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Nonhippocampal Muscarinic Receptors Are Required for Nonspatial Working Memory

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WAN, R-Q., K. PANG AND D. S. OLTON. *Nonhippocampal muscarinic receptors are required for nonspatial working memory* PHARMACOL BIOCHEM BEHAV. **58**(2) 361–367, 1997.—The effects of scopolamine on nonspatial working memory were examined in rats with hippocampal lesions and sham operations. Performance was examined using a continuous conditional discrimination task in an operant box. Choice accuracy measured nonspatial working memory. Response bias, delay interval responses, and response probability measured response preference, stimulus control, motivation, and sensorimotor ability. Scopolamine (0.05, 0.075, 0.1, and 0.15 mg/kg) or methylscopolamine (0.1 mg/kg) was injected (IP) 15 min prior to behavioral testing. In both control and hippocampal lesioned groups, choice accuracy declined as the delay interval increased. Scopolamine, but not methylscopolamine, produced a dose-dependent impairment of choice accuracy (interaction of Dose × Delay) in both groups. The scopolamine-induced impairment was not different between the control and hippocampally lesioned rats. Response bias, delay interval responses, and response probability were not affected by scopolamine except at the highest dose, which increased delay interval responses. The results suggest that central muscarinic receptors outside the hippocampus are important for working memory of nonspatial stimuli. © 1997 Elsevier Science Inc.

Anticholinergic Hippocampus Lesions Nonspatial working memory Operant discrimination Scopolamine

THE basal forebrain cholinergic system (BFCS) has important roles in memory and other cognitive functions (see review in 13,36,38). Many studies of BFCS-mediated cognitive functions have focused on the medial septal area (MSA), which projects to the hippocampus (HIP), and nucleus basalis magnocellularis (NBM), which innervates the neocortex.

The septohippocampal cholinergic system has been implicated in the modulation of working memory (7,18,20, see reviews in 36,50). Working memory is a short-term memory that is used to store information for a single trial of an experiment. In contrast, reference memory is used to store general information for an entire experiment (33). Although the septohippocampal cholinergic system may mediate some types of reference memory (2,50), this study focused on its role in working memory. Lesions of either the HIP or MSA impaired working memory (24,30,34,59, see reviews in 2,22,38,47). High affinity choline transport in the HIP was altered following training in a variety of tasks in which working memory was required (11,57). Intraventricular injections of AF64A, a cholinergic neurotoxin, selectively impaired working memory (8,48) and reduced choline acetyltransferase (ChAT) activity in the HIP without altering these measures in the frontal cortex, striatum, and other areas (8). Intraventricular and intrahippocampal injections of 192 IgG-saporin, an immunotoxin, produced substantial reductions in cortical and hippocampal ChAT activity or high affinity choline transport (49,51) and impaired working memory in an operant task (49). Intraseptal injections of 192-saporin selectively decreased high affinity choline uptake in the HIP and impaired working memory (52). Scopolamine (SCOP), a muscarinic antagonist, impaired working memory in a variety of spatial tasks (6,12,41,55). Infusions of SCOP and pirenzepine, a M1 muscarinic antagonist, into the HIP impaired spatial working memory in a delayed T-maze task (7,28) and an operant delayed non-matching

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to position task (15). The results of the association between cholinergic manipulations and behavioral alterations suggest that cholinergic innervation in the HIP is likely to be involved in the modulation of working memory.

The cholinergic system projecting from the NBM to the neocortex may mediate some mnemonic and attentional functions (19,31, see reviews in 13,32,36). Excitotoxic lesions of the NBM impaired working memory in a number of behavioral tasks and reduced ChAT activity in the neocortex (16,24,27). However, other studies examining the role of the neocortical cholinergic system in mnemonic functions have suggested otherwise. An extensive cholinergic cell loss in the NBM and reduction of ChAT activity in the cortical regions induced by excitotoxins (32,46,56) or 192-saporin (5,58) did not produce severe memory impairments.

Although the effect of the central cholinergic system as a whole on memory has been extensively studied, the functional role of the septohippocampal or NBM-neocortical cholinergic system in nonspatial working memory remains unclear. Nonspatial working memory is the one that features of the discriminable stimuli such as frequency of tone, color of light, or shape and texture of objects, but not their spatial locations, are relevant to perform the task. Hippocampal lesions impaired nonspatial working memory in a delayed non-matching-to-sample task in rats (44,59). Recent studies indicated that hippocampal lesions or systemic administration of SCOP impaired nonspatial working memory in an operant nonspatial task, continuous conditional discrimination (CCD; 43,53). However, the contribution of the septohippocampal or NBM-neocortical cholinergic system to nonspatial working memory in the CCD task has remained unclear. Thus, the present study examined the role of the nonhippocampal cholinergic muscarinic receptors in nonspatial working memory. The effects of SCOP on nonspatial working memory were examined in rats with hippocampal lesions and compared to sham-operated rats. The hippocampal muscarinic receptors, which have been implicated in modulation of working memory (7,15,28), were eliminated following extensive hippocampal lesions. Systemic injections of SCOP into rats with hippocampal lesions must affect muscarinic receptors outside the HIP. If nonhippocampal muscarinic receptors are important for the modulation of nonspatial working memory, then injections of SCOP into rats with hippocampal lesions should impair working memory in the task.

METHODS

Subjects

Male Long-Evans rats (Charles River) were 8–9 weeks old at the beginning of the experiment. The rats were housed in standard rodent cages with a 12:12 hour light:dark cycle. Water was restricted to reduce body weight to approximately 80% of the ad lib weight. Additional water was given daily for 4 min in the home cage at least 2 hours after behavioral training was finished. Seven controls and 6 rats with hippocampal lesions were included in the present study. The subjects of this study were previously involved in an experiment that examined the effect of hippocampal lesions on nonspatial working memory (53).

Surgery

Bilateral hippocampal lesions were produced by passing current (Grass LM4 Lesion Maker; Grass Instruments, Quincy, MA) through a stainless steel electrode, insulated except for 1.0 mm at the tip. Each rat was anaesthetized with Nembutal (pentobarbital sodium injection, USP, 50 mg/kg, i.p.). A stereotaxic apparatus held the rat's head with the incisor bar set 5 mm above the ear bars (42). The scalp was cut and retracted. Multiple holes were drilled through the skull (see Table 1 for the coordinates). The electrode was lowered at each coordinate. Current was 16–18 mA for 18 sec. Control rats received the same surgical procedure, except as follows. The holes were drilled through the skull at the same coordinates as those used in rats with hippocampal lesions but the electrode was not lowered. The skin was sutured. Food and water were given ad libitum for 7 days.

Apparatus and Behavioral Procedure

Nonspatial working memory was examined using the CCD task in an operant box (27 × 30 × 26 cm) that was enclosed in a sound-attenuating chamber. A stainless steel lever (BRS/LVE, Model SRL-003) was mounted on each side of the front panel of the chamber, 4 cm above the floor and 7 cm from the center of the front panel. A water dispenser was centered between two levers on the front panel and 5 cm above the floor, delivering about 0.1 ml water following each correct response. The CCD task had two nonspatial discriminative stimuli, a Sonalert (2900 Hz) and a panel light (Sylvania No.1819, 28 V) that were located 17 cm and 14 cm above the water dispenser, respectively. All events were controlled, and the data were recorded by an IBM PC computer with software and interface (MED, Associates, East Fairfield, VT).

Rats were tested in a 90 min session. For half of the rats, the left lever was the nonmatch (NM) lever and the right lever was the match (M) lever. The other half of the rats had the opposite contingency. For each trial, either a light or a tone was presented. A NM trial was one in which the stimulus of the current trial was different from the stimulus on the previous trial; the correct response was to press the NM lever to obtain reinforcement (water). For NM trials, 60% of the correct responses were followed by water. A M trial was one in which the stimulus of the current trial was the same as the stimulus on the previous trial; the correct response was to press the M lever. For M trials, only 20% of the correct responses were followed by water. In each session, one half of the trials were NM trials and the other half were M trials. NM and M trials were presented randomly. The interval between the presentation of two stimuli was the delay interval. Three delay intervals, 2.5, 10, or 20 sec, were delivered randomly.

TABLE 1

STEREOTAXIC COORDINATES USED FOR BILATERAL HIPPOCAMPAL LESIONS

Placement	Anterior or Posterior to Bregma	Lateral to Sagittal Suture	Ventral from Surface of Cortex
1	+0.4	1.0	4.2
2	−0.8	1.2	3.2
3	−1.6	1.5	3.2
4	−2.4	2.5	3.3
5	−2.4	4.6	8.5
6	−3.6	3.0	3.3
7	−3.6	5.3	5.5
8	−3.6	5.3	7.5
9	−4.8	4.5	4.0
10	−4.8	5.5	6.0

The CCD task had four behavioral measures: 1) choice accuracy (A′), which measured nonspatial working memory; 2) response bias (B′′), which measured a relative response preference for the NM or M lever. Choice accuracy and response bias were calculated at each delay interval using the equations by Grier (23); 3) response probability, which measured the probability of responding to a stimulus when it was presented. Response probability was the number of trials with any response (correct or incorrect) divided by the total number of trials (53); 4) delay interval responses, which measured the total number of responses during the delay interval.

To maintain a stable performance, all rats were tested daily in the CCD task following recovery from surgery. The working memory deficits induced by hippocampal lesions were examined during the first two months after lesions. The present study examining SCOP-induced working memory impairments was conducted immediately after completing evaluation of lesion-induced deficits during a period corresponding to 60-150 days after lesions.

Drugs

SCOP hydrobromide (Aldrich Chemical Company Inc, Milwaukee, WI) and SCOP methylbromide (Sigma, St. Lois, MO) were diluted in physiological saline at an injection volume of 1 ml/kg. Drugs were administered IP 15 min prior to the behavioral testing. The doses of SCOP were 0 (saline), 0.05, 0.075, 0.1 and 0.15 mg/kg. A single dose of SCOP methylbromide was 0.1 mg/kg. The drugs and doses were randomized. Each dose was repeated at least twice. A minimum of 4 sessions without an injection intervened between drug sessions. The data obtained from sessions without injections represented basal performance in both groups.

Statistics

Multivariate analysis of variance (MANOVA) with repeated measures was performed to analyze choice accuracy and response bias. Analysis of variance (ANOVA) with repeated measures was used to analyze delay interval responses and response probability.

RESULTS

Histology

Electrolytic lesions consistently destroyed most of the hippocampal structures (CA1, CA3, and dentate gyrus) and fimbria-fornix (Figure 1). The corpus callosum and a large portion of the subiculum were damaged bilaterally in all rats. A small portion of entorhinal cortex was damaged bilaterally in most of the rats. Slight unilateral damage to the anterodorsal and laterodorsal thalamic nuclei occurred in one rat (53).

Lesion-Induced Memory Impairments

The results of lesion-induced impairments in working memory had been published elsewhere (53). Briefly, hippocampal lesions impaired severely working memory shortly after lesions. This impairment was delay dependent. During the first two weeks of post-operative testing, the hippocampal lesion group had mean choice accuracy of 0.72, 0.66, and 0.59 as compared to the mean choice accuracy of 0.84, 0.77, and 0.72 in the control group at 2.5, 10, and 20 sec delay intervals, respectively. Following continuous testing, performance of lesioned rats was improved substantially. Immediately preceding the present study, all control and lesioned rats performed at nearly asymptotic levels. However, hippocampal lesions produced long-lasting and delay-dependent memory impairments. Lesioned rats had consistently lower choice accuracy than control rats. Impairments in choice accuracy of lesioned rats were particularly evident as the delay interval was extended and the number of NM trials increased in a session. Regardless of the lesion-induced impairments in the function of working memory, the lesions had no impairments in other aspects of performance, which was indicated by an absence of group differences for response bias, response probability, and delay interval responses

Basal Performance

Control and lesioned rats performed at asymptotic and stable levels during the entire period of assessing the effects of SCOP. Choice accuracy of lesioned rats was impaired relative to control rats (main effect of Lesion, $F(1, 11) = 12.48$, $p < 0.01$, Figure 2). Choice accuracy decreased as the delay interval increased in both groups (main effect of Delay, $F(2, 22) = 49.15$, $p < 0.001$). However, lesioned rats had a larger decrease than control rats (interaction of Lesion × Delay, $F(2, 22) = 4.32$, $p < 0.03$, see no injection on Figure 2).

Effect of Scopolamine

In both groups of rats, SCOP decreased choice accuracy in a dose-dependent manner (Figure 2, main effect of Dose, $F(4, 44) = 5.64$, $p < 0.001$). An increase in dose of SCOP produced a larger impairment at a long delay interval than at a short one (interaction of Dose × Delay, $F(8, 88) = 7.49$, $p < 0.001$). Although the lesioned group had lower choice accuracy than the control group (main effect of Lesion, $F(1, 11) = 9.28$, $p < 0.01$), this difference in choice accuracy was produced originally by hippocampal lesions and not due to an interaction of SCOP and hippocampal lesions. There were no interactions of Lesion × Dose and Lesion × Dose × Delay, indicating that the magnitude of impairments produced by SCOP at different doses was similar between groups.

Response bias for both groups was not influenced by SCOP. A responding bias to the NM lever was present in both groups following a short delay interval regardless of injection of SCOP (main effect of Delay, $F(2, 22) = 8.15$, $p < 0.01$, data not shown). Delay interval responses increased as the dose of SCOP increased (main effect of Dose, $F(4, 55) = 3.72$, $p < 0.01$, Figure 3). However, the effects of SCOP on delay interval responses were not different between groups (no interaction of Lesion × Dose). Response probability for both groups was not altered by injections of SCOP.

Effect of Methylscopolamine

Choice accuracy for both groups was not altered by methylscopolamine (Figure 1). At a dose of 0.1 mg/kg, SCOP impaired choice accuracy (SCOP vs. saline, $F(1, 11) = 12.50$, $p < 0.01$), but methylscopolamine did not (methylscopolamine vs. saline, non significant; methylscopolamine vs. SCOP, $F(1, 11) = 8.21$, $p < 0.02$). Injections of methylscopolamine had no effect on response bias, delay interval responses and response probability.

DISCUSSION

The present study had two significant results. First, SCOP impaired working memory as assessed in a nonspatial task using operant boxes. Second, SCOP produced similar memory impairments in controls and rats with hippocampal lesions.

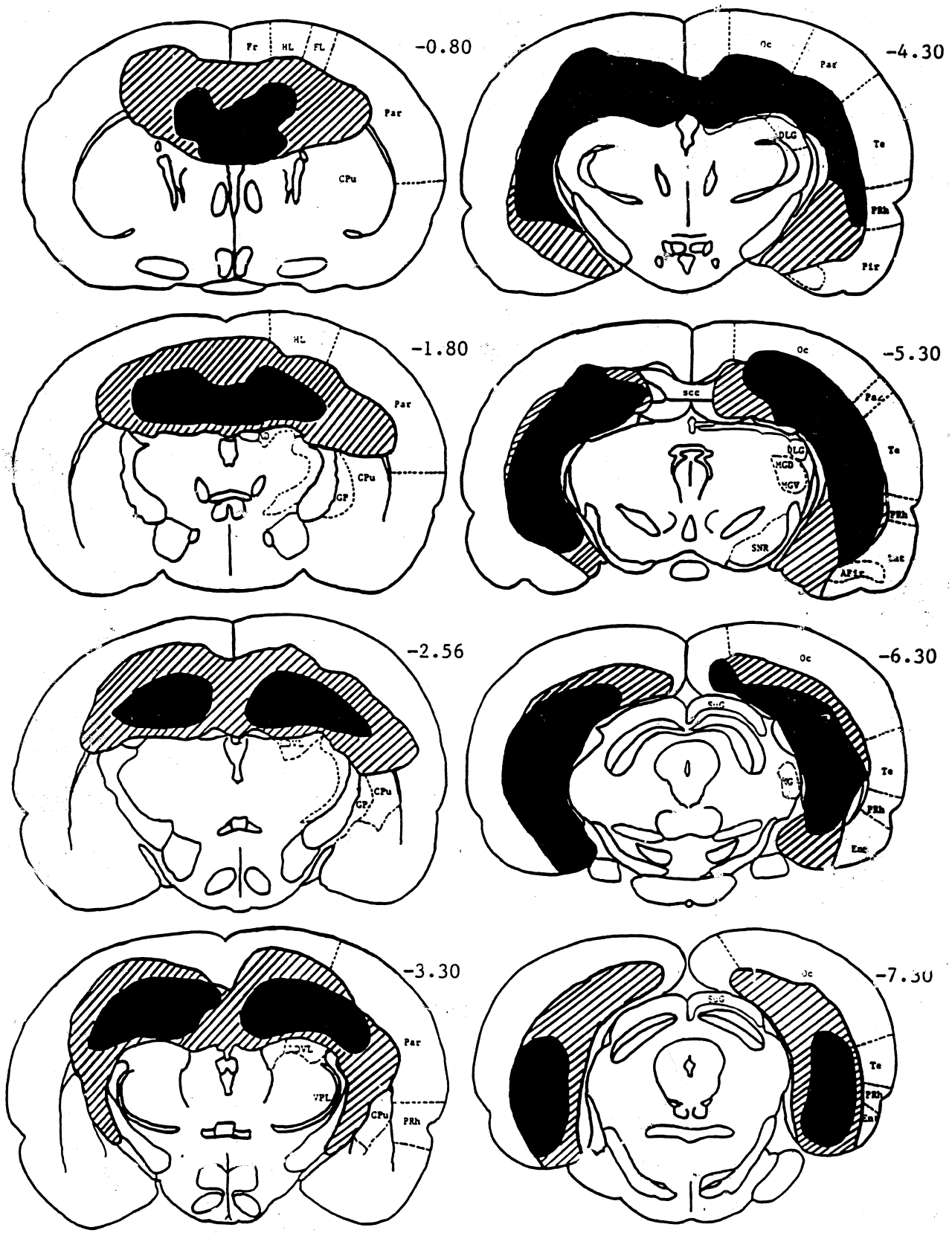

FIG. 1. Reconstructions of the largest (hatched) and smallest (black) hippocampal lesions. Numbers on coronal sections indicate distance posterior to bregma in millimeters. Sections are redrawn from the atlas of Paxinos and Watson (40; Wan et al, 1994, reprinted with permission from APA).

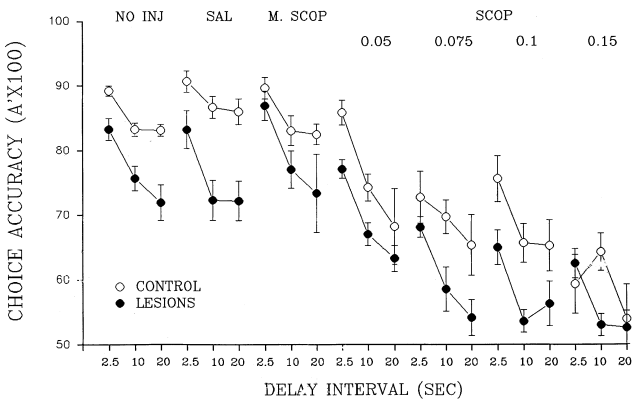

FIG. 2. Choice accuracy in the CCD task following injections of saline, methylscopolamine, and scopolamine. Symbols indicate the mean and vertical bars indicate the SEM. Abbreviations: NO INJ: no injection; M. SCOP: methylscopolamine; SAL: saline; SCOP: scopolamine.

Although previous studies using a similar nonspatial working memory task indicated that SCOP impaired working memory (9,43), the results of the present study is the first to demonstrate that SCOP impairs nonspatial working memory in rats with complete hippocampal lesions.

The impairment of choice accuracy induced by SCOP is likely due to its antimuscarinic effect on nonspatial working memory as suggested by three sets of results from the present study. First, the effect of SCOP on working memory was due to its actions on muscarinic receptors of the central system because methylscopolamine, an agent that does not readily pass the blood brain barrier, did not affect choice accuracy. Second, only choice accuracy, a measure of accuracy of working memory, was impaired. By contrast, response bias, which measured a preference to either of the response levers, and response probability, which reflected a responding capacity of rats, were not influenced by SCOP. Thus the impairment of choice accuracy cannot be readily interpreted as disruptions in other psychological processes such as perception, responding preference and motivation. Third, an increase in dose of SCOP produced a larger impairment of choice accuracy at a long delay interval than at a short one (an interaction of Dose × Delay). Deficits in choice accuracy as a function of delay interval have been interpreted as a primary impairment of short-term memory or working memory (14,37). Thus, the dose- and delay-dependent memory impairments produced by SCOP in hippocampally lesioned rats provide evidence that muscarinic receptors outside the HIP are important for nonspatial working memory.

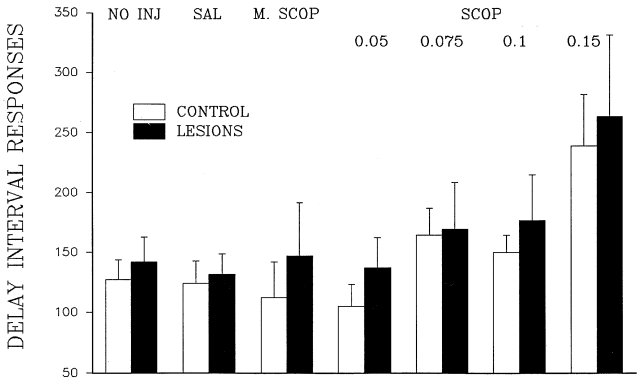

FIG. 3. The number of delay interval responses in the CCD task following injections of saline, methylscopolamine, and scopolamine. The height of the bar indicates the mean and the vertical line indicates the SEM. See Figure 1 for the abbreviations.

Of importance was the lack of interactions of Lesion × Dose and Lesion × Dose × Delay in memory impairments produced by SCOP. Because of the presence of a significant main effect of Dose, the lack of interactions suggests that SCOP-induced memory impairments in hippocampally lesioned rats are attributable to the effect of SCOP on muscarinic receptors outside the HIP but not to hippocampal lesions. These results also suggest that SCOP at given doses in the present study induced similar memory impairments in lesioned and control rats. Thus, the SCOP-induced impairments are independent of the lesion-induced memory deficits. This result was partially supported by a recent study indicating that spatial working memory in an operant task was impaired in rats with partial hippocampal lesions following intrahippocampal injections of saporin. However, SCOP did not produce greater impairments in lesioned rats relative to controls (49).

The results that SCOP produced similar memory impairments in controls and rats with hippocampal lesions do not exclude a role of the hippocampal muscarinic receptors in the modulation of nonspatial working memory. Previous studies indicated that intraseptal injections of saporin or intrahippocampal injections of muscarinic antagonists impaired nonspatial as well as spatial working memory (7,15,19,20,28,49,52), suggesting that the septohippocampal cholinergic system and possibly hippocampal muscarinic receptors are involved in the modulation of working memory. It remains to be further studied why SCOP did not produce greater impairments of nonspatial working memory in hippocampally lesioned rats relative to controls from the present study. There are several possibilities that may explain the lack of greater impairments in lesioned rats. First, all rats had received extensive pre- and post-surgical training. Extensive behavioral training may improve postoperative performance (35), possibly due to some compensatory mechanisms occurring in different neural systems. Future studies are required to investigate the involvement of other neural systems in the functional compensation. Second, some non-cholinergic systems may contribute to the modulation of nonspatial working memory, particularly following lesions. The septum contains cholinergic and noncholinergic neurons that project to the HIP and other cortical regions (17,29). Activities of noncholinergic neurons may be altered by intraseptal infusions of a variety of agents, SCOP, muscimol, and β-endorphin, which all induced working memory impairments in a number of tasks (18,19,20,54). Third, the central nicotinic receptors may be involved in cholinergic modulation of memory (10,25,26). SCOP blocked muscarinic receptors, but did not alter the function of nicotinic receptors. A recent study indicated that a blockade of either muscarinic or nicotinic receptors in the prefrontal cortex impaired working memory in spatial tasks (21). Thus, a role for nicotinic cholinergic receptors in nonspatial working memory, particularly in hippocampally lesioned rats, may be important.

Nonhippocampal muscarinic receptors have an important role in the modulation of nonspatial working memory as suggested by the fact that SCOP impaired working memory in rats with complete hippocampal lesions. Further studies would be necessary to localize those muscarinic receptors out-

side the HIP that are functionally involved in the modulation of nonspatial working memory. In addition to the septohippocampal cholinergic system, the cholinergic projection from the NBM to the neocortex has been proposed to be involved in some psychological functions (see reviews in 13,32,37,38). The role of the NBM-neocortical projection in attentional function has been well supported by a number of recent studies. Lesions or pharmacological manipulations in the NBM impaired attentional functions in a variety of tasks (31,39,45,46). An involvement of the NBM-neocortical system in nonspatial working memory has been suggested by lesions of the NBM in primates and rats (1,3,27). A large number of studies have examined mnemonic functions of the NBM in a variety of spatial tasks and the results have been inconsistent, possibly due to differences in neurotoxin and behavioral tasks (13,32,38). Previous studies using selective lesions of the NBM with 192 IgG-saporin indicated that a selective loss of NBM cholinergic cells was not sufficient to impair spatial working memory in several behavioral tasks (5,58), although histological, biochemical, and electrophysiological results confirmed the specificity and selectivity of lesions in the NBM-neocortical projection (58). However, a recent study demonstrated that spatial memory deficits in rats with NBM lesions were ameliorated by neocortical grafts with genetically modified cells that produce acetylcholine (60). This result supports the notion that the neocortical cholinergic activity may be important for mediation of some mnemonic functions. Thus the use of highly selective cholinotoxins and anticholinergic agents would be important for further characterization of the NBM-neocortical cholinergic systems in nonspatial working memory.

SCOP was suggested to produce relatively selective impairments of working memory (4), and has been frequently used as a reference amnestic agent (9,43). However, SCOP at high doses may impair reference memory in addition to working memory (50). In the present study, the highest dose of SCOP (0.15 mg/kg) markedly increased the number of delay interval responses, suggesting an impairment of reference memory. Other studies have also reported a general disruption of performance following high doses of SCOP (0.2 and 0.3 mg/kg), i.e., decrease in response probability, increase in delay interval responding, and alteration of response bias (9,43,47). Thus, the results from the present and previous studies suggest that a disruptive effect of SCOP at high doses may not be limited to working memory. Reference memory and sensory discriminative processes may be disrupted by high doses of SCOP.

In summary, the present study examined the SCOP-induced impairments of nonspatial working memory in rats with hippocampal lesions. SCOP produced dose- and delay-dependent working memory impairments in both lesioned and control rats. However, rats with hippocampal lesions had similar SCOP-induced memory impairments relative to controls. The results suggest that the central muscarinic receptors outside the HIP plays an important role in the modulation of nonspatial working memory.

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