Spatial memory retention is enhanced by acute and continuous estradiol replacement

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Abstract

Estradiol replacement to ovariectomized female rats causes dramatic changes in hippocampal structure and function as well as in performance on hippocampally dependent tasks. Using a delayed matching-to-place version of the water maze, the present study examines the time course of estradiol-induced enhancements in memory retention as well as the effectiveness of acute and continuous patterns of replacement. One 10-\mu g injection of estradiol administered on each of two successive days resulted in significant improvements in memory retention that persisted for approximately 4 days following the second injection. When estradiol administration continued for 10 consecutive days, these improvements in memory retention persisted. These findings indicate that estradiol replacement can improve memory retention and that these improvements can be maintained by continuous replacement for at least 10 days.

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Ovarian hormones have been shown to exert a powerful influence on learning and memory processes and their neural substrates under a variety of experimental conditions. The exact nature of these effects, however, appears to depend on a variety of factors including the timing, duration, pattern, and dose of hormone exposure. For example, numerous studies have examined learning during various phases of the estrous cycle. The results, however, have been rather equivocal with some studies suggesting no significant effect of cycle phase on spatial learning (Berry et al., 1997; Stackman et al., 1997) and other studies reporting that periods of high estradiol are associated with impairments in learning (Chesler and Juraska, 2000; Frye, 1995; Warren and Juraska, 1997). In these studies, the exposure to ovarian hormones is physiological, however, it is difficult to separate the effects of estradiol from other hormones that also vary across the cycle.

Acquisition of spatial learning tasks also appears to be impaired following replacement estradiol in ovariectomized voles (Galea et al., 2002) and one strain of mice (Rissman et al., 2002). Thus, it is likely that high estradiol slows learning rate.

In contrast, there are many reports that low-physiologic levels of estradiol replacement (approximately 15–30 pg/ml) to ovariectomized female rats over periods ranging from 10 days to 2 months is associated with improved performance on a variety of tasks that assess trial-specific (episodic) memory (called ‘working memory’ by Olton and Papas, 1979) including the t-maze (Fader et al., 1998), delayed matching-to-place version of the water maze (O’Neal et al., 1996), and radial-arm maze (Daniel et al., 1997; Fader et al., 1999; Luine et al., 1998; Williams, 1996). Furthermore, estradiol improves performance on a water version of the radial-arm maze, particularly as the number of spatial locations to be remembered increased (Bimonte and Denenberg, 1999). In all these studies, circulating estradiol was continuously elevated for 10–60 days before behavioral evaluation, so it is difficult to determine when or how estradiol may be causing improved performance as well as the time frame over which estradiol-induced improvements persist during continuous treatment and following estradiol withdrawal.
Recently, we have reported that estradiol administered at doses and times that have been shown to increase excitatory connectivity in the hippocampus improves spatial memory retention of ovariectomized rats (Sandstrom and Williams, 2001). In our study, rats received two injections of estradiol benzoate (10 μg, sc) or vehicle separated by 24 h. The rats were then behaviorally evaluated 48 h following the second injection using a matching-to-place version of the water maze. The memory demands of this task were varied by altering the retention interval between the train trial and the test trials. We found that on trials following estradiol treatment, rats were better at remembering the location of the escape platform at longer delays than on trials following vehicle treatment. That is, when the delay between training and testing was short, all rats, regardless of hormone treatment, performed equally well. Only at long delays (i.e., 100 min) was the effect of estradiol apparent. Using the same estradiol replacement paradigm, Woolley and McEwen (1993) found a transient increase in dendritic spine density of CA1 pyramidal neurons that peaks approximately 48 h following the second injection and returns to baseline levels over the course of a week. Progesterone administered 48 h following priming with estradiol initially causes a further increase in spine density followed by a rapid decline in spine density back to baseline levels within 12 h (Woolley and McEwen, 1993). Our improvements in memory retention were similarly affected by progesterone with enhancements in memory evident immediately following progesterone but not when testing occurred 24 h after progesterone administration (Sandstrom and Williams, 2001). Thus, the improvements in memory induced by estradiol may be due to alterations in excitatory connectivity to CA1 pyramidal neurons—a phenomenon that requires 24–48 h of estradiol exposure and can be rapidly reversed by progesterone administration. To date, we do not know whether estradiol-induced increases in spine density and connectivity of CA1 pyramidal cells are sustained when estradiol is administered continuously for many days or weeks.

One clue that the temporal characteristics of estradiol replacement may be critically important for its behavioral and neural effects is that in 18-month-old ovariectomized female rats, spine density of dentate granule neurons increases following two 10-μg injections of estradiol; yet, continuous replacement of estradiol for many months does not maintain spine density at high levels (Miranda et al., 1999). These findings suggest that the behavioral effects of acute and continuous estradiol replacement may be quite different.

The goal of the present study was to investigate the temporal characteristics of estradiol replacement on spatial memory retention of ovariectomized rats. In Experiment 1, we examine the time course over which two 10-μg injections of estradiol separated by 24 h alters memory retention. In Experiment 2, we compare the time course of effects on memory retention when rats are given an acute, 2-day, treatment with estradiol, 10 days of continuous replacement, or no replacement of estradiol. Both of these experiments utilize a repeated-measures design, in which each rat is tested over a series of days to examine the time course of changes in performance following various hormone manipulations. Furthermore, each rat is repeatedly tested in each of the different treatment conditions allowing each rat to serve as its own control. We report improvements in memory retention of ovariectomized female rats that persist for only 3–4 days following acute estradiol priming. Furthermore, when daily injections of estradiol continue over a 10-day period, the improvement in memory retention can be maintained.

Materials and methods

Animals

Twelve female Sprague–Dawley (CD strain) rats were ovariectomized at 4 months of age. Rats were anesthetized for surgical procedures using a cocktail of 60 mg/kg ketamine (Fort Dodge Laboratories, Fort Dodge, IA) and 3.3 mg/kg xylazine (Sigma, Inc., St. Louis, MO) administered intraperitoneally. The ovaries were removed through a small midline incision on the abdomen. All surgical procedures were performed using aseptic techniques and in accordance with Duke University’s Institutional Care and Use Committee guidelines. All rats had free access to Purina Rat Chow and were maintained on a 12-h light–dark cycle with lights on at 7:30 a.m. Behavioral training began at approximately 8 months of age and was performed during the light phase of the cycle, between 8:30 a.m. and 4:00 p.m.

Apparatus

A circular black plastic pool (diameter = 164 cm, height = 50 cm) was filled to a level of 35 cm with water (22–24°C) colored black with nontoxic black paint. A circular escape platform (diameter = 10.8 cm; height = 33 cm) with a nonskid surface was hidden just under the surface of the water. The water maze was in a rectangular testing room with a variety of extramaze cues including a computer, holding cages, cabinets, door, etc. Swimming behavior was recorded by a video camera connected to a tracking system (HVS Image, Buckingham, UK) and each trial was recorded on a computer for later analysis.

Hormone administration

Hormones were dissolved in sesame oil (Sigma) and injected subcutaneously. Estradiol benzoate and progesterone (Steraloids, Inc., Newport, RI) were dissolved to concentrations of 0.2 and 10 mg/ml, respectively. Oil, estradiol (10 μg), and progesterone (500 μg) were injected
subcutaneously in volumes of 50 µl at different locations at the nape of the neck. All injections were performed at 8:30 a.m.

Behavioral training

Rats received three pairs of delayed matching-to-place trials each test day. For each pair of trials, the escape platform was placed in a random pool location but the platform remained in the same location between train and test trials of each pair. On the train trial of each pair, the rat was placed in the water at a random location on the peripheral edge of the pool and was allowed to swim for a maximum of 60 s or until it located the escape platform. If the rat failed to escape to the platform within 60 s, it was gently guided to it. After climbing onto the platform, the rat was allowed to rest there for 20 s after which it was placed on a dry towel in an opaque holding cage for 90 s. It was then transferred to an individual holding cage with fresh bedding which was located behind a curtain in the maze room where it remained for a retention interval of 10, 30, or 100 min. Following the retention interval, the rat was placed back in the water at a random position at the edge of the pool and allowed to swim until it located the escape platform or until 60 s had elapsed. Again, if the rat failed to escape within 60 s, it was manually guided to it. Immediately following the test trial of each pair, the rat was returned to its home cage in the colony room where it remained for at least 2 h until the onset of the next pair of trials. Rats experienced each of the three retention intervals in random order on each test day. The length of the swim path was recorded for each trial.

Experiment 1

Rats were first pretrained on the delayed matching-to-place task for approximately 1 week. Over this period, rats received three pairs of trials each day. The train trial and test trial of each pair were separated by a retention interval of 10, 30, or 100 min, and an interval of approximately 2 h separated the test trial of one pair with the train trial of the following pair. By the end of the pretraining period, rats demonstrate consistent forgetting curves with large improvements between train and test trials separated by a 10-min retention interval and small improvements when these trials are separated by a 100-min retention interval.

Following pretraining, rats were cycled three times through a 10-day hormone regimen with behavioral testing occurring daily. On days 1 and 2 of the cycle, rats received injections of estradiol (10 µg in 50 µl sesame oil); on days 3–10, rats received injections of sesame oil (50 µl). All injections were administered at 8:30 a.m. Daily behavioral training sessions began 30 min following estradiol or vehicle injection and consisted of three pairs of trials with retention intervals of 10, 30, and 100 min separating the train and test trial of each pair. This 10-day cycle (2 days of estradiol administration followed by 8 days of vehicle administration) was repeated three times. Data were grouped into five blocks of 2 days (1–2, 3–4, 5–6, 7–8, and 9–10) for analysis.

Experiment 2

The same rats tested in Experiment 1 were used in Experiment 2 and the behavioral training and hormone treatments were similar to those described for Experiment 1. In this experiment, rats were tested in each of three 10-day replacement conditions: Oil, Acute estradiol, and Continuous estradiol. During the Oil cycle, rats received a single injection of sesame oil (50 µl) on each day of the 10-day cycle. During the Acute estradiol cycle, rats received an injection of estradiol (10 µg) on each of days 1 and 2 followed by an oil injection (50 µl) on each of the next 8 days. During the Continuous estradiol cycle, rats received an injection of estradiol (10 µg) on each day of the 10-day cycle. The order in which rats were cycled through these three conditions was counterbalanced across animals. Because we know that memory (Sandstrom and Williams, 2001) and CA1 dendritic spines (Woolley and McEwen, 1993) return to low baseline levels within 24 h of treatment with progesterone, we ended each 10-day cycle by treating all rats with a single injection of progesterone (500 µg). A new cycle began on the next day. Data were grouped into two blocks of 4 days (Days 3–6 and Days 7–10) for analysis.

Data analysis

All analyses were performed using SPSS (SPSS, Inc., Chicago, IL) with an alpha level of 0.05. The length of the swim path was recorded on the train and test trial of each pair. In addition, the difference between the length of the swim path on the train trial and the length of the swim path on the test trial was computed for each pair of trials. This difference score reflects the degree of improvement (in centimeters) between the training trial and the test trial with larger difference scores indicative of better memory of the platform location. The use of a difference score controls for individual differences in swim performance and limits the extent to which the effects of ovarian steroids on activity, mood, and sensory responsivity influence the measure of memory (e.g., Becker et al., 1987; Bernardi et al., 1989; Galea et al., 2002; Stackman et al., 1997). If, for example, estradiol caused motor biases such that rats swam in a particular pattern, this would similarly influence performance on train and test trials and computing a difference score would subtract out the effects of this motor bias on this measure of memory (see also Sandstrom and Williams, 2001). It is, of course, possible that some non-mnemonic factors may affect performance on train trials differently than they affect performance on test trials. For this reason, performance on train trials and performance on test trials...
were separately analyzed for both experiments. These analyses revealed that none of the hormone treatment regimens significantly affected the length of the swim path on training trials (data not shown). Furthermore, the results of the analyses of test trial pathlength (data not shown) were consistent with the results of the analyses of the difference score (presented below).

Results

Experiment 1

The rats were cycled three times through the 10-day cycle and the median difference in the length of the swim paths on training and test trials (i.e., the difference score) for each rat was analyzed using a two-factor analysis of variance (ANOVA) with Retention Interval (10, 30, and 100 min) and 2-day Block (Days 1–2, 3–4, 5–6, 7–8, and 9–10) as repeated measures. Overall, the data reveal that estradiol improves memory retention and that this improvement persists for approximately 4 days following the second estradiol injection.

The repeated-measures ANOVA revealed significant main effects for both Retention Interval \[ F(2,22) = 10.05, P < 0.01 \] and 2-day Block \[ F(4,44) = 6.29, P < 0.01 \]. In addition, the Retention Interval × Block interaction was significant \[ F(8,88) = 2.12, P < 0.05 \]. Because of the significant interaction, separate linear contrast analyses were performed for each block of days to determine whether performance declined with increasing retention interval. These contrast analyses revealed no effect of increasing retention interval during the first three blocks of days (Days 1–2, 3–4, and 5–6) \[ F's(1,11) < 2.50, P's > 0.10 \]. For the final two blocks of days (Days 7–8 and 9–10), however, longer retention intervals were associated with a significant decline in performance \[ F'(s)(1,11) > 6.20, P's < 0.05 \]. These data can be seen in Fig. 1.

To determine whether estradiol-enhanced retention of the spatial location was apparent on the first training day (within 8 h after the first estradiol injection) or not until the second day (after the second estradiol injection), an additional two-factor ANOVA was performed with Retention Interval (10, 30, and 100 min) and Day (1 and 2) as repeated measures. This analysis revealed no significant main effect of Retention Interval \[ F(2,22) = 1.48, P > 0.20 \] or Day \[ F(1,11) = 2.55, P > 0.10 \]. The Retention Interval × Day interaction, however, was statistically significant \[ F(2,22) = 3.54, P < 0.05 \]. Separate linear contrast analyses performed for each of the days confirmed that performance declined with increasing retention interval on Day 1 (when rats were tested within 8 h of their first estradiol injection) \[ F(1,11) = 7.34, P < 0.05 \]. However, there was no effect of retention interval on Day 2 \[ F(1,11) = 0.72, P > 0.40 \]. These data indicate that it takes between 8 and 24 h for estradiol to enhance memory retention.

Experiment 2

Based on the results of Experiment 1, the data for Experiment 2 were grouped into two 4-day blocks. These blocks consisted of the period during Experiment 1 when clear improvements in performance were evident (Days 3–6) and the period during which no improvements in performance were evident (Days 7–10).

The difference in the length of the swim paths on training and test trials (i.e., the difference score) was analyzed using a three-factor ANOVA with Retention Interval (10, 30, and 100 min), 4-day Block (Days 3–6 and 7–10), and hormone treatment condition (Oil, Acute estradiol, and Continuous estradiol) as repeated measures. The data revealed that not only does acute administration of estradiol causes a transient improvement in memory, as found in Experiment 1, but that continuous estradiol administration is capable of maintaining that improvement for at least 10 days. These data can be seen in Fig. 2.

![Fig. 1. Retention functions for female rats across pairs of trial days (Days 1–2, Days 3–4, Days 5–6, Days 7–8, and Days 9–10). The ovariectomized female rats \( N = 12 \) received injections of estradiol on Days 1 and 2 and oil injections on Days 3–10. Each rat was tested at each retention interval on each day of testing and the difference score was computed for each pair of trials by subtracting the length of the swim path on the test trial from the length of the swim path on the training trial. Linear contrast analyses confirmed that the difference score declined significantly as the retention interval increased from 10- to 100-min for rats tested on Days 7–8 and 9–10. (Data are expressed as mean ± SEM; *P < 0.05, indicates significant linear contrast.)](image-url)
The repeated-measures ANOVA revealed significant main effects for Retention Interval \( F(2,22) = 10.48, P < 0.01 \), 4-day Block \( F(1,11) = 8.70, P < 0.05 \), and Treatment \( F(2,22) = 10.86, P < 0.01 \). All possible two-way interactions were significant: Retention Interval \( \times \) 4-day Block \( F(2,22) = 4.40, P < 0.01 \), 4-day Block \( \times \) Treatment \( F(2,22) = 3.64, P < 0.05 \), and Retention Interval \( \times \) Treatment \( F(4,44) = 6.77, P < 0.01 \). The three-way Retention Interval \( \times \) 4-day Block \( \times \) Treatment interaction was also significant \( F(4,44) = 3.31, P < 0.05 \). Separate linear contrast analyses were performed for each forgetting function to determine whether performance declined significantly with increasing retention interval. These contrast analyses confirmed significant declines in performance as the retention interval increased for both blocks of days during the Oil cycle and for Days 7–10 during the Acute estradiol cycle \( F'(s)(1,11) > 22.00, P's < 0.05 \). During Days 3–6 of the Acute estradiol cycle and during both blocks of days during the Continuous estradiol cycle, however, there were no significant declines in performance as the retention interval increased \( F'(s)(1,11) < 0.70, P's > 0.40 \). These findings confirm that a 10-μg injection of estradiol administered on each of two successive days causes a transient improvement in memory retention and that continued daily administration of estradiol maintains that improvement for at least 10 days.

**Discussion**

The data reported here are the first to delineate a time course for estrogen’s action on memory retention and to determine whether acute and continuous treatments with estradiol have similar cognitive consequences. We find that improvements in memory retention can be detected 24 but not 8 h after the first priming injection of estradiol and last for approximately 4 days after a second estradiol injection (Experiment 1). We also find that estradiol-induced improvement in memory retention can be maintained for at least 10 days if estradiol is administered daily (Experiment 2). These findings may be a useful first step in determining the underlying neural mechanism(s) for estradiol-induced improvements in memory. We now know the time course for cognitive decline following a brief rise in estradiol and we know that daily pulses of estradiol will maintain improved memory function.

These data are particularly compelling for several reasons. Using a delayed matching-to-place water maze task in which rats repeatedly perform pairs of train and test trials, we were able to compute a difference score reflecting memory of the platform location. To the extent that hormonal manipulations have non-mnemonic effects that similarly affect performance on training trials and test trials (e.g., sensory responsivity, motor ability, motivation), the difference score is an accurate reflection of memory. Unlike the typical experimental design in which the performance of
one group of estradiol-treated subjects is compared to the performance of a control ovariectomized group, our repeated-measures design results in each rat serving, in effect, as its own control, minimizing the extent to which individual differences influence the measure of memory. Finally, by using a series of retention intervals, we are able to vary the memory demands of the task to better assess hormonal influences on memory retention.

The improvement in memory retention seen after two daily 10-μg injections of estradiol follows a time course that parallels changes in dendritic spine density of CA1 pyramidal neurons after an identical hormone treatment regimen (Gould et al., 1990; Woolley and McEwen, 1993). That is, a significant increase in dendritic spine density is evident within 24 h following the second injection of estradiol. This increase in spine density is associated with an increase in the sensitivity of CA1 pyramidal neurons to NMDA receptor-mediated synaptic input (Gazzaley et al., 1996; Weiland, 1992; Woolley et al., 1997) and decreases in the induction threshold for long-term potentiation (Cordoba-Montoya and Carrer, 1997; Warren et al., 1995). Peak levels of spine density occur between 2 and 3 days after the second estradiol injection and spine levels return to baseline approximately 8–10 days following estradiol. Our improvements in memory retention mirror these morphological changes. It is not yet known whether continued daily injections of estradiol maintain elevated density of spines on CA1 pyramidal cells in the hippocampus but the present behavioral results suggest that possibility.

Although we have shown that estradiol injected daily can improve memory for at least 10 days, the exact duration over which daily estradiol administration can maintain improvements in memory retention is not yet known, though others have reported enhancements in spatial memory assessed with the radial-arm maze between 10 days and 2 months following the implantation of estradiol-releasing capsules (Daniel et al., 1997; Fader et al., 1999; Luine et al., 1998; Williams, 1996). We do know, however, that very long periods of estradiol replacement via silastic capsule (>1 year) do not result in increases in dendritic spine density of dentate granule cells in the hippocampus while very acute periods of replacement (i.e., two 10-μg injections) do enhance spine density in the dentate granule cells of aged female rats (Miranda et al., 1999). These findings suggest the interesting possibility that, although continuous estradiol replacement for days or perhaps several weeks may have short-term benefits on neural plasticity and memory function, very long-term continuous replacement for months or years may be associated with a decreased sensitivity to estrogen.

Our findings lend support to the view that estradiol may enhance memory retention by binding to and activating cytoplasmic estrogen receptors which are translocated to the nucleus resulting in changes in genomic activity. We find that it takes more than 8 and less than 24 h for estrogen effects to become apparent, suggesting that some genomic process is activated rather than a much slower process such as estradiol-induced neurogenesis (Tanapat et al., 1999). The cytoplasmic estrogen receptors ER-α and ER-β are both expressed in the hippocampus (Adams et al., 2002; Blurtom-Jones and Tuszyński, 2002; Hart et al., 2001) and it has been recently suggested that the combined activation of ER-α expressed on inhibitory GABA interneurons and activation of ER-α on CA1 pyramidal neurons may be one mechanism that contributes to the dramatic changes in hippocampal structure and function (McEwen, 2002).

In addition to acting within the hippocampus, estradiol also binds to receptors in cholinergic neurons of the basal forebrain (Mufson et al., 1999; Shughrue et al., 2000) and this mechanism may underlie or contribute to our observed improvements in memory retention. ChAT activity in these hippocampally projecting neurons is dramatically affected by estradiol (Gibbs, 1994, 1996, 1997) and the integrity of these basal forebrain cholinergic neurons appears to be necessary for the beneficial effects of estradiol on cognition (Gibbs, 1999, 2002). Interestingly, the response of basal forebrain cholinergic neurons to estradiol replacement is strongly influenced by the time frame of replacement. For example, ChAT mRNA expression in the basal forebrain is elevated after 2 days or 2 weeks of continuous replacement but not after 1 week (Gibbs et al., 1994). Furthermore, the number of ChAT-immunoreactive neurons in the basal forebrain is elevated by 1 week of estradiol replacement but not 2 or 4 weeks of continuous replacement (Gibbs, 1997). Recently, it has been shown that estradiol-induced disinhibition of hippocampal CA1 pyramidal cells is partially dependent on intact basal forebrain cholinergic projections to the hippocampus (Rudick et al., 2003). Furthermore, both the estradiol-induced increase in NMDA receptor binding in the CA1 region of the hippocampus and the estradiol-induced improvement in radial-arm maze performance are blocked by administration of an M2 acetylcholine receptor antagonist (Daniel and Dohanich, 2001). Together, these findings suggest that changes in hippocampal morphology and physiology are likely to be influenced by direct estrogenic stimulation as well as indirect stimulation of cholinergic projections to the hippocampus.

While our improvements in memory are not evident for at least 8 h following estradiol administration, there have been reports of very fast-acting effects of estradiol on memory. When an estradiol–cyclodextrin inclusion complex is administered peripherally or directly to the hippocampus immediately following training on the standard Morris water maze task, memory retention for the platform location is improved 24 h later (Packard and Teather, 1997a,b). However, delaying the estradiol administration for 2 h following training does not cause an improvement in memory assessed 24 h later. Performance on object recognition and place recognition tasks is similarly improved when estradiol is administered 30 min before or immediately after the training trial but not when administration is delayed for 2 h after the training trial (Luine et al., 2003).
Together, these findings suggest that estradiol may also have a fast-acting effect on memory storage processes and that this may translate into improved performance at a later time point when estradiol levels are no longer elevated. The temporal characteristics of this effect of estradiol on memory make it unlikely that estrogen-induced changes in dendritic spines are the underlying mechanism.

Although our findings reveal the temporal relationship between a rise in plasma estradiol and improvements in memory retention, they do not provide any information about the phase of the learning and memory process that might be altered. That is, in our studies, the hormonal status of the rat was the same across all phases of the learning and memory process (i.e., acquisition, rehearsal, consolidation, and recall) for a particular pair of trials. In fact, it is quite possible that the increased memory retention seen here may be the result of estradiol influencing many factors (e.g., altering the sensory processing of the coordinates of the platform location, the attention to or perception of the environment, or the neuronal architecture that aids memory formation).

The effectiveness of hormone replacement therapy (HRT) and estrogen replacement therapy (ERT) for improved cognition in postmenopausal or surgically menopausal women may also be due, in part, to the duration and pattern of hormone replacement. Many experimental studies report beneficial effects of short-term estrogen replacement on memory (e.g., Phillips and Sherwin, 1992; Wolf et al., 1999). In contrast, the recent Women’s Health Initiative (WHI) Study on the health effects of combined estrogen and progestin replacement reported higher incidence of probable dementia in women randomly assigned to receive hormone replacement as compared to placebo controls (Shumaker et al., 2003). This finding was surprising given the extensive data from rodent (e.g., Daniel et al., 1997; Fader et al., 1999; Luine et al., 1998; Sandstrom and Williams, 2001; Williams, 1996), nonhuman primate (e.g., Rapp et al., 2003), and experimental and epidemiological studies in humans (see Janowsky, 2002, for review) which reported beneficial effects of estrogens on cognition. One potential explanation for the negative effect of hormone replacement in the WHI study involves the pattern and duration of hormone replacement. In the WHI study, participants assigned to the hormone replacement condition were given concurrent estrogens and progestin in the form of a pill taken daily for approximately 4 years. We know that the neural effects of acute and very long-term estrogen replacement can be dramatically different (Miranda et al., 1999). As such, it is likely that the duration of continuous replacement is an important factor in determining the cognitive and physiological effects. The present study begins to examine the important relationship between the duration and timing of estradiol replacement and the cognitive consequences and reports that improvements in memory retention induced by acute estradiol replacement in ovariectomized female rats can be maintained over at least 10 days by daily administration of replacement estradiol. Continued investigation of the relationships among different patterns of hormone replacement, neural changes, and cognition will improve our understanding of the ways in which ovarian steroids alter brain and cognition in humans.

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References


