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


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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 and criticized, with some arguing that sex should be considered as a biological variable only when it can be shown to have a significant impact on outcomes [3]. Additional time and money are required to include both sexes in research studies, which can strain already limited grant budgets in a time of unprecedented funding competition. Forcing researchers without 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 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
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 life-
spans [12,13]. According to recent reports from the Alzheimer’s Asso-
ciation, 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 sig-
nificant hormonal alterations, including dramatic increases in gona-
dotropin secretion and decreases in circulating estrogen and progesterin
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 Alzhei-
mer’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 rever-
sing memory loss in older women has not borne fruit. For example,
treatment with conjugated equine estrogens, with or without an ac-
companying synthetic progestin, does not maintain or improve cogni-
tive function in post-menopausal women over age 65, and in fact, can
be detrimental to cognitive function in this population [22,23]. More-
over, 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 (E2), appears to have no adverse e-
cfects 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 ovariec-tomy lasting throughout middle age
diminishes the beneficial effects of E2 on hippocampal synaptic plastici-
ty and hippocampal-dependent memory [28–30]. As such, de-
termining how estrogens affect brain function and why the brain’s re-
 sponsiveness 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 est-
rogens 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 E2 can be found endogenously in the hippocampus
of both male and female rats [33,34]. Thus, numerous pieces of evi-
dence suggest that E2 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
E2 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 interven-
tions for men and women. As discussed below, future work must ex-
amine potential sex differences at the cellular and molecular level to
determine if distinct sex-specific mechanisms underlie phenotypic dif-
f erences.

In this vein, our laboratory has spent the past decade identifying
molecular mechanisms in the hippocampus through which E2 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 E2 influences memory formation in an
optimally functioning system. We believe that these data from young
subjects can then provide the foundation for determining how E2, 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
E2 may regulate memory consolidation in young males as well, and
have found potentially interesting sex differences that support the no-
tion that E2 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 di-
rections that illustrate the importance of hippocampally-synthesized E2
and interactions between the hippocampus and prefrontal cortex. The
remainder of the review will discuss work from our lab and others
describing effects of E2 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 E2 regulates memory
consolidation in female mice

2.1. Background

Our laboratory’s work on this subject has focused on the hippo-
campus 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 E2. For example, acute E2 treat-
m ent 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 hippo-
campal infusion [54–58]. E2 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 E2-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 E2 on memory con-
solidation.

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