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EFFECTS OF OVARIAN HORMONES ON COGNITIVE FUNCTION IN NONHUMAN PRIMATES

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Abstract—Several studies have suggested that estrogen benefits verbal memory and lowers the risk of Alzheimer's disease in women, and improves cognitive function in animal models. However, the negative outcome of the Women's Health Initiative Memory Study has challenged the rationale for using estrogen as a protective agent against age-related cognitive decline. In view of the limitations of the Women's Health Initiative Memory Study, it is clear that our understanding of estrogen effects would greatly benefit from further interactions between clinical and basic science. Animal models of menopause can provide crucial information regarding the consequences of estrogen loss and replacement on several systems, including cognition.

In this paper, I review the evidence that nonhuman primates, who share numerous cognitive and physiological characteristics with humans, can substantially contribute to our understanding of estrogen influences on the brain and cognition. Studies in young adult females suggest that some aspects of cognition fluctuate with the menstrual cycle, but that ovariectomy and estrogen replacement have only modest effects on cognitive function. In contrast, data in aged, naturally or surgically menopausal monkeys indicate that estrogen modulates a broad range of cognitive domains. Neurobiological data are consistent with the cognitive findings and demonstrate an array of morphological and physiological changes in brain areas important for cognition following ovariectomy and/or estrogen replacement. It is concluded that nonhuman primates, by providing a bridge between rodent and human data, constitute invaluable models to further our understanding of hormonal actions on the brain and cognition and to develop effective hormonal interventions against brain and cognitive aging.

Key words: brain, estrogen, learning, memory, menopause, monkey.

Cognitive impairment is one of the most devastating consequences of old age. It has been estimated that nearly 10% of the total US population aged 70 and over is affected by moderate to severe cognitive impairment. This estimate increases to 35% at ages 90 and older (Suthers et al., 2003). With life expectancy steadily rising, preventing or slowing the development of normal and pathological age-related cognitive decline has become a pressing need for public health. Estrogen has been proposed as a potential agent against age-related cognitive decline in women. The rationale for using estrogen replacement therapy (ERT) to slow or even prevent cognitive decline in women stems from the idea that the dramatic decrease in circulating ovarian hormones that accompanies menopause may accelerate age-related cognitive decline (Halbreich et al., 1995) and increase vulnerability to dementia (Paganini-Hill and Henderson, 1994). Although specific mechanisms by which estrogens could affect cognition remain to be elucidated, it is clear that estrogens have broad effects on brain regions important for cognitive function (reviewed in McEwen and Alves, 1999). Estrogen receptors are found in the cerebral cortex, hippocampus and amygdala (in monkeys: Blurton-Jones et al., 1999; Gundlah et al., 2000; in humans: Osterlund et al., 2000; in rats: Shughrue and Merchenthaler, 2000), and estrogens alter neuronal morphology and physiology in some of these areas (in monkeys: Hao et al., 2003; Leranth et al., 2002; Tang et al., 2004; in rats: Tanapat et al., 1999; Woolley, 1999). In addition, estrogens have a number of neurotrophic and neuroprotective effects against a broad range of toxic stimuli (reviewed in Brinton, 2001; Gandy, 1999; Green and Simpkins, 2000; Maggi et al., 2004; Wise, 2003).

Many studies have shown beneficial effects of ERT on some aspects of cognition, especially verbal memory in older nondemented women (reviewed in Hogervorst et al., 2000; LeBlanc et al., 2001; Maki et al., 2001; Sherwin, 2003; Yaffe et al., 1998). In addition, ERT has been reported to lower the risk of developing Alzheimer's disease or delay the onset of the disease (Tang et al., 1996; Zandi et al., 2002), but is ineffective in women already diagnosed with the disease (Henderson et al., 2000; Mulnard et al., 2000). In parallel with these clinical data, animal studies have provided compelling evidence that estrogens influence cognition. In numerous studies, most of them using rats or mice in spatial tasks, estrogen-treated animals exhibit enhanced learning and/or memory compared with non-treated controls (reviewed in Dohanich, 2002; Gibbs and Gabor, 2003).

These findings are in striking contrast with the results of the first large randomized study conducted in women, the Women's Health Initiative Memory Study (WHIMS). The WHIMS reported that women over 65 years old taking an hormonal preparation of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) over a 5 year period had a small increased risk of cognitive decline

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Abbreviations: CEE, conjugated equine estrogens; chAT, choline acetyltransferase; DMS, delayed matching-to-sample; DNMS, delayed non-matching-to-sample; DPLC, dorsolateral prefrontal cortex; DR, delayed response; DRST, delayed recognition span test; ERT, estrogen replacement therapy; fMRI, functional magnetic resonance imaging; MPA, medroxyprogesterone acetate; OVX, ovariectomy; PET, positron emission tomography; WHIMS, Women's Health Initiative Memory Study.

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(Rapp et al., 2003b) and increased risk of dementia (Shumaker et al., 2003) on the modified Mini Mental State Examination, a dementia screening test, compared with women taking a placebo. The estrogen-only arm of the study reached similar conclusions (Espeland et al., 2004). Since then, WHIMS has received much criticism for its biases and confounds and for its failure to take into account data from basic and animal studies in the study design and methodology (Asthana and Middleton, 2004; Gibbs and Gabor, 2003; Sherwin, 2005; Turgeon et al., 2004). In particular, the specific hormonal preparation used, the use of a rather insensitive memory test, the old age of the study population and the timing of hormonal replacement with regard to the onset of menopause, have been evoked as potential explanations for the failure of WHIMS to find beneficial effects of estrogen on cognition. The goal of the present review is not to repeat these criticisms, but rather to emphasize the value of animal models for understanding the fundamental mechanisms of hormonal action and for the development and refinement of hormonal interventions. It is argued that nonhuman primates, because of their close proximity to humans in terms of cognitive, endocrine and brain function, are useful models to address pressing questions concerning hormonal effects on the brain and cognition.

Nonhuman primate models of menopause

The female rat remains the animal model of choice for studying the effects of estrogen on learning and memory, in spite of significant differences between human and rodent endocrine function. Unlike human menopause, the rat estropause, which is largely ovarian independent, is not accompanied by a dramatic loss of estrogens, but is characterized by irregular cyclicity of various length after which females enter either a phase of persistent estrus (moderate levels of ovarian hormones) or pseudopregnancy/persistent diestrus (high levels of progesterone; Huang and Meites, 1975). Thus, rather than considering the rat as a model for menopause per se, studies in rats attempt to elucidate the fundamental mechanisms underlying estrogen effects on the brain and behavior. Considerable insights, both from a cognitive and neurobiological perspective, have been gathered from this model (e.g. Gibbs and Gabor, 2003; McEwen and Alves, 1999).

However, nonhuman primates, because of their similarity to humans both in terms of endocrine physiology and cognitive function provide additional advantages for the study of estrogen effects on brain function. Macaques, such as rhesus monkeys (*Macaca mulatta*) or cynomolgus monkeys (*Macaca fascicularis*) are the species phylogenetically closest to humans in which it is practical to conduct neurobiological and cognitive studies. These species can perform a variety of cognitive tasks in settings comparable to those used with humans (Voytko and Tinkler, 2004), and display patterns of brain (reviewed in Hof and Duan, 2001; Peters, 2002) and cognitive aging that closely resemble those of humans (reviewed in Albert and Moss, 1996; Gallagher and Rapp, 1997; Herndon and Lacreuse, 2002; Roberts, 2002; Voytko and Tinkler, 2004). In addition, the endocrine physiology of the female macaque is very similar to that of the woman with regard to both the menstrual cycle (Knobil and Hotchkiss, 1988) and menopause (Gilardi et al., 1997; Walker, 1995). For both women and female rhesus monkeys, the normal 28-day menstrual cycle consists of two main phases. Starting with day one of the menses, the first 14 days constitute the follicular phase in which progesterone levels are low and estradiol levels become progressively high to reach a peak at the time of ovulation (ovulatory phase). The second half of the cycle is the luteal phase, characterized by high levels of progesterone. In women, a second peak of estradiol occurs during the midluteal phase of the cycle, but luteal estradiol levels remain low in the female rhesus monkey. Menopausal profiles in the female rhesus monkey are similar to those of women, with estradiol levels falling to very low levels (Gilardi et al., 1997; Gore et al., 2004). Yet, rhesus monkeys have a short postmenopausal life, as menopause occurs after 25 years old in a species that rarely survives past 30 (Tigges et al., 1988).

Because of these similarities to humans in cognitive, neural and endocrine characteristics, studies in macaques offer great promise in the investigation of the effects of hormonal interventions on the brain and cognition. Nevertheless, there is also a series of drawbacks associated with this model, including seasonal cessation of reproductive function during summer months, short menopausal life compared with women, limited availability of aged animals, and high cost relative to rodents (Bellino and Wise, 2003). Therefore, studies in monkeys typically involve a limited number of animals and use pre-menopausal ovariectomized monkeys rather than naturally menopausal aged monkeys. Despite these shortcomings, much can be learned from the monkey model. This model can complement data gathered from the rat to effectively bridge basic research and human clinical studies. The evidence that ovarian hormones affect cognitive function in monkey models is reviewed below and summarized in Table 1.

Studies in intact females

Human studies have provided inconsistent data concerning the effects of the menstrual cycle on cognitive function. On one hand, several studies have reported higher verbal fluency, but poorer spatial skills during periods of high estrogen levels, and improved spatial skills and lower verbal skills when estrogen levels are low (Broverman et al., 1981; Hampson, 1990a,b; Hampson and Kimura, 1988; Hausmann et al., 2000; Phillips and Silverman, 1997; Silverman and Phillips, 1993). However, these results have not been consistently confirmed (reviewed by Epting and Overman, 1998). The use of different methodologies across studies and the lack of precise measures to identify the phase of the cycle may explain, at least in part, discrepancies in the literature.

There are very limited data on the effect of the menstrual cycle and cognitive function in the monkey. In one experiment (Lacreuse et al., 2001), we tested four young intact female rhesus monkeys across one menstrual cycle on two memory tasks dependent on medial temporal lobe