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Estrogen Improves Working But Not Reference Memory and Prevents Amnestic Effects of Scopolamine on a Radial-Arm Maze

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FADER, A. J., P. E. M. JOHNSON AND G. P. DOHANICH. *Estrogen improves working but not reference memory and prevents amnestic effects of scopolamine on a radial-arm maze.* PHARMACOL BIOCHEM BEHAV **62**(4) 711–717, 1999.—This study investigated the effect of estrogen treatment on working memory and reference memory of female rats. In addition, the impact of estrogen on the sensitivity of these two types of memory to the cholinergic antagonist scopolamine was investigated. At 35 days of ages, rats were ovariectomized and implanted chronically with Silastic capsules containing either 25% crystalline estradiol or 100% cholesterol. Thirty days after surgery, animals were trained on an eight-arm radial maze with four arms baited to assess both working and reference memory performance. Following training, females were given scopolamine hydrobromide (0.2 mg/kg IP) prior to retesting on the task. Results indicated that estrogen treatment improved working memory performance during maze acquisition but did not affect reference memory performance. Scopolamine treatment impairmed performance on the working memory component, but not the reference memory component, while estrogen prevented the impairment of working memory by scopolamine. Results support previous evidence that estrogen selectively enhances performance on tasks that depend on working memory. © 1999 Elsevier Science Inc.

Scopolamine Estradiol Radial arm maze Working memory Reference memory

THE steroid hormone estrogen can influence performance on tasks that assess learning and memory function in mammals. Ovariectomized rats treated with estrogen demonstrate improvements in performance of some tasks and impairments on others compared to ovariectomized, untreated controls. For example, improved performance by estrogen-treated rats has been reported for tasks that require spatial working memory, such as the eight-arm radial arm maze (10,30,32,61,62). In contrast, estrogen from either endogenous or exogenous sources can impair performance on the Morris water maze task, a test of spatial reference memory (15,16,28,58), and preliminary evidence indicates that estrogen may affect working and reference memory differentially when tested on the radial maze task with four arms baited (32).

The standard radial maze test of spatial working memory, in which all arms are baited with food rewards, can be modified to allow for the assessment of both working and reference memory function simultaneously. In this paradigm, the same subset of arms is baited on every trial, and the remaining arms are always left unbaited (27,43). An animal commits a working memory error by reentering a baited arm, a reference memory error by entering an arm that is never baited, and a combination working/reference memory error by reentering an arm that is never baited. When administered to rats prior to testing, the muscarinic cholinergic antagonist scopolamine produces impairments in radial maze performance. Although there is general agreement in the literature that working memory is disrupted following scopolamine administration (21,46,54,59), the effect of scopolamine on reference memory has been more difficult to establish. Some laboratories have reported no effect of scopolamine on reference memory (3,63), while others have reported dramatic impairments (34,40).

The objectives of the current study were to use the radial maze task with four arms baited to determine the effect of estrogen treatment on the acquisition of both the working and reference memory components of the task, and to determine if animals treated with estrogen were resistant to the effects of scopolamine. Previous studies from our laboratory have demonstrated that estrogen treatments can enhance working memory performance during acquisition of the radial maze task

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with eight arms baited (10), and that estrogen can prevent scopolamine-induced impairments in performance of a working memory task in the T maze (11,12). The procedure employed in the present experiment enabled us to examine simultaneously in the same animals the effects of estrogen on the acquisition of tasks that assess working and reference memory performance, and on the resistance to scopolamine-induced performance impairments.

METHODS

Subjects

Twenty-four female Long–Evans hooded rats were purchased from Harlan–Sprague–Dawley, Inc. (Indianapolis, IN) at approximately 28 days of age. Rats were housed four to a cage in a temperature-controlled vivarium under a 12 L:12 D cycle, with lights on at 0700 h. During this study, all animals were treated in accordance with the specifications of the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*.

At approximately 35 days of age, all rats received bilateral ovariectomies while under anesthesia induced by ketamine (100 mg/kg im, Bristol Laboratories, Syracuse, NY) and xylazine (7 mg/kg im, Miles Laboratories, Shawnee, KS). While still under anesthesia, rats were implanted subcutaneously in the nape of the neck with 5-mm long Silastic capsules (0.058 in. i.d., 0.077 in. o.d., Dow Corning, Midland, MI). Twelve subjects received capsules containing 25% crystalline 17β-estradiol (Sigma Chemical Co., St. Louis, MO) diluted with cholesterol (Sigma Chemical Co.), and 12 subjects received capsules containing 100% cholesterol. Capsules of the same dimensions and estrogen concentration generated circulating estradiol levels typical of diestrus [15–20 pg/ml; V. Luine personal communication; (32,52)], although the capsules used in the present experiment may have produced slightly higher levels in younger females. Work from our laboratory has demonstrated that these capsules enhanced working memory performance when administered to female rats at 35 days of age, as well as at 2 or 10 months of age [(10); Daniel and Dohanich, unpublished data]. In a previous study, estradiol failed to improve working memory performance of ovariectomized rats when delivered by Silastic implants that produced proestrous levels of estradiol [90 pg/ml, (32)]. However, capsules that generated lower levels of estradiol typical of diestrus (15 pg/ml) did enhance performance in ovariectomized rats on trials with delays of 3 to 5 h between the fourth and fifth arm choices (32). No differences in the acquisition or performance of an eight-arm radial maze were found across the estrous cycle in female rats, although sensorimotor and motivational factors were affected at proestrus (53). Therefore, evidence indicates that estrogen can enhance performance during acquisition and retention of radial maze tasks specifically when estradiol is present at low levels over a number of days or weeks.

Apparatus

Testing was conducted in an eight-arm radial maze purchased from Lafayette Instrument (Lafayette, IN). The maze was located in the colony room, and the testing surface was 96.5 cm above the floor. The arms (10-cm wide × 70-cm long) were made of aluminum painted black, and the walls (20 cm high) were made of Plexiglas. The eight arms radiated from an octagonal center chamber (33 cm wide) made of the same materials as the arms. At the end of each arm was a recessed food cup located below the surface of the floor. A variety of fixed extramaze cues surrounded the maze.

Procedure

At approximately 60 days of age all animals were placed on an individual schedule of restricted food intake designed to maintain body weight at 85% of the free-feeding level. Body weights were monitored at least four times a week for the duration of the experiment.

Testing in the radial maze began at approximately 65 days of age. Before each trial, one-half of a Kellogg's Froot Loop was placed into four of the recessed food cups located at the ends of the arms, according to the pattern specified for the animal being tested. For each animal, a pattern of four baited and four unbaited arms was generated by random permutation. To begin each trial, an animal was placed into the center chamber of the maze and all eight doors were opened simultaneously by a silent electric relay system. The animal was allowed to enter the arms until it had entered all four baited arms or 5 min had elapsed. An arm entry was scored when an animal traversed at least half the length of an arm. A working memory error was recorded when a rat reentered a baited arm, a reference memory error when an animal entered an arm that was never baited, and a working/reference memory error when an animal reentered an arm that was never baited. Each animal received one trial per day for 32 days. On day 33, all animals received injections of scopolamine hydrobromide (0.2 mg/kg IP, Sigma Chemical Co.) 15 min prior to testing.

RESULTS

Data from the first 32 days of the experiment were collapsed into 4-day blocks and analyzed by separate, two-factor, repeated-measures ANOVAs (treatment group × block), one for each of the three types of memory investigated. After the first block, none of the animals used recognizable patterns of response, such as adjacent arm strategies, to locate food rewards within the maze. The performance of animals in both the estrogen and cholesterol-treated groups improved over the course of the experiment, as indicated by a significant effect of blocks for working memory errors, $F(1, 7) = 5.866$, $p < 0.0001$ (Fig. 1A), reference memory errors, $F(1, 7) = 24.754$, $p < 0.0001$ (Fig. 1B), and working/reference memory errors, $F(1, 7) = 18.026$, $p < 0.0001$ (Fig. 1C). However, animals that received estrogen treatments made significantly fewer working memory errors than cholesterol-treated animals over the course of the experiment as indicated by a significant main effect of treatment, $F(1, 94) = 4.723$, $p < 0.03$ (Fig. 1A). A significant treatment × block interaction for working memory errors, $F(1, 7) = 2.140$, $p < 0.0378$ (Fig. 1A) indicated that the performance of the two groups changed at different rates, and

FIG. 1. Effect of estradiol and cholesterol treatment on performance during acquisition of the radial maze task with four arms baited. (A) Mean (±SEM) number of errors committed over the course of acquisition on the working memory component of the task. Estrogen and cholesterol groups ($n = 12$) differed over the course of acquisition (*$p < 0.03$). (B) The mean (±SEM) number of errors committed during acquisition by the two groups on the reference memory component of the task were not significantly different. (C) The mean (±SEM) number of errors committed on the working/reference memory component of the task were not significantly different.

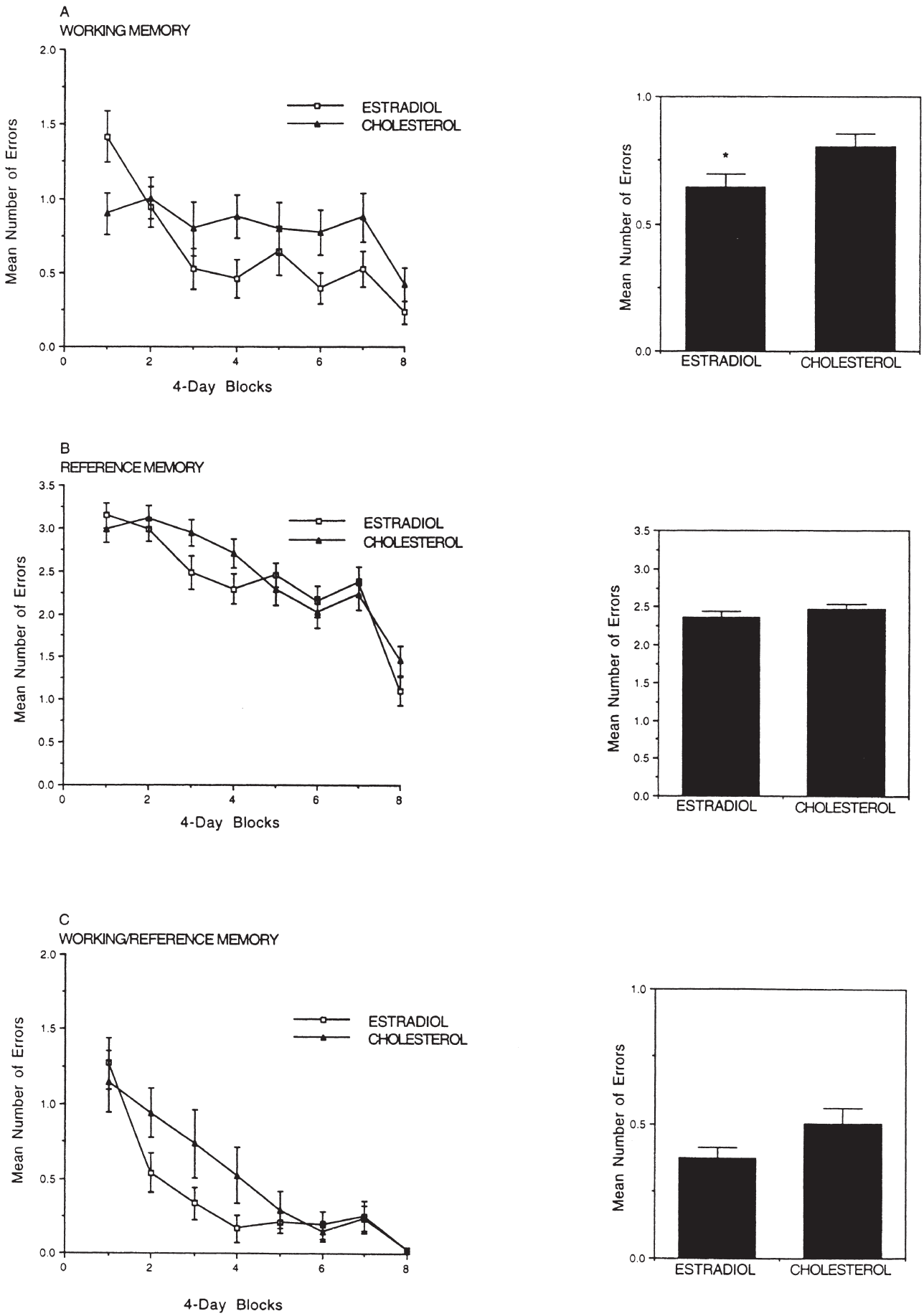
A
WORKING MEMORY
Mean Number of Errors
ESTRADIOL
CHOLESTEROL
4-Day Blocks
*
ESTRADIOL
CHOLESTEROL
B
REFERENCE MEMORY
C
WORKING/REFERENCE MEMORY

Fig. 1A illustrates that much of this difference occurred over the first three blocks. There were no significant differences in the number of reference, $F(1, 94) = 1.132$, $p < 0.2902$, or working/reference memory errors, $F(1, 94) = 3.221$, $p < 0.08$, committed by the estrogen-treated and cholesterol-treated females (Fig. 1B and 1C, respectively) over the course of acquisition. In addition, no significant treatment × block interactions existed for reference, $F(1, 7) = 1.392$, $p < 0.206$, or working/reference memory, $F(1, 7) = 1.444$, $p < 0.185$, errors.

Data from day 32 were compared to data collected on day 33 after administration of scopolamine by separate, two-factor (treatment × day), repeated-measures ANOVAs. Cholesterol-treated animals made significantly more working memory errors after scopolamine administration than on day 32, $F(1, 11) = 8.587$, $p < 0.0137$ (Fig. 2A), but estrogen-treated animals did not (Fig. 2A). Scopolamine did not affect the numbers of reference or working/reference memory errors (Fig. 2B and C, respectively).

Although plasma levels of estradiol were not determined in this study, postmortem inspection indicated uterine proliferation only in females with estradiol capsules.

DISCUSSION

The results of this experiment demonstrate that estradiol, delivered continuously via Silastic capsules to ovariectomized rats, improved working memory performance during acquisition of the radial-arm maze task with four arms baited, and prevented the disruptive effects of scopolamine on that task. Performance on the reference memory and working/reference memory components of the task was not affected by estrogen or scopolamine.

The reduction in number of working memory errors committed by estrogen-treated animals during the acquisition phase of the present study is consistent with the results of studies that employed other tasks that depend on working memory such as the eight-arm baited radial maze (10), T maze (12), and two-way active avoidance (52). However, the lack of a significant difference between the estrogen-treated and cholesterol-treated groups during acquisition of the reference memory component of the task was not unexpected, as there are no reports in the literature of estrogen treatments producing positive effects on reference memory performance. The mild reduction in working/reference memory errors in estrogen-treated females did not reach statistical significance.

The prevention by estrogen of impairments in working memory performance following scopolamine administration in the present study may be the result of the action of the hormone on the hippocampus. Lesion studies have demonstrated that disruptions of hippocampal functioning impair performance on working-memory-dependent tasks such as the eight-arm radial maze (23,41), and behavioral deficits induced by lesions of the hippocampal system mimic those produced by systemic administration of scopolamine (8). Recent work

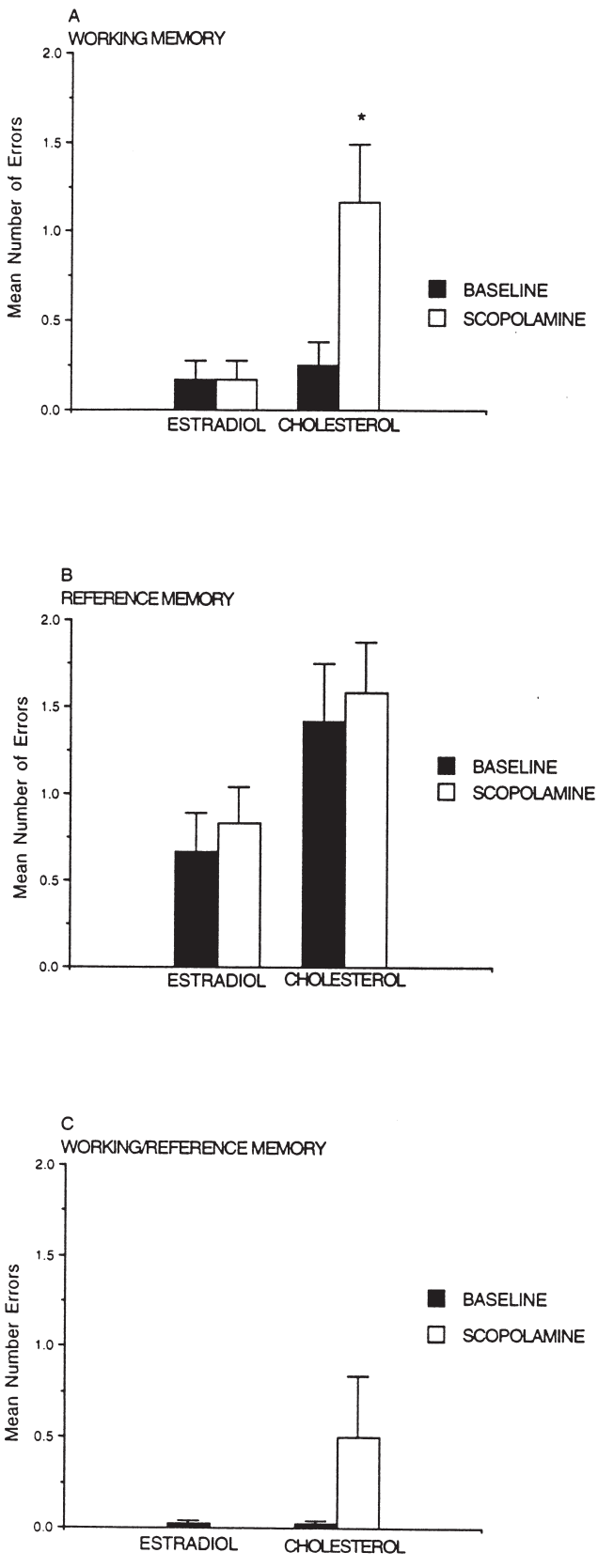

FIG. 2. Effect of estradiol and cholesterol treatment on resistance to the amnestic effects of scopolamine hydrobromide (0.2 mg/kg). (A) Scopolamine produced no increase in mean (±SEM) number of working memory errors among the estradiol-treated group, but did cause a significant change in the mean (±SEM) number of reference memory errors committed by the estradiol or cholesterol groups. (C) Scopolamine caused no significant change in the mean (±SEM) number of working/reference memory errors committed by the estradiol or cholesterol groups.

from our laboratory has demonstrated that scopolamine produces disruption of working memory performance in the T maze when delivered to the CA1 field of the dorsal hippocampus (12), a result that has also been demonstrated in the CA3 field (6). In contrast, systemic estrogen treatments bolster cholinergic functioning in the hippocampus, as evidenced by increases in activity of choline acetyltransferase (29,52), as well as relative levels of its mRNA in the medial septum (19), an area that projects cholinergic efferents to the hippocampus. Estrogen also acts as a growth factor for cholinergic neurons (26), facilitates reactive fiber growth in hippocampi of ovariectomized rats (36,49), and increases dendritic spine density in area CA1 (38,64) by reducing GABAergic neurotransmission within interneurons in this region (37). GABAergic interneurons in the CA1 subfield of the hippocampus contain estrogen receptors while pyramidal cells in this area do not (60), indicating that the hormone may exert its actions on the hippocampus via these interneurons. The estrogen treatments employed in the present study may have caused changes in hippocampal cholinergic function sufficient to counter the effects of scopolamine.

Estrogen improved performance during acquisition of the working memory component of the current experiment but did not affect reference memory or working/reference memory performance. Estrogen has produced beneficial effects on performance of working memory tasks such as the eight-arm radial maze (10,32,33), while in the Morris water maze, a test of spatial reference memory, no effect of the hormone or mild impairments have been reported (15,16,28,58). Estrogen may affect working and reference memory differentially because receptors for the hormone are located on cholinergic neurons in the medial septum and horizontal limb of the diagonal band, basal forebrain structures that send the majority of cholinergic input to the hippocampus (13,17,56). The medial septum is critically involved in working memory function, but does not regulate reference memory (20,21,42). Estrogen administration increases the number of basal forebrain neurons immunoreactive for choline acetyltransferase, the synthetic enzyme for acetylcholine, or its mRNA (17–19), and increases choline acetyltransferase activity in the horizontal limb of the diagonal band and its associated projection sites, such as the hippocampus (29,31,52). Lesions of the basal forebrain produced by the cholinergic immunotoxin 192 IgG-saporin induce performance impairments in spatial working memory tasks (50,57) but not spatial reference memory tasks (1,2,4). Therefore, if estrogen is acting on basal forebrain cholinergic neurons that influence working memory performance through their projections to the hippocampus, the impact of the steroid on working memory function without an effect on reference memory is not surprising.

The inconsistencies in the literature pertaining to the effect of scopolamine on reference memory errors have been attributed to differences in doses of the drug used and the level of training of the animals [for review, see (34)]. The dose of scopolamine employed in the present study (0.2 mg/kg), as well as some lower doses, reduced working memory performance on the T maze task to chance levels (9,11), and impaired choice accuracy in a standard eight-arm radial maze task (35) and in an eight-arm maze task with delays between the fourth and fifth choices (7). However, higher doses of scopolamine, ranging from 0.4 mg/kg to 1.0 mg/kg, can produce impairments in tests of reference memory as well (34,40). The lack of a scopolamine effect on reference memory in the current experiment may reflect the relatively low dose used. Alternatively, because the dose was sufficient to impair working memory performance, it is possible that the larger amounts of scopolamine used in other studies disrupt working and reference memory performance by causing generalized impairments in cognitive functioning (47,48). It has been suggested that in the four-arm baited radial maze task, reference memory errors will increase significantly following scopolamine administration if a sufficient number of training trials have been conducted to reduce the within-group variability in number of errors committed (34). Although there was some variance in both groups in the present study, the amount of variance within the two groups actually decreased after scopolamine was administered, implying that any differences in the magnitude of response to scopolamine should not have been masked by variability within the groups; however, the small increase in reference memory errors caused by scopolamine was not found to be significant.

The results of the current experiment indicate that estrogen exerts a selective effect on spatial working memory without affecting reference memory. When administered to rodents, estrogen treatments improved performance on spatial working memory tasks such as the T maze, eight-arm baited radial maze, and eight-arm maze with delays between the fourth and fifth arm choices (10,12,32,33), as well as nonspatial working memory tasks such as two-way active avoidance and a working memory version of the water maze (52,44). In contrast, estrogen impaired performance on the standard Morris water maze task, a test of spatial reference memory (15,28).

Research into the effects of estrogen on human memory also demonstrates that the hormone selectively improves performance on tests of certain types of memory. For example, estrogen has beneficial effects on delayed paragraph recall, delayed and immediate paired associate learning, and verbal ability, but impairs spatial memory (45,51). Estrogen may also improve memory in women with Alzheimer's disease (14,25,39), and reduce the incidence rate of the disease (24,55), although not all studies support this finding (5,22). The collective evidence from studies with both human and nonhuman subjects indicates that estrogen selectively improves functioning on certain measures of memory that require temporary storage of information, such as working memory in rodents and paragraph recall in humans.

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