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Reproductive experience modifies the effects of estradiol on learning and memory bias in female rats

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ABSTRACT

Previous studies have shown that estrogen affects whether a hippocampus-mediated place (allocentric) or a striatum-mediated response (egocentric) memory system is employed by female rats when searching for a food reward in a maze. Because it has been suggested that reproductive experience alters some of the responses to E in the brain, two experiments were carried out to investigate whether reproductive experience would also alter the effect of E on place and response learning. In experiment 1, 152 ovariectomized nulliparous ($n=77$; no reproductive experience) and primiparous ($n=74$; having had and raised one litter of pups) Wistar rats were trained on an ambiguous t-maze task and tested for memory system bias. In experiment 2, 35 ovariectomized nulliparous ($n=16$) and primiparous ($n=19$) Wistar rats were trained on place and response plus-maze tasks. All rats were exposed to no, chronic low or chronic low with pulsatile high 17β-estradiol (E2) replacement. Congruent with previous findings, low E2 nulliparous rats showed predominant use of response memory and faster response learning, whereas high E2 nulliparous rats showed a trend towards predominant place memory use. Interestingly, the facilitatory effect of low E2 on response task learning and memory seen in nulliparous rats was not observed in low E2 primiparous rats in either experiment. In conclusion, E2 levels do dictate the rate at which female rats learn a response task and utilize response memory, but only in those with no reproductive experience.

Introduction

The effects of estrogen (E) on the female brain are not exclusive to reproductive function. Research carried out in rats, for example, suggests that E affects which memory system is used to solve a task. Specifically, in female rats the level of circulating E affects whether a hippocampus-mediated place (allocentric) or a striatum-mediated response (egocentric) memory system is employed when searching for a food reward in a maze (Korol, 2004; Quinlan et al., 2008). Thus, varying responsivity to E, as has been described in female rats with reproductive experience (e.g., Byrnes et al., 2012), would be expected to affect memory bias.

There is evidence in the male rat that place learning and response learning are separate competing memory systems that rely on different brain pathways. When hippocampal integrity is impaired, performance on tasks that rely on spatial cues is diminished (Packard and McGaugh, 1996), and both hippocampal lesions and pharmacological inhibition of the hippocampus lead to impaired spatial memory and place learning (McDonald and White, 1994; Packard and McGaugh, 1996). For example, when muscimol (a $GABA_A$ receptor agonist) is injected into the dorsal hippocampus, place memory is impaired (Mao and Robinson, 1998) and when hippocampal function is impaired using lidocaine, rats rely on response memory instead (Packard et al., 1994).

Conversely, damage to the dorsal striatum results in impaired response memory, but not place memory (Kesner, 1990). Lesions to the dorsal striatum result in impaired performance on tasks dependent on response memory (McDonald and White, 1994), and lidocaine infusions into the dorsal striatum also lead to impaired response memory. Inactivation of the hippocampus has been shown to result in deficient place memory, while damage to the dorsal striatum leads to impaired response memory in a cross-maze task (Packard and McGaugh, 1996).

It has been shown that E affects the brain areas underlying these two memory systems in female rats. In ovariectomized (OVX) rats, 17β-estradiol (E2) replacement enhances learning of a place task, but impairs learning of a response task (Korol and Kolo, 2002). In an ambiguous t-maze task, it has been found repeatedly that OVX rats with E2 replacement predominantly use place memory, whereas the opposite pattern is seen in those without E2 (Korol et al., 2004; Quinlan et al., 2008). The same effect is observed in naturally cycling females. Rats in proestrus, the phase of the estrous cycle when E is highest, use a place strategy more often on a t-maze task. Conversely, rats in estrus, the phase when E is lowest, are more likely to use a response strategy (Korol et al., 2004). These findings indicate that E

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plays a key role in memory system bias in females when completing a task.

E has also been linked to a variety of morphological and neurochemical alterations in the hippocampus, such as increased spine density (Woolley, 1998; Woolley and McEwen, 1992), increased excitatory synapses and synaptic boutons (Woolley et al., 1996) and increased synaptic proteins (Brake et al., 2001). Physiologically high (50–90 pg/ml) levels of E are also linked to increased acetylcholine levels in the hippocampus, especially during place learning (Gabor et al., 2003; Marriott and Korol, 2003). In the dorsal striatum, on the other hand, it has been suggested that E modulates response learning via potentiation of dopamine release (Quinlan et al., 2008).

Although it is well established that E modulates memory system bias in female rats, these effects have been investigated only in rats with no reproductive experience (viz. nulliparous). There is accumulating evidence that the experience of pregnancy and pup rearing causes long-term changes in female rats that are still apparent after the young are weaned. These organizational effects are wide ranging and include alterations in stress and anxiety behavior (Lambert et al., 2005; Wartella et al., 2003) and spatial learning (Byrnes and Bridges, 2006). Neither the particular aspects of reproductive experience nor the precise mechanism(s) underlying these effects have been fully elucidated. However, the fact that nulliparous females who were induced to show maternal behavior by exposure to foster pups learned a spatial task as quickly as reproductively experienced rats, suggests that the act of caring for young may by itself be sufficient to induce these long-term changes (Kinsley et al., 1999).

Indeed, long-term changes in sensitivity to E following parturition have been reported in reproductively experienced rats. Bridges and Byrnes (2006) found that reproductively-experienced rats showed higher prolactin secretion two days after high doses of E were administered, suggesting that these rats were more sensitive to E than their nulliparous counterparts (Bridges and Byrnes, 2006). Furthermore, aged parous rats have also been shown to outperform age-matched nulliparous rats on spatial learning tasks at up to 22 months of age, indicating that parity-induced differences in learning and memory function are long-lasting (Love et al., 2005).

These results raise the possibility that E would have differential effects on learning and memory systems in nulliparous and reproductively experienced rats. As shown previously, nulliparous OVX rats tend to utilize hippocampus-mediated place memory when given high levels of E2 replacement, whereas they use striatum-mediated response memory under low E2 replacement (Korol, 2004; Quinlan et al., 2008). Here we compared the behavior of nulliparous OVX rats with either no, chronic low, or chronic low with pulsatile high E2 replacement with that of OVX females that had previously raised one litter (viz. primiparous) given the same hormone replacements. In experiment 1, rats were tested in an ambiguous t-maze task to determine memory system bias. In experiment 2, rats were trained on either a place or response task to determine if there were learning differences.

Methods

Experiment 1

A total of 152, three- to four-month old female Wistar rats were used in this experiment (Charles River, St-Constant, QC). Seventy-four of these rats were primiparous females, which had given birth one month prior to testing. For breeding, these rats were group-housed (5 females and 1 male per cage) in hanging cages (dimensions: 37.6 cm wide × 56.3 cm long × 22.2 cm high) for a maximum duration of 21 days, after which the pregnant rats were moved to single shoe-box cages (dimensions: 25.5 cm wide × 46.6 cm long × 21.6 cm high). Immediately after birth, the number of pups was culled to 8 per dam. The pups were then kept with the dams for 3 weeks, after which they were all weaned and dams were then housed in pairs until surgery.

The remaining 77 rats were age-matched nulliparous females with no prior reproductive experience. Both nulliparous and primiparous groups were randomly assigned to 3 treatment conditions: no E2 ($n = 39$), chronic low E2 ($n = 58$), and chronic low with pulsatile high E2 ($n = 55$) dose. All rats were housed in plastic shoe-box cages, under a 12 h reverse light–dark cycle (2100 to 0900). Rats were housed in pairs prior to OVX surgery, after which they were housed singly. All rats had ad libitum access to rat chow and water, except for the training and testing periods, during which they were food restricted. Starting three days prior to the beginning of training, food was restricted and weight was maintained at 90% of free-feeding levels. The rats were handled daily prior to and throughout the experiment. All procedures involving rats were in accordance with the guidelines established by the Canadian Council on Animal Care and approved by the Concordia Animal Research Ethics Committee.

Apparatus

All training and testing was carried out in a black Plexiglas t-maze situated on a table 1 m above the floor (see Fig. 1). The t-maze was comprised of black walls (28 cm high), grid floors, a start arm (130 cm long) and two goal arms (75 cm long), which were each positioned at a 90° angle to the start arm. The start arm contained a removable door, which created a start chamber. Each goal arm contained a white ceramic bowl placed at its end. Froot Loops (Kellogg's) were placed underneath the maze at each bowl to later avoid odor cues during testing. Two guillotine doors separated the goal arms from the choice point of the start arm and could be closed to prevent animals from leaving the goal arm once they were inside. An additional arm (identical in dimensions to the start arm) was added to the t-maze to form a plus-shaped maze. Another guillotine door closed off access to this part of the maze at all times, except during probe testing. The t-maze was situated in a room dimly lit with overhead red fluorescent lamps, a lamp facing the wall (40 W light

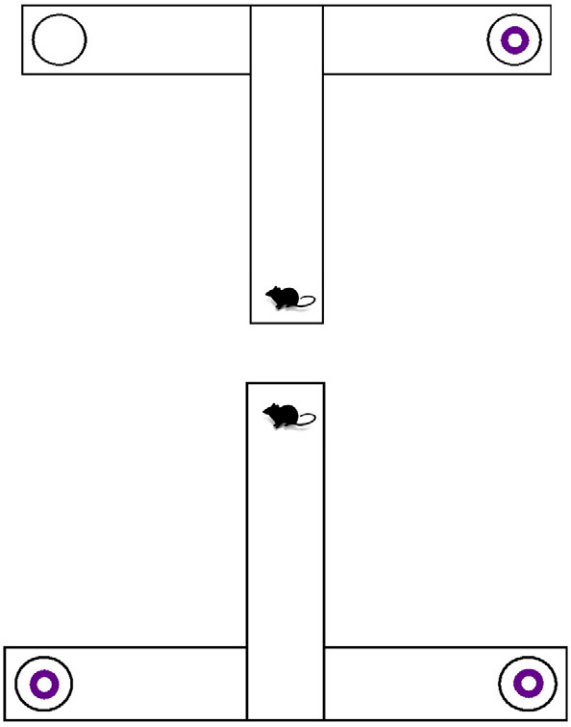

Fig. 1. The t-maze and modified plus-maze designs used were adapted from Korol et al. (2004). Top panel: Rats were initially trained to receive a reward in either the left or right goal arm. Bottom panel: Upon reaching criterion, rats were then placed in the opposite arm for the probe trial. The dark ring represents the reward.