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Research Report

Factors influencing the cognitive and neural effects of hormone treatment during aging in a rodent model ☆

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ABSTRACT

Whether hormone treatment alters brain structure or has beneficial effects on cognition during aging has recently become a topic of debate. Although previous research has indicated that hormone treatment benefits memory in menopausal women, several newer studies have shown no effect or detrimental effects. These inconsistencies emphasize the need to evaluate the role of hormones in protecting against age-related cognitive decline in an animal model. Importantly, many studies investigating the effects of estrogen and progesterone on cognition and related brain regions have used young adult animals, which respond differently than aged animals. However, when only the studies that have examined the effects of hormone treatment in an aging model are reviewed, there are still varied behavioral and neural outcomes. This article reviews some of the important factors that can influence the behavioral and neural outcomes of hormone treatment including the type of estrogen administered, whether or not estrogen is combined with progesterone and if so, the type of progesterone used, as well as the route, mode, and length of treatment. How these factors influence cognitive outcomes highlights the importance of study design and avoiding generalizations from a small number of studies.

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1. Introduction

Aging in human females is accompanied by a cessation of the menstrual cycle, known as menopause, which usually occurs between 45 and 55 years of age and results from a depletion of ovarian follicles. The depletion in follicles leads to increased follicle-stimulating hormone and luteinizing hormone levels and a dramatic decrease in estrogen and progesterone levels. Because of the decrease in ovarian hormones, menopause is associated with several symptoms including vaginal dryness, bone loss, and hot flashes. In addition, lower levels of naturally occurring estradiol (E_2) correlated with poorer performance on a verbal task in middle-aged females (Wolf and Kirschbaum, 2002), indicating that the decline in ovarian

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hormones may also play a part in the cognitive decline observed during aging.

Hormone therapies, including Premarin (conjugated equine estrogens; CEE) and Prempro (CEE in combination with medroxyprogesterone acetate; MPA), have been approved to alleviate the symptoms of menopause. Moreover, studies have found beneficial effects of estradiol treatment on several cognitive tasks including measures of verbal and working memory (Joffe et al., 2006; Krug et al., 2006; LeBlanc et al., 2001). However, results from the Women's Health Initiative (WHI) indicate that CEE alone or CEE administered with MPA results in an increased risk of stroke and dementia (Anderson et al., 2004; Shumaker et al., 2004; Wassertheil-Smoller et al., 2003). Because of this, whether hormone treatment has beneficial effects on cognition during aging has recently become a topic of debate.

This review aims to discuss the factors that are known to influence the cognitive outcome of hormone treatment and will focus on the rodent literature. What is known about how these factors influence neural mechanisms important for cognition will also be reviewed. As discussed in the sections below, the length of hormone deprivation and the age of the subjects tested are known to alter behavioral outcomes, and therefore this review will focus on studies that have treated middle-aged or aged females.

2. Length of hormone deprivation

There is evidence that the length of hormone deprivation influences the outcome of hormone treatment and may partially explain the negative findings of the WHI studies (Daniel and Bohacek, 2010; Gibbs, 2000; Sherwin, 2009). This research has indicated that there is a "window of opportunity", which means that waiting too long after menopause, or estropause in rats, to begin hormone treatment could lead to the treatment having no effect or negative effects on cognition. In WHIMS, the memory study of the WHI, the ages of the subjects ranged from 65 to 79 years which may have been too late to initiate hormone treatment in order to have beneficial effects on cognition. Animal studies have provided support for the "window of opportunity" with the length of hormone deprivation affecting both behavioral and neural outcomes. In a study by Gibbs (2000), animals treated with E_2 or E_2 in combination with progesterone immediately following ovariectomy or within three months of ovariectomy performed significantly better than ovariectomized controls on a delayed matching to sample task. This difference in performance did not occur when hormone treatment was initiated 10 months after ovariectomy (Gibbs, 2000). Furthermore, females ovariectomized at 12 months of age and immediately treated with E_2 performed better than controls on the radial arm maze when tested after 5 months of treatment (Daniel et al., 2006). In contrast, females that were ovariectomized at 12 months of age but not treated with E_2 until 17 months of age did not perform better than ovariectomized controls (Daniel et al., 2006).

Ovarian hormones affect neuroanatomy in cognitive brain regions including the hippocampus and prefrontal cortex, and not surprisingly the factors that influence behavioral outcome also influence neuroanatomy. Recent work found that E_2 treatment within 15 months of ovariectomy increased dendritic spine density in the hippocampus whereas treatment initiated after 19 months failed to alter this measure (McLaughlin et al., 2008; Smith et al., 2010). Importantly, E_2 treatment immediately following ovariectomy of 21 month old females also enhanced long term potentiation in the hippocampus indicating that the lack of effect after 19 months of ovariectomy was a result of the length of hormone deprivation rather than aging (Smith et al., 2010). The issue of hormone deprivation has been discussed more thoroughly in several recent reviews (Daniel and Bohacek, 2010; Rocca et al., 2011). Given the evidence for the "window of opportunity", only studies that initiated hormone treatment close to the loss of naturally circulating hormones were included in the discussion below of factors influencing outcomes of hormone treatments.

3. Age: Using an appropriate model

There is an extensive body of literature that has examined the neural and cognitive effects of hormone treatments in young ovariectomized animals (Daniel, 2006). However, studies suggest that the effects of hormone treatment in young female animals are often not the same as the effects of hormone treatment during aging. Our laboratory found that young adult females who were ovariectomized and given E_2 and progesterone were impaired in the acquisition of the Morris water maze (Chesler and Juraska, 2000), while treatment with E_2 and progesterone in ovariectomized middle-aged animals facilitated performance of the same task (Markham et al., 2002). Similarly, Foster et al. (2003) found that young ovariectomized females perform worse on the Morris water maze when treated with estradiol benzoate, whereas aged ovariectomized females receiving estradiol benzoate perform better. Other laboratories have found beneficial treatment effects in young or middle-aged animals, but no effects of hormone treatment in older animals. Although treatment with estradiol enhanced performance of ovariectomized young and middle-aged animals on the Morris water maze, estradiol treatment did not improve performance of ovariectomized aged animals (Talboom et al., 2008). Similarly, a single E_2 injection enhanced novel object recognition in 6 month old animals but not at 22 months of age (Gresack et al., 2007).

These age related differences in the effects of hormone treatments on cognition are not surprising given that the percentage of ERα immunoreactive synapses (Adams et al., 2002) and the number of ERβ mRNA positive cells (Yamaguchi-Shima and Yuri, 2007) decrease in the hippocampus during aging. Studies have also found age-related differences in neural outcomes after hormone treatment. For example, E_2 increased synapse number in the hippocampus of young females, whereas treatment during aging failed to result in an increase in synapses (Adams et al., 2001). However in this study, there was an increase in NR1, a subunit of the NMDA receptor, in the hippocampus of aged females that was not observed in young animals (Adams et al., 2001). A more recent study found that E_2 in combination with progesterone increased synaptophysin in hippocampal CA1 of young rats