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Estradiol and striatal dopamine receptor antagonism influence memory system bias in the female rat

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ABSTRACT

Estradiol (E2) has been shown to influence learning and memory systems used by female rats to find a reward. Rats with high levels of E2 tend to use allocentric, or place, memory while rats with low levels of E2 use egocentric, or response, memory. It has been shown that systemic dopamine receptor antagonism interacts with E2 to affect which memory system is used. Here, dopamine antagonists were administered directly into either the dorsal striatum or nucleus accumbens to determine where in the brain this interaction takes place. Seventy-four young adult, female, Sprague-Dawley rats were trained and tested in a modified plus-maze. All rats were ovariectomized, received a subcutaneous low E2 implant, and were implanted with bilateral cannulae into either the dorsal striatum or the nucleus accumbens. Additionally, high E2 rats received daily injections of E2 in a sesame oil solution while low E2 rats received daily injections of vehicle. After reaching criterion levels of performance in a plus-maze task, rats were administered microinjections of either a dopamine D1 receptor (SCH 23390; 0.1 μg/ml and 0.01 μg/ml) or D2 receptor (raclopride; 2 μg/ml and 0.5 μg/ml) antagonist or a vehicle control (saline) in a counterbalanced manner. High E2 rats exhibited a trend towards a place memory bias while low E2 rats showed a response memory bias. Dorsal striatal administration of a D1, but not D2, dopamine receptor antagonist caused a switch in the memory system used by both high and low E rats. There was no significant effect of dopamine receptor antagonism in the nucleus accumbens group. Thus, E2 determined which memory system controlled behavior in a plus-maze task. Moreover, this effect was modulated by dopamine D1R antagonism in the dorsal but not ventral striatum suggesting that memory systems are, in part, mediated by E2 and dopamine in this region.

1. Introduction

Rats solving a maze can use one or a combination of several strategies (Blodgett & McCutchan, 1947; Tolman, Ritchie, & Kalish, 1946). For example, they may use environmental, or allocentric, cues around the maze to develop a cognitive map and obtain a reward. This is referred to as place memory and is predominantly mediated by the hippocampus (Packard, Hirsh, & White, 1989; Packard & McGaugh, 1996; White & McDonald, 2002). Another approach to navigating a maze involves the use of internal, or egocentric, cues; in this case, rats learn to employ a series of habitual motor responses such as 'turn left' or 'turn right' to obtain a reward. This is referred to as response memory and is predominantly mediated by the dorsal striatum (DS), also known as the caudate/putamen (Chang & Gold, 2004; Packard & McGaugh, 1996; Packard et al., 1989). As would be expected, rats typically use a combination of these memory systems when navigating their environment (Chang & Gold, 2003). However, when the brain region responsible for one memory system is made unavailable (e.g. via lesion or lidocaine) the other predominates (Packard & McGaugh, 1996; Packard et al., 1989; White & McDonald, 2002), meaning that the use of either place or response memory can be influenced by altering the function of either the hippocampus or the DS. For example, Packard and White (1991) demonstrated that both D1 and D2 receptor agonists injected directly into the DS improve performance on a response task but have no effect on a place task. However, when these agonists are injected into the hippocampus, they improve performance on a place task but not a response task.

There is evidence demonstrating that increases in circulating estrogens affect the type of memory a rat uses to navigate. A study by Korol, Malin, Borden, Busby, and Couper-Leo (2004) showed that when cycling female rats were allowed to solve a modified plus-maze using either strategy the majority of proestrus (high estradiol [E2]) rats use a place strategy while most estrus (low E2) rats use a response strategy. These findings were replicated in ovariecto-

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mized (OVX) rats administered either high or low E2 replacement (Quinlan, Hussain, & Brake, 2008). It is believed that high levels of E2 impair performance on tasks regulated by the DS, such as those which require use of the response memory system. For example, direct infusion of E2 into the DS impairs response learning (Zurkovsky, Brown, Boyd, Fell, & Korol, 2007). Higher levels of circulating E2 also diminish performance in other cognitive tasks regulated by the DS, viz. response learning in a radial arm maze (Davis, Jacobson, Aliakbari, & Mizumori, 2005), latent inhibition (Nofrey, Ben-Shahar, & Brake, 2008; Quinlan, Duncan, Loiselle, Graffe, & Brake, 2010), and pre-pulse inhibition (Koch, 1998). These tasks are all particularly sensitive to levels of dopamine in the striatum (Lubow, 1997; Swerdlow, Braff, & Geyer, 2000).

It has also been shown that E2 increases dopamine transmission in the DS (Becker, 1990; Di Paolo, Poyet, & Labrie, 1981; Levesque & Di Paolo, 1989), which has led to the hypothesis that E2 interacts with dopamine to influence the memory system used by rats in a maze. Previous work in this lab (Quinlan et al., 2008) has shown that dopamine D1 receptor (D1R) and D2 receptor (D2R) antagonists administered systemically prior to probe trials shift the memory used by OVX females administered low E2 from a response strategy to a place strategy, but have no effect on the memory strategy used by OVX females administered high E2. It is hypothesized that higher E2 levels may not only enhance hippocampal-dependent place memory, as shown by others (Zurkovsky, Brown, & Korol, 2006), but may also impair DS-dependent response memory, specifically by altering DS dopamine transmission in this region (Daniel, 2006; Korol, 2004).

Although our previous findings are consistent with this hypothesis, it cannot yet be concluded that E2 is interacting with dopamine in the DS to produce these behavioral effects because the antagonists were administered systemically. Other neuronal systems, including the mesolimbic dopamine system, that innervate the ventral striatum (nucleus accumbens; NAc) also play a role during performance of a task to obtain a reward (e.g. Grace, Floresco, Goto, & Lodge, 2007). The current study was designed to examine the interaction between chronic E2 and dopamine within the DS and NAc. The NAc was examined because it is in close proximity to the DS and is a region heavily innervated by dopamine neurons. It was hypothesized that D1R and D2R antagonist microinjections into the DS, but not the NAc, would alter the memory system used by low but not high E2 rats.

2. Materials and methods

2.1. Subjects and surgery

Eighty-six female, Sprague-Dawley rats (Charles River, St. Constant, QC, Canada), approximately three months of age and weighing between 225 and 250 g were initially included in this study. Before training began, rats were housed in pairs in polyurethane shoebox cages and maintained on a reverse 12 h:12 h light/dark cycle with lights off from 0900 to 2100. Standard lab chow and water were available *ad libitum* until training began.

Approximately one week after arrival all rats were anesthetized using isofluorane gas (4% for induction; 2% for maintenance) and bilaterally ovariectomized using a standard aseptic procedure through a single lumbar incision. During the ovariectomy procedure all rats were subcutaneously implanted in the nape of their neck with a Silastic tube (1 cm long; i.d. 1.47 mm; o.d. 1.96 mm) containing 5% 17β-estradiol benzoate (Sigma Chemical Co., St. Louis, MO) in cholesterol (Sigma). These E2 capsules have been reported to produce plasma E2 concentrations of approximately 20–25 pg/ml (Mannino, South, Inturrisi, & Quinones-Jenab, 2005), which is consistent with naturally circulating levels of E2 during the estrus phase of the rat estrous cycle (Butcher, Collins, & Fugo, 1974; Mannino et al., 2005). Post-surgical care included administration of the antibiotic Baytril, (0.03 ml/animal, SC; CDMV, St. Hyacinthe, Quebec), the analgesic, banamine (0.03 ml/animal, SC; CDMV), and 0.9% saline (3 ml/animal, SC). Rats were allowed to recover in their home cages for several days prior to implantation of the cannulae.

Rats were randomly assigned to be implanted with cannulae directed at either the DS (DS group) or NAc (NAc group). Rats were anesthetized using Halothane gas and were secured in a stereotaxic device to allow for bilateral implantation of 21 g stainless steel tubing guide cannulae (Plastics One, Roanoke, VA). Cannulae were secured with dental cement and skull screws. Stereotaxic coordinates (from bregma) were AP −0.3, ML ±4.0, and DV −5.0 for the DS group, and AP +1.4, ML ±2.8 at 10°, and DV −6.8 for the NAc group (Paxinos & Watson, 1998). Cannulae were blocked with 26 g obdurators (Plastics One) which extended 1 mm below the tip of the guide cannulae. Rats received the same post-surgical care as after the ovariectomy surgery and were allowed several days to recover in their home cages. All animal protocols were in accordance with guidelines established by the Canadian Council on Animal Care and approved by the Concordia University Animal Research Ethics Committee.

2.2. Hormone administration

The DS and NAc groups were each randomly divided in half and assigned to either low or high E2 conditions. In addition to the low constant levels of E2 supplied by the Silastic implants to all rats, rats in the high E2 condition received additional daily subcutaneous injections of 17β-estradiol (10 μg/kg) dissolved in sesame oil (Sigma). This was intended to achieve E2 serum levels comparable to those observed during the proestrus phase of the estrous cycle (75–90 pg/ml; Mannino et al., 2005). To control for the daily injection procedure, rats in the low E2 condition received daily subcutaneous injections of sesame oil (1 ml/kg). All rats received their first injection approximately 2 days before habituation to the maze began (∼day 10, see Fig. 1). Injections were given between 1200 and 1400 h each day.

2.3. E2 plasma levels

At the end of behavioral testing, which was approximately 37 days following the implantation of the Silastic tubes, blood was collected from the tail vein 22 h following the previous E2 or sesame oil injection. Blood samples were immediately centrifuged and plasma was collected and stored at -20 °C until assayed. E2 was measured using a commercially available ELISA kit (Immuno-Biological Laboratories Inc., Minneapolis, MI). The assay antibodies have 100% cross-reactivity with E2 and 0.2% and 0.05% cross-reactivity with estrone and estriol, respectively. The reported inter-assay variation is 7–9%.

2.4. Dopamine antagonist administration

Animals received bilateral intracerebral injections of dopamine antagonists on different testing days; all drugs were administered 5 min prior to the start of testing at a rate of 0.5 μl/min/side using a Harvard Apparatus Model 22 automatic dual pump with 10 μl Hamilton syringes, and 26 g stainless steel injectors which extended 1 mm below the tip of the cannulae. Injections lasted for 1 min after which the injectors were left in place for an additional minute to allow for drug diffusion. Drugs were only infused on drug probe testing days and not on training days.

The D1R antagonist SCH 23390 (Sigma) was administered in a moderate dose of 0.1 μg/ml and a low dose of 0.01 μg/ml.