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Chronic estradiol replacement to aged female rats reduces anxiety-like and depression-like behavior and enhances cognitive performance

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Summary Decline in the ovarian steroid, estradiol (E_2), with the menopause transition may influence cognitive and affective processing of older women and there is evidence that hormone replacement therapies (HRTs) with E_2-mimetics may provide benefit in some, but not all, women. The parameters that play a role in determining whether the response to HRTs is positive are of interest. It may be that the likelihood for positive responses is related to the timing of E_2-replacement following E_2 decline. As such, in the present study an animal model was utilized to investigate this. We investigated the effects of long- versus short-term E_2-replacement by examining cognitive (object placement task), anxiety (open field, mirror maze, light–dark transition task), and depression (forced swim task) behavior of female rats that were ovariectomized (OVX) at middle-age (14 months) or older (19 months) and implanted with E_2-filled implants at the time of surgery or after a delay of 5 months, or OVX at 14 months of age and never replaced with E_2. Rats were tested at 20 months of age. The hypothesis that was tested was that rats would have reduced anxiety and depression behavior and improved cognitive performance with E_2-replacement at ovarian cessation, compared to a delay in E_2-replacement. Performance in the object placement task was improved in rats that were OVX and then received continuous E_2-replacement, compared to those that were OVX and continuously administered placebo vehicle. In the open field and forced swim task, there was an increase in anti-anxiety and anti-depression behavior, respectively, among rats that were OVX and then received continuous E_2-replacement, compared to OVX rats administered vehicle or those that experienced a delay in E_2-replacement. In the mirror maze and light–dark transition task, E_2-replacement at OVX, or after a delay, reduced anxiety-like behavior. Thus, E_2-replacement reduced anxiety and depression behavior and improved cognitive performance of aged female rats; however, delay in E_2 treatment influenced whether there were favorable effects of E_2 in some tasks.

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1. Introduction

Steroid hormones secreted by the ovaries, such as 17β-estradiol (E_2), can have profound effects on women's physiological and/or psychological function. Physical and psychological effects of E_2 are most evident with ovarian decline in E_2 secretion at menopause. About 75% of women experience, and seek treatment for, negative physical (hot flashes, night sweats, drying of eyes and vaginal mucosa) and/or psychological/quality-of-life (forgetfulness, anxiety, depression, sleeplessness, reduced sex drive) symptoms (Henriques and Dickson, 1992). Some women choose hormone replacement therapies (HRTs) with compounds that act similar to E_2 (E_2-mimetics) to manage these effects. Furthermore, treatment of post-menopausal women with E_2-mimetics HRTs improves performance in verbal, visual, and semantic memory tasks (Asthana et al., 2001; Janowsky, 2002; Linzmayer et al., 2001; Nappi et al., 1999; Sherwin, 2003). Despite some support from clinical studies for E_2 to ameliorate negative physical and psychological effects of E_2 decline, the large Women's Health Initiative (WHI) trials were ended early because some women on the most commonly prescribed HRTs, conjugated equine estrogen and/or progesterone, experienced negative prothrombotic (stroke, cardiovascular complications) and/or oncogenic (increased risk of breast, uterine cancer) effects (Anderson et al., 2003; Cunat et al., 2004). Additionally, not all studies find a clear benefit of HRTs in women (Sherwin, 2007), but this may be due to the nature of the therapy utilized, age, and delay between menopause and the onset of HRT.

Little evidence for beneficial effects of E_2-mimetic therapies on mood or cognitive processes of elderly, post-menopausal women found in the WHI trials suggest that, in addition to age, differences in length of time in an E_2-deficient state before initiation of E_2-therapy may be an important factor to consider. The average age of women in the WHI trials was 73 years old at recruitment, and few had previously utilized HRT, which is typically initiated at the onset of menopausal symptoms (Gleason et al., 2005; Pinkerton and Henderson, 2005). It may be that the aging system may be more responsive to E_2 if E_2 treatment is initiated with, not after, ovarian decline (i.e. "critical period" hypothesis reviewed in Sherwin, 2007). Less cognitive decline with aging was found among women who initiated E_2-based treatments at menopause compared to those who were older, had more recent exposure to E_2 and/or longer delay in initiation of E_2 following menopause (MacLennan et al., 2006; Matthews et al., 1999). HRT initiated at menopause reduced risk of Alzheimer's Disease (Zandi et al., 2002). Among women who had received E_2-based therapies for 2—3 years, better cognitive performance was reported 15 years later, compared to placebo (Bagger et al., 2005). Although these data support the notion of a critical period for beneficial effects of E_2-replacement, inherent limitations in clinical studies warrant further investigation in animal models to begin to ascertain the parameters of E_2-therapy that may be most favorable.

There is some evidence from animal studies that supports the critical period hypothesis. An approach that is often utilized to begin to determine functional effects of ovarian cessation (e.g. post-menopausal osteoporosis, psychological changes) is surgical removal of the ovaries (ovariectomy; OVX; Daniel et al., 2006; Gürkan et al., 1986; Kalu et al., 1989; Kalu, 1991; Walf and Frye, 2006). Chronic E_2-replacement to middle-aged rats that have been OVX for 6 months was effective in improving cognitive performance when it was paired with injections of E_2 (Markowska and Savonenko, 2002). Aged rats' performance was enhanced when chronic E_2 was administered 3, but not 10, months post-OVX (Gibbs, 2000). Working memory improvements are only observed among 12 or 17 month old rats that were administered chronic E_2 immediately following OVX, and not when E_2 administration was delayed 5 months (Daniel et al., 2006). Furthermore, choline acetyltransferase (ChAT; as a measure of cholinergic function) was increased in the hippocampus, a region important for cognitive and affective behavior, of 10 and 15 month old rats if E_2 was administered at time of OVX, but not 5 months later (Bohacek et al., 2008). Thus, the duration of E_2 deprivation may be an important factor that influences the nature of the beneficial effects of E_2-replacement.

In the present study, an animal model was utilized to investigate the hypothesis that rats would have improved cognitive performance and affective behavior with E_2-replacement at ovarian cessation, compared to with a delay in E_2-replacement. Effects of E_2-replacement on cognitive, anxiety-like, and depression-like behavior were examined among female rats that were OVX at middle-age (14 months) or older (19 months) and implanted with E_2-filled implants at the time of surgery, or after a delay of 5 months, or rats OVX at 14 months and administered a vehicle/placebo implant.

2. Methods

The methods utilized were pre-approved by the Institutional Animal Care and Use Committee at the University of Albany-SUNY.

2.1. Animals and housing

Adult (14 months old) female Long-Evans rats ($N = 23$) were obtained from in-house breeding from rats originally obtained from Taconic Farms (Germantown, NY). Rats were experimentally naïve, and had all been breeders from our colony until they began to show acyclicity and reduced fertility and fecundity (at approximately 12—14 months of age). Rats were group-housed (3—4 per cage) in polycarbonate cages (45 cm × 24 cm × 21 cm) in a temperature-controlled room (21 ± 1 °C) in the core Laboratory Animal Care Facility in The Life Sciences Building at The University at Albany-SUNY. Rats lived on a 12/12-h reversed-light cycle (with lights off at 8:00 am) and continuous access to rodent chow and tap water in their home cages.

2.2. Surgery and E_2-replacement

At 14 months of age, rats were OVX under xylazine (12 mg/kg IP) and ketaset (80 mg/kg IP) anesthesia. Because there can be great variability in levels of ovarian steroids that are circulating among older rats as they progress through reproductive senescence, rats were OVX and replaced back with E_2 in a regimen that produces known circulating E_2 levels, or vehicle, to obviate this potential for ambiguity in interpreting the results based upon variations in ovarian function. Rats were implanted with a silastic capsule (0.062 i.d., 0.125 o.d.; 10 mm/100 g body