK12 or H4K12, acetylation in the DH 30 min later (Zhao et al., 2012). Consistent with the E_2-induced increase in H3 acetylation levels, levels of HDAC2 protein in the DH were decreased 4 h following DH E_2 infusion relative to vehicle-treated controls (Zhao et al., 2010), and DH garcinol infusion prevented the E_2-induced increase in HDAC2 4 h later (Zhao et al., 2012), suggesting that HAT activity regulates expression of this memory-repressing HDAC. These findings collectively indicate that E_2 regulates object recognition memory consolidation in ovariectomized female mice by increasing H3 acetylation levels and decreasing expression of HDAC2 protein. These data are also consistent with other observations that E_2 regulates synaptic plasticity and memory formation by upregulating expression of memory-relevant genes (Finney et al., 2020; Frick, 2015; Kovács et al., 2020; Sheppard et al., 2019).

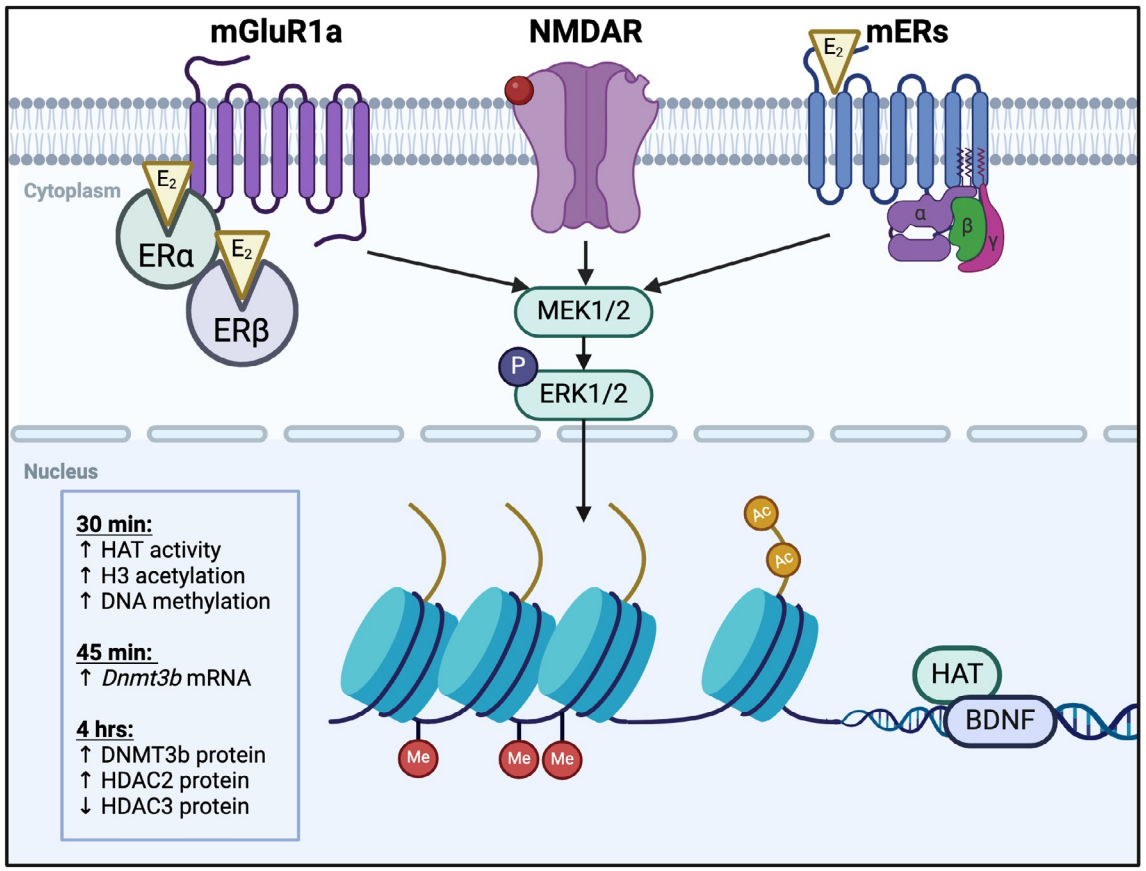

Fig. 3 Schematic representation of the cellular mechanisms through which E_2 regulates memory in ovariectomized mice. In the dorsal hippocampus, E_2 interacts with intracellular ERs (ERα and ERβ), mERs, and neurotransmitter receptors to rapidly increase ERK phosphorylation. ERK can enhance gene transcription via alterations in H3 acetylation, HDAC protein levels, and DNA methylation. These changes all contribute to the memory-enhancing effects of acute dorsal hippocampal E_2 infusion on memory consolidation. Abbreviations: ER, estrogen receptor; ERK, extracellular signal-regulated kinase; MEK1/2, MAPK kinase; NMDAR, *N*-methyl-D-aspartate receptor; mGluR, metabotropic glutamate receptor; mER, membrane estrogen receptor, H3, histone 3; HDAC, histone deacetylase; BDNF, brain derived neurotrophic factor.

Coincident with our examination of E_2 effects on histone acetylation, we also demonstrated that infusion of E_2 into the DH significantly increased expression in the DH of mRNA for de novo DNA methyltransferases (DNMTs) *Dnmt3a* and *Dnmt3b*, but not *Dnmt1*, within 45 min, which was consistent with increased levels of DNMT3a and DNMT3b, but not DNMT1, protein 3 and 4 h later, respectively (Zhao et al., 2010). Bilateral DH infusion of the DNMT inhibitor 5-aza-2deoxycytidine (5-AZA) prevented E_2-induced enhancements in object recognition memory consolidation 48 h later when it was administered immediately, but not 3 h after, training (Zhao et al., 2010). These findings suggest that E_2 preferentially increases expression of enzymes that catalyze de novo methylation of previously unmethylated cytosine residues in the DH, and that this methylation is necessary for the memory-enhancing effects of E_2. Interestingly, our follow-up study in ovariectomized female mice showed that DH infusion of the HAT inhibitor garcinol prevented E_2-induced increases in DNMT3b, but not DNMT3a or DNMT1, protein 4 h later (Zhao et al., 2012), suggesting a key role for histone acetylation in the E_2-induced regulation of de novo DNA methylation. Taken together, these findings suggest that both histone acetylation and de novo DNA methylation are necessary in the DH of ovariectomized female mice for E_2 to enhance object recognition memory consolidation within a 3-h window after training. However, the specific E_2-induced alterations in methylated DNA that influence memory remain unknown, which is an area ripe for future study.

Similarly, many of the specific gene targets affected by E_2-mediated H3 acetylation remain to be defined, although genes involved in neuroplasticity are likely candidates. One such example is the neurotrophin brain derived neurotrophic factor (BDNF), which has an established role in regulating spine density, synaptic plasticity, and memory (Luine and Frankfurt, 2013; Spencer et al., 2008). To explore this possibility, we showed that E_2 infusion into the DH specifically increases H3 acetylation at *Bdnf* promoters pII and pIV 30 min after infusion in both young and middle-aged ovariectomized mice (Fortress et al., 2014). The E_2-induced increase in H3 acetylation at pII and pIV preceded a significant increase in BDNF and pro-BDNF protein levels that occurred in the DH 4 and 6 h after infusion (Fortress et al., 2014). Thus, one potential mechanism through which E_2 exerts its beneficial effects on

memory is via epigenetic regulation of BDNF in the hippocampus. However, many genes are involved in memory formation, so additional research is needed to elucidate how histone alterations may impact the expression of other genes that contribute to the beneficial effects of E_2 on memory.

Epigenetic alterations and memory in low estrogen conditions

The evidence discussed thus far suggests that E_2 can regulate the epigenome in ovariectomized females to modulate consolidation of object recognition memories. However, it is important to note that ovariectomy eliminates endogenous ovarian hormone fluctuations that may influence how endogenous circulating estrogens regulate the epigenome to shape long-term memory formation. In one such study, Maddox et al. (2018) examined DNA methylation of *HDAC4* in serum from women with post-traumatic stress disorder (PTSD) and in mice exposed to a fear-inducing tone-shock pairing. They first showed that women with PTSD had increased methylation of *HDAC4*, greater fear responsivity, and greater functional coupling between the amygdala and cingulate cortex than controls (Maddox et al., 2018). They next determined the extent to which estrogen levels might regulate *HDAC4* expression in response to tone-shock fear conditioning among naturally cycling and ovariectomized female mice implanted with silastic capsules containing vehicle or E_2. In naturally cycling females, tone-shock presentations were associated with increased *Hdac4* expression in the basolateral amygdala (BLA) in metestrus (low estrogen), but not proestrus, females relative to metestrus homecage controls (Maddox et al., 2018). In ovariectomized mice, tone-shock presentations increased *Hdac4* expression in vehicle-treated, but not E_2-treated, females relative to vehicle-treated homecage controls (Maddox et al., 2018). Together, these data suggest that fear-inducing stimuli can increase methylation of *HDAC4* in the amygdala and point to low estrogenic tone at the time of fear exposure as permissive of this increase, which could elevate risk of PTSD in women.

Using a pharmacological approach to manipulate histone acetylation under low circulating estrogen conditions, another group investigated the extent to which quercetin, a natural dietary compound known to activate HATs and repress HDACs in cancer cells, alleviates memory deficits and regulates chromatin remodeling in ovariectomized female mice. They found that daily oral quercetin treatment rescued ovariectomy-induced impairments in spatial memory and object recognition (Aggarwal et al., 2020). Quercetin also reversed ovariectomy-induced decreases in global levels of H3K9/14 acetylation and H3 acetylation of the *Bdnf* promoters *II* and *IV*, *cFos*, *synaptophysin*, and *Psd-95*, as well as increases in expression of HDAC2 and HDAC3 protein in the hippocampus and cortex. Although the mechanism of action of quercetin remains unclear, these findings provide additional support to the notion that removing circulating estrogens negatively affects cognition and increases epigenetic marks that are associated with silencing gene transcription.

Gaps in knowledge and implications for future studies

Understanding the mechanisms through which ovarian hormones like E_2 can orchestrate epigenetic processes to regulate memory is important for understanding cognitive function in conditions of both health and disease. At this point, the study of these mechanisms remains in its infancy. As our understanding of chromatin biology grows, so does our list of questions about the ways in which E_2 regulates epigenetic processes to promote memory formation. For example, to what extent does exogenous E_2 regulate higher-order chromatin organization on its own, and following learning, to regulate memory formation mediated by the hippocampus and other cognitive brain regions? Through what cell-signaling mechanisms does E_2 regulate the myriad histone posttranslational modifications, histone cross-talk, and histone variant exchange? And importantly, which critical memory-related genes are epigenetically regulated by E_2? Understanding which epigenetic modifications are regulated by E_2 and the downstream transcriptional and translational consequences of these modifications will be vital next steps for the field.

This chapter also discussed ways in which sex differences in behavior arise from sex-specific epigenetic regulation of gene expression in the brain. Although we are only beginning to understand how epigenetic signaling differs between the sexes to produce behavioral phenotypes, the extent to which these sex differences are driven by hormone status remain unclear. Determining the functional implications of estrogenic regulation of neuroepigenetics will be imperative to better understanding the etiology of neurological diseases and improving the design of future drugs for reducing memory dysfunction in both sexes.

Summary

The past four decades of research has provided exciting new information about the molecular mechanisms underlying memory formation and dysfunction. In particular, neuroepigenetic studies have illuminated the complexities of gene regulation and revealed a multitude of ways in which epigenetic processes can alter behavior without changing the genetic code. Combined with behavioral neuroendocrinology, neuroepigenetics is advancing our understanding of how hormones regulate the epigenetic processes that influence behavior. Such regulation could explain how environmental, chromosomal, and psychological factors determine individual responses to specific situations. Although information on E_2-mediated epigenetic alterations in the brain remains limited, there is ample potential to explore how sex-steroid hormones modulate behavior and disease in numerous brain regions with implications across a spectrum of disorders. This work is sure to open many new avenues for development of next generation neurotherapeutics.

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Conflict of interest disclosure

Dr. Frick is a co-founder and the Chief Scientific Officer of Estrigenix Therapeutics, Inc., a company which aims to improve women's health by developing safe, clinically proven treatments for the mental and physical effects of menopause. The other authors have no conflicts of interest to disclose.

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