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The Impact of Age-Related Ovarian Hormone Loss on Cognitive and Neural Function

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Abstract On average, women now live one-third of their lives after menopause. Because menopause has been associated with an increased risk of dementia, an increasing body of research has studied the effects of reproductive senescence on cognitive function. Compelling evidence from humans, nonhuman primates, and rodents suggests that ovarian sex-steroid hormones can have rapid and profound effects on memory, attention, and executive function, and on regions of the brain that mediate these processes, such as the hippocampus and prefrontal cortex. This chapter will provide an overview of studies in humans, nonhuman primates, and rodents that examine the effects of ovarian hormone loss and hormone replacement on cognitive functions mediated by the hippocampus and prefrontal cortex. For humans and each animal model, we outline the effects of aging on reproductive function, describe how ovarian hormones (primarily estrogens) modulate hippocampal and prefrontal physiology, and discuss the effects of both reproductive aging and hormone treatment on cognitive function. Although this review will show that much has been learned about the effects of reproductive senescence on cognition, many critical questions remain for future investigation.

Keywords Estradiol · Hippocampus · Prefrontal cortex · Memory · Menopause · Aging

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The female reproductive system is a complex network in which interactions between ovarian and neural processes are crucial for the expression of behaviors related to sexual maturation, procreation, mood, and cognition. Like other organ systems in the body, the reproductive system is vulnerable to the ravages of aging. However, the impact of aging on the reproductive system of females is unique due to its inevitable failure during middle age. Understanding the influence of reproductive senescence in females on biological and psychological processes is of mounting importance given the ever-increasing amount of time that women now live beyond menopause. In 2006, the average life expectancy of women in the United States was 80.2 years and is estimated to increase to nearly 82 years in the next decade (United States Census Bureau 2008; United States National Center for Health Statistics 2009). Yet the average age of menopause onset has remained stable, and thus, women are spending significantly more of their lifetimes in a state of reproductive senescence.

The impact of this prolonged period of ovarian hormone deprivation on peripheral organs and tissues (e.g., heart, breast, uterus, and bone) has long been studied. However, research in the past two decades has revealed that ovarian sex-steroid hormones, such as estrogens and progestagens, can also rapidly and profoundly affect parts of the brain critical for cognitive function, such as the hippocampus and prefrontal cortex [for review, see (Sherwin and Henry 2008)]. As such, a growing literature has assessed the effects of ovarian hormone loss and replacement on cognitive processes such as learning and memory. Much of this literature stems from the two most common animal models of reproductive senescence, nonhuman primates and rodents (rats and mice). These species are attractive model systems because of their short lifespans, similarities to humans in the effects of aging and sex-steroid hormones on cognitive function, and the ability to conduct invasive studies that permit examination of neural function at the cellular and molecular levels. Therefore, the goal of this chapter is to review the literature on reproductive senescence as it pertains to humans, nonhuman primates, and rodents. Because extensive reviews have been published recently for these species (e.g., see (Dumitriu et al. 2010; Frick 2009; Lacreuse 2006; Sherwin and Henry 2008; Voytko et al. 2009), this chapter will provide a brief overview of the most seminal findings published in recent years. The chapter will conclude by discussing future avenues for research.

1 Background

Estrogens, such as estrone, estriol, and the potent 17β-estradiol (termed "estradiol" or "E_2"), are synthesized and secreted in both males and females, albeit, at higher levels in females. In females, estrogen synthesis begins in the theca interna cells of the ovaries, where cholesterol is first converted into pregnenolone (Farkash et al. 1986). Acting mostly as a prohormone, pregnenolone is the precursor for both progesterone and androstenedione. The enzyme aromatase then converts androstenedione and testosterone into estrogens including estrone and E_2 (Brodie et al. 1976). In addition to the ovaries, recent evidence demonstrates that estrogens and progesterone are also synthesized in small quantities in the brain (Hojo et al. 2004; Kretz et al. 2004).

Once synthesized, estrogens are released into the bloodstream where they can bind to intracellular ligand-activated transcription factors, termed estrogen receptor α (ERα) and β (ERβ) (Koike et al. 1987; Spreafico et al. 1992; Tremblay et al. 1997). Binding at or near the cell nucleus to ERα and ERβ initiates the traditional "genomic" actions of estrogens, whereby the hormone–receptor complex binds to an estrogen response element on the DNA and serves as a nuclear transcription factor. Both ERs are expressed in brain regions critical for cognitive function, thereby providing an opportunity for estrogens to modulate multiple cognitive processes. For example, ERα and ERβ are both expressed in the dorsal and ventral hippocampus, where they are primarily found in CA1 and CA3 pyramidal neurons (Shughrue and Merchenthaler 2000). Both ERs are also expressed in the cerebral cortex, basal forebrain, and amygdala (Milner et al. 2005, 2001; Osterlund et al. 2000; Shughrue et al. 1997). In the cortex, ERβ is expressed in greater abundance than ERα, especially within frontal, parietal, and entorhinal cortices (Osterlund et al. 2000; Shughrue et al. 1997). Basal forebrain cholinergic neurons projecting to the hippocampus and neocortex also express both ERα and ERβ, although ERα is predominant (Shughrue et al. 2000). Although their nuclear localization suggests a relatively slow genomic mechanism of action, both ERs have been identified at extranuclear sites within the hippocampus, including dendritic spines, axons and axon terminals (Milner et al. 2005, 2001), where they may be involved in rapid effects of estrogens on cell signaling and epigenetic mechanisms (Fernandez et al. 2008; Zhao et al. 2010).

The vulnerability of the hippocampus and prefrontal cortex to aging and Alzheimer's disease (deToledo-Morrell et al. 2007; Driscoll and Sutherland 2005) has driven the fledgling field of hormones and cognition to focus primarily on these brain regions. The hippocampus is a bilateral medial temporal lobe structure critical for memories involving spatial, relational, and contextual information, and is necessary only for consolidation of such memories, not their long-term storage (Eichenbaum 1997, 2002; Squire 1992). As detailed in the sections below, E_2-induced alterations in the hippocampus have been most often observed in the CA1 subregion, the dentate gyrus, and to a lesser extent, the CA3 subregion. The prefrontal cortex, particularly the dorsolateral prefrontal cortex, is also

critically necessary for memory, particularly a form of short-term memory called working memory (Goldman-Rakic 1992). However, the prefrontal cortex is thought to subserve a broader array of cognitive processes than the hippocampus, including attention, executive function (e.g., planning, judgment, mental flexibility, and verbal fluency), source memory, and episodic memory (Kandel et al. 2000). Despite the prevalence of deficits in both memory and executive functioning in the elderly (Woodruff-Pak 1997), the majority of studies on the neurobiological effects of hormone loss in rodents have focused on the hippocampus, in part because the preponderance of early studies were conducted in the hippocampus. As such, the rodent section below will focus primarily on hippocampal morphology and hippocampal-dependent memory. However, prefrontal function has long been of interest to human and nonhuman primate researchers, and so considerably more information on prefrontal function is available for primates than for rodents. Thus, hormonal effects on both prefrontal and hippocampal function will be discussed in the human and nonhuman primate sections.

2 Humans

As the human female ages, the reproductive system undergoes a plethora of changes that eventually lead to the cessation of reproductive abilities known as the menopause. The gradual transition to menopause occurs at approximately age 51 and can last anywhere from 2 to 7 years, with the most notable changes being amenorrhea, significant decreases in ovarian hormone levels, and ultimate ovarian failure (Bellantoni and Blackman 1996). The menopausal transition requires a highly orchestrated series of events within the Hypothalamic–Pituitary–Ovarian axis that include changes in both the brain (e.g., elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels secreted by the pituitary) and ovaries (e.g., depletion of ovarian follicles and resultant drop in circulating ovarian estrogen concentrations) (Bellantoni and Blackman 1996). Because these events occur over the course of several years, the menopausal transition is generally divided into three phases based on the regularity and occurrence of the menses (Soules et al. 2001). The late reproductive years (often referred to as "premenopause") are characterized by regular menstrual cycles and an enduring increase in FSH that lasts for the remainder of a woman's life (Soules et al. 2001). Perimenopause, which can be divided into early and late stages, is defined by variable cycle lengths, skipped cycles, and at least one period of ammenorhea lasting over 60 days (Soules et al. 2001). Finally, postmenopause is characterized by the complete cessation of menses for at least 12 months (Gold et al. 2000; Soules et al. 2001). The dramatic decline of circulating ovarian hormones, which is a defining characteristic of reproductive senescence, is theorized to be the driving factor behind the apparent decline in cognitive functioning that is observed in postmenopausal women.

Anecdotally and in the laboratory, perimenopausal and postmenopausal women report more difficulties with memory and concentration than premenopausal

women (Amore et al. 2007; Gold et al. 2000). Women are also three times more likely to develop Alzheimer's disease than men (Yaffe et al. 1998). Nevertheless, relatively few studies have examined the effects of reproductive senescence on brain and cognitive function; these studies are far outnumbered by those testing the effects of hormone replacement in postmenopausal women. The comparatively slim literature associating menopausal status or E_2 levels with cognition and brain function in women may stem from methodological challenges, including difficulties in accurately assessing menopausal status and measuring circulating E_2 in older women (Barrett-Connor and Laughlin 2009). With regard to brain function, a recent functional neuroimaging study reported that perimenopausal women (mean age 47.5 yrs) with moderate to severe menopausal symptoms (e.g., hot flashes) have reduced cerebral blood flow in the medial prefrontal cortex compared to age-matched asymptomatic controls (Abe et al. 2006). Also of note are post-mortem data showing that nuclear ERα expression, aromatase expression, and neuronal metabolic activity in the hippocampus are significantly higher in postmenopausal women (mean age 72.8 yrs) relative to pre- and perimenopausal women (Ishunina and Swaab 2007). This increase could arise if the drop in ovarian hormone levels triggers an increase in de novo estrogen production that up-regulates nuclear ERα expression (Ishunina et al. 2007). The possibility that increased E_2 levels negatively impact cognitive function in aging is supported by another study of postmenopausal women (mean age 70 yrs) in which higher total E_2 levels were associated with smaller hippocampal volumes and worse verbal memory (den Heijer et al. 2003). This result suggests that in older women, an up-regulation of E_2 synthesis and ERα expression may be detrimental to cognitive functioning.

Cross-sectional data on menopausal status suggest detrimental effects of menopause on executive functioning tasks such as mental flexibility, planning and reaction time (Elsabagh et al. 2007; Halbreich et al. 1995). However, no effects on verbal fluency, spatial ability, and episodic memory were reported in these studies (Elsabagh et al. 2007; Halbreich et al. 1995; Herlitz et al. 2007; Thilers et al. 2010). In contrast, longitudinal studies indicate that perimenopause is associated with reduced verbal fluency (Fuh et al. 2006) and postmenopause with impaired verbal fluency and visuospatial abilities (Thilers et al. 2010). Interestingly, this last study reported a significant interaction between menopausal status and body mass index (BMI), such that overweight postmenopausal women exhibited less cognitive decline than those with normal BMIs (Thilers et al. 2010). Serum E_2 levels were also positively correlated with BMI (Thilers et al. 2010), suggesting an association between lower E_2 levels and a faster rate of verbal and visuospatial decline. This relationship is consistent with findings showing that women with higher total or bioavailable E_2 levels exhibit better global cognitive function, verbal memory, executive function, and a lower risk of mild cognitive impairment and Alzheimer's disease than those with lower levels [(Drake et al. 2000; Lebrun et al. 2005; Wolf and Kirschbaum 2002; Yaffe et al. 2000; Zandi et al. 2002); but see (Barrett-Connor et al. 1999; den Heijer et al. 2003; Herlitz et al. 2007; Laughlin et al. 2010)]. Notably, the only study to examine a substantially biracial population found that both African-American and Caucasian women with low

bioavailable E_2 levels were 2–3 times more likely to exhibit verbal memory impairments and global cognitive decline than those with high E_2 levels (Yaffe et al. 2007). Collectively, these findings provide some support for the notion that the menopausal transition is associated with cognitive dysfunction.

Perhaps the most convincing argument for the role of ovarian hormones in maintaining cognitive function (particularly verbal memory) in women comes from studies of women who underwent bilateral oophorectomy for benign disease prior to menopause. In an influential series of studies, women who were treated with E_2 immediately after surgery maintained performance on tests of verbal memory, whereas those receiving placebo experienced significant verbal memory decline (Phillips and Sherwin 1992; Sherwin 1988). In contrast, visuospatial abilities were not affected by treatment, suggesting an effect specific to verbal learning and memory. Despite this specificity, these findings, as well as data from animal models demonstrating potent effects of E_2 on hippocampal synaptic plasticity, neuroproliferation, and neuroprotection [reviewed in (Spencer et al. 2008; Wise et al. 2001)], initially provided robust support for the notion that the loss of ovarian hormones at menopause renders cognitive regions of the brain more vulnerable to the detrimental effects of aging. This work subsequently stimulated numerous investigations into the effects of hormone therapy (both estrogens alone or estrogens plus a progestin) on cognitive function in menopausal women.

Observational and longitudinal studies in postmenopausal women generally suggest that estrogen use after surgical or natural menopause is beneficial for cognitive function. In observational studies, estrogen use has been associated with better verbal fluency (Hogervorst et al. 1999), verbal memory (Kampen and Sherwin 1994; Maki et al. 2001), working memory (Duff and Hampson 2000), and visuospatial function (Duka et al. 2000). Similar findings have been reported in longitudinal studies (Grodstein et al. 2000; Matthews et al. 1999; Steffens et al. 1999). Hormone therapy has also been associated with a lower risk of dementia (LeBlanc et al. 2001), although this decreased risk is most evident among women who initiated hormone therapy during or soon after the menopause (Yaffe et al. 1998).

Data from randomized clinical trials have been mixed, with those testing the effects of E_2 in recently menopausal women reporting beneficial effects of treatment on verbal and working memory [e.g., (Joffe et al. 2006; Phillips and Sherwin 1992; Viscoli et al. 2005; Wolf et al. 1999)], and those testing effects of conjugated equine estrogens in older postmenopausal women generally reporting no effect or detrimental effects of treatment on global cognitive decline and verbal memory [e.g. (Barrett-Connor and Kritz-Silverstein 1993; Binder et al. 2001; Grady et al. 2002; Janowsky et al. 2000; LeBlanc et al. 2007); reviewed in (Maki 2005; Sherwin and Henry 2008)]. In particular, data from the Women's Health Initiative Memory Study (WHIMS), the largest randomized clinical trial of the commonly prescribed conjugated equine estrogens, demonstrate that estrogen (with or without a synthetic progestin) significantly increases the risk of global cognitive decline and dementia in postmenopausal women over age 65 (Espeland et al. 2004; Rapp et al. 2003b; Shumaker et al. 2004). A follow-up study from the WHI Study of Cognitive Aging (WHISCA) reported that treatment impaired verbal memory and had no effects on

tests of attention, working memory, spatial ability, affect, or depression (Resnick et al. 2009a; Resnick et al. 2006). A subsequent neuroimaging study of WHIMS subjects found that estrogen treatment was associated with smaller hippocampal, frontal cortex, and total brain volumes (Resnick et al. 2009b). This finding is inconsistent with several smaller studies that show a positive association between estrogen use and volumes of the hippocampus and cortical regions (Berent-Spillson et al. 2010; Boccardi et al. 2006; Eberling et al. 2003; Lord et al. 2008), but are in keeping with findings that postmenopausal women with naturally higher levels of E_2 had smaller hippocampi and worse verbal memory (den Heijer et al. 2003). Although the large sample size of the WHI provides greater statistical power than the smaller studies demonstrating a positive relationship between estrogen use and hippocampal volumes, a number of design flaws limit the generalizability of the WHI findings as has been discussed elsewhere (Maki 2006; Sherwin and Henry 2008), including the type of hormone treatment used and an older subject population at high risk for cardiovascular and cerebrovascular disease.

Despite the apparent inconsistencies in the clinical literature, several important principles about hormone treatment have begun to emerge from these studies. First, treatment is most effective for younger women. For both cognitive and neural function, the data support a limited window of opportunity in which treatment during a "critical period" at or near the onset of menopause protects against cognitive decline, whereas treatment several years after menopause is ineffective or detrimental to cognitive health (Erickson et al. 2010; Maki 2006; Sherwin and Henry 2008). Data from nonhuman primates and rodents also support the existence of a critical period for estrogen treatment (Frick 2009; Sherwin and Henry 2008). Second, E_2 may be a more effective treatment than conjugated equine estrogens, as suggested by several randomized clinical trials (Joffe et al. 2006; Phillips and Sherwin 1992; Viscoli et al. 2005; Wolf et al. 1999). Third, clinical trials of hormone therapies are susceptible to a "healthy user bias" due to the fact that women who initiate hormone therapy are generally healthier and more educated than women who do not elect treatment (Keating et al. 1999; Matthews et al. 1996). As such, this bias must be considered when interpreting data and generalizing to a broader population. Finally, too little is known about how factors like timing of treatment (cyclic vs. continuous) and addition of progestagens influence the effectiveness of hormone therapy, so addressing these issues will be critical in future clinical studies.

3 Nonhuman Primates

Nonhuman primates, such as rhesus monkeys (*Macaca mulatta*) and cynomolgus monkeys (*Macaca fascicularis*), are the most common model systems for the study of reproductive aging. Similar to humans, female macaques exhibit a 28 day menstrual cycle and experience ovarian hormone fluctuations comparable to human women (Gilardi et al. 1997; Goodman et al. 1977; Knobil and Neill 1988). Further, menopause in macaque females is very similar to that of women

(Gilardi et al. 1997), although the post-menopausal life of these monkeys is much shorter, given that the onset of menopause occurs after age 25 in species with lifespans of around 30 (Tigges et al. 1988). As in humans, the transition to reproductive senescence involves multiple parallel processes, including increasing irregularity of the menstrual cycle, depletion of the follicular reserves, decreased levels of circulating estrogen, and elevated levels of FSH, LH, and gonadotrophin releasing hormone (GnRH) (Downs and Urbanski 2006; Gore et al. 2004). Given these multiple commonalities, macaque females are an excellent model system to examine the effects of reproductive senescence and hormone therapy on cognitive and neural function. However, monkey research is limited by the high cost and low availability of animals, particularly postmenopausal females (Bellino and Wise 2003). Thus, much of the work examining effects of reproductive aging on the brain has been conducted in younger ovariectomized monkeys. Nevertheless, studies in young and aging macaque monkeys provide a valuable glimpse into how reproductive senescence may affect human women, and serve to bridge the gap between rodent models and human clinical studies.

E_2 can profoundly affect the hippocampus and prefrontal cortex of both young and aging female macaques. Cyclic E_2 treatment increased the number of CA1 dendritic spines by over 1 billion in both young (6–8 yrs) and aged (19–23 yrs) ovariectomized rhesus monkeys (Hao et al. 2003), suggesting a similar responsiveness to E_2 in the young and aged primate brain. In 7–15 year-old ovariectomized rhesus monkeys, chronic E_2 treatment increased the expression in CA1 of pre- and post-synaptic proteins such as syntaxin, synaptophysin, and spinophilin (Choi et al. 2003). However, progesterone blocked these changes, suggesting that progesterone interferes with the positive effects of E_2 on hippocampal synapses. Interestingly, progesterone alone increased the expression of synaptophysin only (Choi et al. 2003), indicating that each hormone may be beneficial to synaptic spine morphology alone, but detrimental in combination. However, according to a recent study in adult (7–14.5 yrs) ovariectomized rhesus monkeys, the combination of both hormones may be beneficial for hippocampal neurogenesis because chronic treatment with E_2 alone or E_2 plus progesterone tended to increase neurogenesis in the dentate gyrus (Kordower et al. 2010). Together, these findings support the notion that E_2 can positively regulate hippocampal morphology in both young and aging female monkeys.

An increasing body of work has shown similar effects of E_2 on the prefrontal cortex. Indeed, long-term cyclic treatment of young and aged ovariectomized rhesus monkeys significantly increases relative to vehicle both apical and basal dendritic spine density, number and morphology within layer III pyramidal cells of area 46 in the prefrontal cortex (Hao et al. 2007; Hao et al. 2006; Tang et al. 2004). This effect has been demonstrated in behaviorally characterized aged monkeys who exhibited improved performance in a prefrontal cortex-dependent spatial-delayed response task (Rapp et al. 2003a), suggesting that E_2-induced increases in prefrontal spine density may lead to enhanced prefrontal-dependent memory in aged females. This conclusion is supported by a recent paper demonstrating a positive correlation in these same monkeys between ERα expression in the

postsynaptic densities of prefrontal excitatory synapses and memory in the delayed response task (Wang et al. 2008).

Other studies in aged rhesus females have also revealed positive effects of ovarian hormones on cognitive processes mediated by the prefrontal cortex. The only study to examine gonadally intact females found that peri-/post-menopausal monkeys (20–27 years) performed significantly worse on the spatial-delayed response task than age-matched premenopausal monkeys and young monkeys (Roberts et al. 1997). Interestingly, different investigators using a battery of spatial and non-spatial memory tasks found that aged rhesus females (19–27 years) who had been ovariectomized for 12 years were better than age-matched intact females on spatial delayed response, but impaired on a delayed non-match to sample task (Lacreuse et al. 2000). The effects of E_2 treatment on naturally menopausal monkeys have not yet been tested, but several studies have examined the effects of E_2 treatment on surgically menopausal monkeys and report beneficial effects of E_2 on tasks mediated by the prefrontal cortex. For example, in aged rhesus monkeys ovariectomized 7–13 years prior to treatment, E_2 improved working memory in the spatial-delayed response task (Rapp et al. 2003a) and spatial-delayed recognition span test (Lacreuse et al. 2002), in some cases to the level of young monkeys (Rapp et al. 2003a). The benefits of E_2 treatment on working memory tasks, even 13 years after ovariectomy, suggests that the aged prefrontal cortex remains sufficiently responsive to E_2 that memory function can be enhanced even after periods of prolonged ovarian hormone deprivation (Lacreuse 2006). However, these studies found that the E_2-induced improvement did not extend to other processes mediated by the prefrontal cortex, as delayed non-matching-to-sample, object discrimination, and Wisconsin Card Sort tests showed no or moderate improvement after treatment (Lacreuse et al. 2004, 2002; Rapp et al. 2003a). Interestingly, studies by Voytko and colleagues of aged cynomolgous monkeys have shown that E_2 can enhance several of these prefrontal-dependent abilities including visuospatial attention, visual recognition memory, and executive function (Voytko 2000, 2002, 2008). The Voytko (2002) laboratory has also shown that E_2 interacts with the basal forebrain cholinergic system to affect attention, but not memory. The discrepancies among the macaque studies in the effects of E_2 on specific prefrontal-dependent tasks may be due to methodological issues or differences between rhesus and cynomolgous monkeys. Nevertheless, the monkey data collectively demonstrate that E_2 can reverse ovariectomy-induced cognitive dysfunction in aged females, and may benefit several cognitive domains including memory, attention, and executive functioning.

4 Rodents

Rats (*Rattus norvegicus*) and mice (*Mus musculus*) are the most common animal models used to study the effects of hormones on cognition because of their compact size, short life spans, and abundant supply. For studies of cognitive aging,

rats and mice are typically considered "aged" at approximately 2 years, "middle-aged" at approximately 16–18 months, and "young" at approximately 3–4 months (Frick 2009). Rodents do not exhibit a true menstrual cycle, as they lack a luteal phase and uterine wall sloughing (Wise 2000). Instead, they undergo 4–5 day-long estrous cycles that feature surges of estradiol and progesterone just prior to ovulation (McCarthy and Becker 2002). Further, rodents experience significant changes in their regular reproductive cycle with aging. Although they do not experience complete follicle loss (Wise 2000) and maintain relatively normal gonadotrophin levels (Wise 2000), reproductive senescence in rodents is similar to menopause in several respects, including increases in FSH, LH, and estradiol levels, variability of cycle length prior to acyclicity, and ultimate cessation of hormone cycling (LeFevre and McClintock 1988; Nelson et al. 1995). In rats, reproductive decline begins at 9–12 months of age, with 70% of 12-month-olds exhibiting irregular cycles or acyclicity, and nearly 75% of females acyclic by 24 months (Markowska 1999). In mice, alterations begin at 13–14 months of age (Nelson et al. 1995), with 80% of 17-month-olds exhibiting irregular cycles or acyclicity, and all females acyclic by 25 months (Frick et al. 2000).

As in humans and nonhuman primates, memory decline has been associated with the loss of reproductive cycling in both rats and mice. This relationship has been particularly well described for spatial memory tested in the Morris water maze, which declines at an earlier age in females than in males. Significant deficits in females are observed by 12 months in rats and 17 months in mice, whereas such deficits are not apparent in male rats until 18 months and in male mice until 25 months (Frick et al. 2000; Markowska 1999). Moreover, the onset of this premature spatial memory decline in females coincides with the cessation of ovarian hormone cycling, as illustrated by the fact that the age at which spatial memory deficits first appear in both species is marked by a sharp decline in regular estrous cycling (Frick et al. 2000; Markowska 1999). Further, performance among 12–24-month-old rats in a daily probe trial was best in regularly cycling females, intermediate in irregularly cycling females, and worst in acyclic females (Markowska 1999), suggesting that the disruption of estrous cycling is detrimental to spatial memory throughout the aging process.

The age-related cognitive decline accompanying the loss of estrous cycling in rodents has most often been attributed to reduced estradiol levels in the hippocampus. In the hippocampus of young rodents, E_2 increases CA1 dendritic spine density (Woolley and McEwen, 1992; Woolley and McEwen, 1993), enhances long-term potentiation (Warren et al., 1995; Foy et al., 1999), increases neurogenesis (Tanapat et al., 1999), and rapidly activates cell signaling cascades including extracellular signal-regulated kinase/mitogen activated protein kinase (ERK/MAPK) and protein kinase A (PKA) (Fernandez et al. 2008; Lewis et al. 2008a). E_2 also enhances the function of hippocampal- and cortically-projecting cholinergic neurons (e.g. Gibbs and Aggarwal, 1998a; Wu et al., 1999; Gibbs 2000), which are involved in attention and cortical information processing, as well as some aspects of learning and memory (e.g. Bartus et al., 1985; Baxter and Chiba, 1999; Berger-Sweeney et al., 2000). However, the effects of E_2 in the aging

hippocampus are not identical to that of young females, perhaps due to reduced hippocampal expression of ERα and ERβ in aged females (Yamaguchi-Shima and Yuri 2007). For example, E_2 in aged females does not increase dendritic spine density in hippocampal CA1, but does increase density in the dentate gyrus (Adams et al. 2001; Miranda et al. 1999). Other studies have shown that the hippocampus of aging female rodents remains generally responsive to E_2, which can increase hippocampal levels of synaptophysin and nerve growth factor, augment dentate gyrus dendritic spine density, activate protein kinases, normalize intracellular calcium homeostasis, and phosphorylate NMDA receptors in aging females (Bi et al. 2003; Fernandez and Frick 2004; Foster 2005; Frick et al. 2002; Miranda et al. 1999). Of these changes, E_2-induced increases in hippocampal synaptophysin protein levels in aged female mice have been associated with improved spatial memory (Frick et al. 2002).

A growing literature has examined the effects of E_2, and to a lesser extent progesterone, on hippocampal-dependent memory in aging rats and mice. To date, E_2 treatments of varying dose, duration, route of administration, and timing relative to testing have improved memory in middle-aged or aged rodents tested in tasks of spatial reference memory, spatial working memory, and object recognition [reviewed in (Frick 2009)]. However, several key factors appear to contribute to treatment effectiveness in rodents. Age at treatment may be a key variable, as several studies that compared the effects of E_2 in rodents of multiple ages report memory improvements in middle-aged, but not aged, ovariectomized females (Gresack et al. 2007; Savonenko and Markowska 2003; Talboom et al. 2008). The duration of hormone loss prior to treatment also appears to be a particularly critical factor; long delays in treatment after ovariectomy in aging females impair basal forebrain cholinergic functioning (Gibbs 1998) and reduce E_2's ability to improve spatial memory (Daniel et al. 2006; Gibbs 2000; Markowska and Savonenko 2002). Collectively, these data support the "critical period hypothesis" of estrogen action originally proposed to explain why hormone therapy in women appears to work best when initiated near menopause (Maki 2006). The origins of this critical period may lie in biochemical alterations in the aged brain, as suggested by a recent study from our laboratory which found that the ability of E_2 to enhance object memory consolidation in young and middle-aged ovariectomized mice was associated with its ability to activate cell signaling cascades that are critical for long-term memory formation; in aged mice, E_2 had no effect on memory or cell signaling (Fan et al. 2010).

Beyond the critical period, the rodent literature has begun to shed light on other important issues, like whether cyclic or continuous hormone administration is most effective, whether treatment should include a progestogen, and whether certain populations might benefit more from treatment than others (Frick 2009). With regard to this last point, we recently showed that exposure to a cognitively and physically enriching environment can reduce the mnemonic benefits of E_2 in young and middle-aged female mice (Gresack and Frick 2004; Gresack et al. 2007). Such data are consistent with clinical data suggesting that estrogen therapy may be most effective in women with less education (Matthews et al. 1999). Data

on the effects of progesterone are inconsistent, with several studies reporting that it blocks the beneficial effects of E_2 on spatial memory in aging females (Bimonte-Nelson et al. 2006; Harburger et al. 2007), and others reporting no such interference (Gibbs 2000; Markham et al. 2002). When given alone, acute progesterone treatment can improve spatial and object recognition memory in aged female mice (Lewis et al. 2008b).

The relative ease and flexibility of the rodent model has also allowed for the development and testing of alternatives to traditional hormone therapy, such as selective estrogen receptor modulators (SERMs). SERMs are non-steroidal compounds that act as estrogen agonists in some tissues and antagonists in others. The most commonly tested SERMs include tamoxifen, raloxifene, phytoestrogens, and ICI 182,780. Although these SERMs exhibit neuroprotective properties in vitro, none have consistently improved memory in women or rodent models (Frick 2009; Zhao et al. 2005). Drugs selective for ERα or ERβ have been developed and are currently being tested in rodents; thus far, ERβ agonism appears to most consistently improve hippocampal memory in young rats and mice (Frick et al. 2010; Walf et al. 2006), but none of these agonist compounds have yet been tested in aging females. An alternative to further refining SERMs is to elucidate the molecular mechanisms underlying memory-enhancing effects of hormones and then develop drugs that target those mechanisms. Our laboratory has published a series of studies in this regard, demonstrating that E_2-induced alterations of cell signaling, epigenetic mechanisms, and gene expression are necessary for this hormone to enhance object memory consolidation in young and middle-aged ovariectomized mice (Fan et al. 2010; Fernandez et al. 2008; Frick 2009; Zhao et al. 2010). In particular, E_2-induced activation of ERK/MAPK signaling, histone acetylation, and DNA methylation are especially critical. As such, these mechanisms may be useful targets to which non-steroidal drugs can be designed that mimic the beneficial effects of E_2. Because these drugs would modulate the downstream effectors of estrogen receptors, rather than the receptors themselves, this approach may prove useful in providing treatments that can safely and effectively reduce age-related memory decline in women.

5 Conclusions

The past 20 years has seen an explosion of research on the roles of hormones on cognition, and much progress has been made. As the studies discussed above illustrate, there is considerable evidence in humans, nonhuman primates, and rodents that the age-related loss of ovarian hormones, particularly estrogens, is detrimental for cognitive function. Although this work has yielded many important insights, much more needs to be done to gain a more complete understanding of how these hormones affect cognition in aging females. For example, research on naturally reproductively senescent women and animals is sorely lacking, thereby limiting conclusions about the impact of reproductive aging on cognition. Further,

clinical trials such as the WHI have raised critical questions about how and when hormone therapy should be administered, and who should receive treatment. Future research on hormone therapy should be directed toward better assessing the efficacy of various treatments on specific cognitive functions in women, pinpointing the best age to begin and length of time to conduct treatment, understanding the role of progestagens in modulating cognitive functions, and identifying specific populations of women (e.g., less well educated) that might benefit the most from treatment. Many of these issues can be addressed relatively easily in rodent and primate models as a first step.

As the numbers of menopausal and postmenopausal women skyrocket in the coming years, addressing these issues will become of paramount importance. The health risks associated with commonly prescribed conjugated equine estrogens, such as increases in breast cancer, heart disease, and stroke (Rossouw et al. 2002), also warrant the accelerated development of alternative approaches to hormone replacement, including SERMs and other treatments that target the molecular mechanisms underlying hormonal modulation of cognitive function (Frick 2009; Frick et al. 2010). The groundbreaking empirical research of the past 20 years has laid the foundation for the next generation of promising breakthroughs in the science of hormones and cognition, which will hopefully lead to a better understanding of the impact of reproductive senescence on cognition and more effective hormone treatments for the prevention of age-related cognitive decline.

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