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

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ABSTRACT

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

1. Introduction

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

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

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

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

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

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

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

2.1. Background

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

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