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BRIEF COMMUNICATION

Differential Effects of Scopolamine on Working and Reference Memory Depend Upon Level of Training

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GRETTE LYDON, R., AND S. NAKAJIMA. *Differential effects of scopolamine on working and reference memory depend upon level of training.* PHARMACOL BIOCHEM BEHAV 43(2) 645–650, 1992.—Controversy exists whether the cholinergic system in the brain is involved in working memory (WM) selectively or in both WM and reference memory (RM). Rats were trained to obtain food from four baited arms of an eight-arm radial maze. The remaining arms were never baited. Three types of errors were recorded: entry into unbaited arms (RM errors), reentry into baited arms (WM errors), and reentry into unbaited arms (WRM errors). There were no differences among three control conditions: methyl scopolamine, physiological saline, and uninjected. Scopolamine increased WM but not RM errors. When rats were trained to a higher criterion of learning, however, both WM and RM were impaired. It appears that when baseline error rate is sufficiently low RM errors under scopolamine become observable. The results suggest that the cholinergic system is involved in both WM and RM, and the selective involvement of WM is the result of insufficient training. The controversy in the literature over the involvement of the cholinergic system in WM and RM was addressed.

Scopolamine Anticholinergic drugs Working memory Reference memory Radial maze
Acetylcholine Cholinergic neurons

THERE is controversy in the literature over the role of the central cholinergic system in learning and memory. Research examining the effects of anticholinergics like scopolamine and atropine has been equivocal. While a number of investigators have reported impairment in various operant or classical conditioning procedures due to cholinergic blockade (1,12), others have not found disruption in learning and memory processes after administration of anticholinergics (2,18). The discrepancy has been attributed to a variety of factors, including the degree of training, complexity of the task, and dosages of the drugs, with anticholinergics causing a greater disruption in partially trained rather than well-trained animals, in more complex tasks (11), and at higher dosages (27). Moreover, anticholinergics may also reflect nonassociative or performance effects, such as interference with attentional or motivational processes (15).

Radial maze techniques have been proposed to offer an inviting alternative to earlier procedures as their requisite tasks may more closely resemble the natural food-seeking behavior of species such as rats (25). When all arms of a radial maze are baited, the solution to the task requires working memory (WM) because the correct response to the arm (to enter it once and obtain the reward) changes within a trial (17). The literature is consistent in demonstrating such working memory deficits following administration of scopolamine during the acquisition (28,31) and also retention of previously learned radial maze tasks (6,9,31). Of particular interest to the present research are studies employing tasks that included a reference memory component. Reference memory (RM) is required when a subset of arms is unbaited because the correct response to the arm (to avoid entering it) always remains the same (24).

There has been inconsistency in the studies that examined both types of memory on a radial maze. While scopolamine has been found to impair WM selectively (3,33), Okaichi and Jarrard (22) reported that scopolamine impaired both WM and RM. The findings of a selective impairment of WM but not of RM are consonant with the early studies of fimbria-fornix lesions to the hippocampus (24). Given that the septo-hippocampal pathways contain cholinergic neurons (19) and that administration of scopolamine results in behavioral defi-

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cits similar to those occurring after hippocampal lesions (7), it has been thought that the selective effects of hippocampal lesions seen are due to disruption of cholinergic pathways.

Beatty and Bierley (3) suggested that the complex statistical tests used by Okaichi and Jarrard (22) may have masked a selective effect on WM. In addition, it is important to assess the peripheral actions of scopolamine as cholinergic receptors are widely distributed in both the central and peripheral systems and as the performance effects due to the peripheral actions of anticholinergics can be substantial (13). Beatty and Bierley (3) included a peripheral control. In their study, however, there is the possibility of residual or carryover drug effects as their rats had previously participated in experiments examining the effects of other drugs.

The present study was conducted to shed a light on the nature of scopolamine effects on performance of a radial maze task requiring WM and RM. Scopolamine methylnitrate, a peripheral anticholinergic that does not readily cross the blood-brain barrier, was used as a control drug. A pilot test was run to determine the highest dosage level that would not substantially disrupt mobility or appetitive behavior. Animals were experimentally naive. Entry into previously visited arms but not unbaited arms would suggest that the cholinergic system is selectively involved in WM. The findings of impairment of both memory components would suggest a more nonspecific involvement of the cholinergic system in both memory functions.

EXPERIMENT 1

METHOD

Subjects

Subjects were 12 experimentally naive, male, hooded rats of the Long-Evans strain. They were housed individually in a colony room on a 12 L : 12 D cycle. Purina Lab Chow diets were supplemented from the onset with Noyes pellets to reduce bait shyness. Food regimen began 2 weeks before training, and initial free feeding weights of 328–433 g were reduced to 85%. Animals were fed upon completion of daily testing; water was always available.

Apparatus

A wooden eight-arm radial maze painted gray was placed in a fixed position in a testing room. The center platform of the maze was 20 cm in diameter, and each arm was 40 × 9 cm with a 2-cm high wall along each side of the length. Every other arm was made detachable so that the apparatus could be used as a four-arm (cross) maze. End borders of the arms were numbered 1–8 for identification, and a black line was drawn across the width of each arm 25 cm from the end to define the animal's entry. The maze was elevated 52 cm from the floor, and the position of each leg was marked on the floor. A brass food cup was placed at the end of each arm. The cup was sufficiently deep to hide the food from an animal standing on the center platform. Stuffed animals, pictures, and wall hangings were placed around the room to serve as distal visual cues. The positions of the planted cues and the furniture (a table, two chairs, and a stool) were marked to ensure constancy with respect to the maze. The test room (3.4 × 2.4 m) was well illuminated by two incandescent 100-W ceiling lights.

Training

Animals received one training session daily 7 days a week. The first five sessions were given using only four arms of the maze. Prior to every session, each food cup was baited with one Noyes pellet (45 mg). On the first day of training, the rat was placed near a food cup to facilitate exploration. For remaining sessions or trials, the rat was placed on the center platform and allowed to move freely until either all four arms were chosen or 10 min elapsed. On day 6, the other four arms were attached with an empty food cup at each end. The procedure was the same as in the earlier sessions.

Four paws beyond the black line marked on the arm constituted an entry, and a correct response was defined as the first entry to a baited arm. A trial was terminated when an animal made all four correct responses. Three types of error were recorded. Reentry to a baited arm was regarded as a WM deficit. First entry to an unbaited arm was considered an error in RM, and reentry to an unbaited arm was regarded as a deficit of both WM and RM (WRM). Rats were trained to a criterion of at least three correct responses on the first four choices for three consecutive trials. Throughout the experiment, the maze was wiped and rotated 90° in a clockwise direction prior to each trial. The rotation discouraged the use of local cues, but the relation of the baited and unbaited arms to extramaze stimuli remained constant.

Drug Testing

Testing began once all rats reached criterion. Scopolamine HCl (0.50 mg/kg) was dissolved in physiological saline and administered IP. An equimolar concentration of scopolamine methylnitrate (0.56 mg/kg) as well as an equal volume of physiological saline (0.5 ml/kg) were similarly administered as control injections. Scopolamine and scopolamine methylnitrate were obtained from Sigma Chemical Co. (St. Louis, MO). Injection was given 20 min prior to testing, and injection test trials were separated by 2- to 3-day intervals. To control for possible effects due to circadian cycles, all trials were given at approximately the same time of day.

Several days before experimental tests, animals were given a practice series of trials to familiarize them with injection procedures and immediate drug effects. One round of experimental testing consisted of five trials. The order of injection was counterbalanced with respect to scopolamine and scopolamine methylnitrate. For the first trial, no injection was given and each rat was tested in the same manner as during training. For the second trial, half the rats were tested after scopolamine injection while the other half were tested after methyl scopolamine. During trial 3, each rat was tested under physiological saline. During trial 4, the order of scopolamine and methyl scopolamine was reversed. An additional no-injection trial was given in the final session and the data were combined with those in the first trial as baseline. This round of five trials was repeated three times.

RESULTS AND DISCUSSION

Among the 12 subjects, 1 died and another completed only one response under scopolamine. The results are based on the remaining 10 rats. They all reached criterion within 32 days of training. In the last 3 days of training, animals made more RM errors (1.67) per trial than WM (0.43) or WRM errors (0.20). The finding that rats made substantially more RM errors during training precludes the interpretation that the differential effects on errors reflect differences in task difficul-

ties. Had scopolamine interfered with the more difficult task, RM errors would have been higher during testing because the animals made more RM errors during training as well as in the baseline trials.

The means for the three types of error under test conditions are shown in Fig. 1A. A one-way analysis of variance (ANOVA) with repeated measures was performed on each type of error. The effect of treatment was significant in WM errors, $F(4, 36) = 7.438$, $p < 0.01$, and in WRM errors, $F(4, 36) = 12.764$, $p < 0.01$, but not in RM errors, $F(4, 36) = 1.434$. For WM and WRM errors, posthoc contrasts (Duncan's new multiple-range test) indicated that the errors under scopolamine were significantly greater in number than the errors under control conditions, $p < 0.01$. There were no significant differences, however, in errors among the three control conditions (baseline, saline, and meth-scop).

The differential effects on the types of errors did not appear due to changes in perceptual, motivational, or motor mechanisms produced by the drug. If animals failed to attend to distal cues, for example, then all types of errors should have increased more or less equally. Under the scopolamine condition, six rats consumed all of the food. The remaining four rats occasionally dropped crumbs from a pellet as they ate in a somewhat clumsy fashion. The fact that all rats showed high WM errors, regardless of whether they finished all the pellets or not, rules out motivational deficit as an explanation. Indeed, Eckerman et al. (9) found that Noyes pellets continue to be reinforcing even after 1.0 mg/kg scopolamine, double the dosage used herein. While slower under scopolamine, subjects were sufficiently mobile to complete the task requirements. The means for the response latencies per trial (time to complete a trial by making four correct choices) were 173.1 s for scopolamine, 109.5 s for methyl scopolamine, 75.9 s for saline, and 53.4 s for the baseline trials. With respect to response patterns, there was little tendency to perseverate or repeat sequences. The crucial determinant for the differential effects of scopolamine on this task appeared to be the type of memory required: working memory vs. reference memory.

EXPERIMENT 2

The results of Experiment 1 suggest that an interference with central cholinergic transmission impairs WM but not RM. This conclusion is congruent with that of Beatty and Bierley (3) and Wirsching et al. (33) but not with that of Okaichi et al. (23), who found scopolamine to impair both WM and RM. One source of this discrepancy may be the different levels of baseline performance for the WM and RM measures. For the WM task, the means in either baseline or control sessions are similar and fairly low across investigations (all under 0.73 errors per trial). On the other hand, the reported means of RM errors for baseline or control sessions seem substantially higher (range = 1.2-2.7) for all but the Okaichi et al. (23) experiment (less than 0.3). It is possible that there were differences between scopolamine and control conditions during the RM task in the former studies but that they were masked by high baseline error rates. Indeed, Beatty and Bierley (3) reported that while WM errors are reduced to

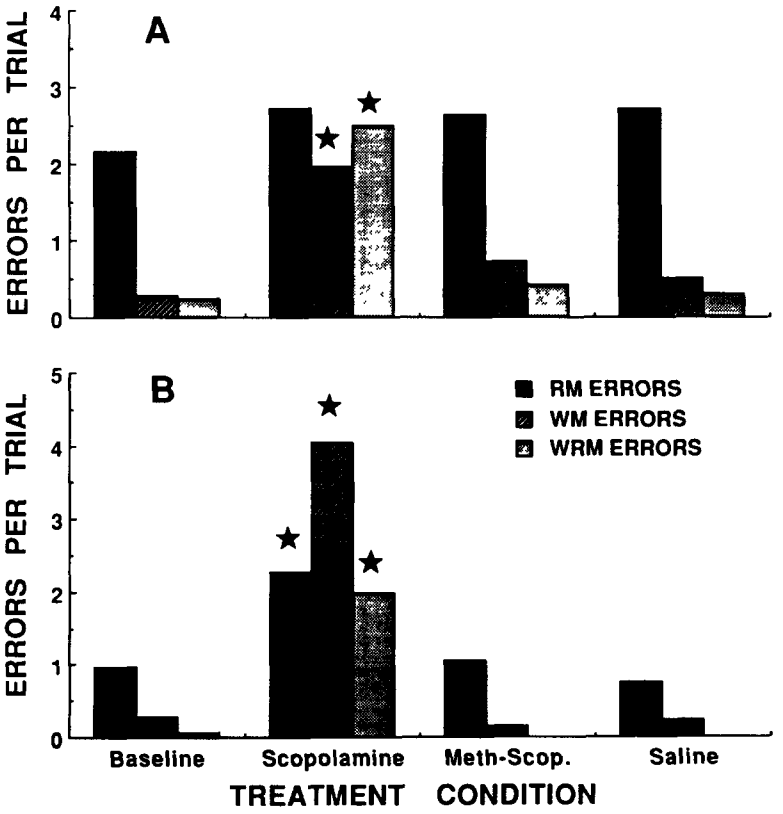

FIG. 1. (A). Means of three types of errors per trial under each condition in Experiment 1. (B). Means of three types of errors per trial under each condition in Experiment 2. *Significant difference from control conditions.

very low or zero levels RM errors decline only after more extensive training.

Earlier studies using radial maze tasks without the WM/RM distinction suggest that level of training may be a critical variable. Eckerman et al. (9), for example, reported that scopolamine reduced choice accuracy in rats with 5–7 days of training. Buresova and Bures (6), however, found that while scopolamine impaired performance after a delay interval between choices it did not disrupt performance of an uninterrupted task in their highly trained animals. It should be noted that Buresova and Bures (6) used a very small dose (0.1 mg/kg). There is likely an optimal dose that affects cognitive performance in individual animals without substantially disrupting appetitive behavior or mobility. That dose was about 0.5 mg/kg for the present animals.

Experiment 2 was designed to determine whether scopolamine would exert differential effects as seen in Experiment 1 after rats had been trained to a more stringent criterion. Were well-trained rats that showed a small number of RM errors in the control sessions to increase their RM errors under scopolamine, then the differential effect would not be a universal phenomenon.

METHOD

Twelve additional rats, experimentally naive, were trained on the maze with the same control conditions and in a similar manner as in Experiment 1. It was found that prior to training a sugar-coated cereal (Froot Loops, Kellogg) seemed highly palatible to the rats, which consumed a great quantity under no food deprivation. We thus decided to use a Froot Loop (about 67 mg) as a reward. Animals were given three trials of training per day. The criterion of learning was: a maximum of one error in three consecutive trials, that is, the animal had to be either completely error free in all three trials or show one error in only one of the three trials. This criterion was more stringent than that in Experiment 1 where the animal could make one error in every trial. During testing, only one trial was given daily. The animal was left on the maze until it had entered all baited arms or 10 min elapsed.

RESULTS AND DISCUSSION

One rat failed to complete the task within 10 min under scopolamine and was excluded from the analysis. The results are therefore based upon 11 rats. All animals reached the criterion of learning in 25–58 days (mean = 41.2). Figure 1B shows the means for the three types of errors under each condition. The differences between conditions were significant for each type of error as indicated by repeated-measures ANOVA, $F(3, 30) = 30.83$ for WM errors, $F(3, 30) = 14.78$ for WRM errors, and $F(3, 30) = 9.90$ for RM errors, all $p < 0.01$. Posthoc contrasts (Duncan's new multiple-range test) indicated that the WM, WRM, and RM errors were all significantly higher under scopolamine than under control conditions ($p < 0.01$). There was no significant difference in errors among the control conditions.

The means for the response latencies per trial were 190.5 s for scopolamine and 106.4 s for the three control conditions. The longer response latency was due partly to the numerous errors made under scopolamine and partly to slower responding. The mean choice latency (time for each rat to enter an arm and to return) was 16.2 s (± 1.7, SEM) under scopolamine and 13.0 (±0.5) under control conditions. It is possible that animals made more WM errors under scopolamine because they took longer to run in each arm. A correlation calculated between the choice latency and the number of WM errors in the scopolamine condition, however, was not significant, $r = -0.32$, $t(10) = 1.88$. Thus, the WM errors under scopolamine were not secondary to increased running time. None of the rats left any food unfinished. This could be construed to indicate a higher level of motivation in Experiment 2 than in Experiment 1, suggesting that a high level of motivation interfered with performance when the learning criterion was more stringent, as suggested by the Yerkes-Dodson law. This interpretation was not supported because the significant difference between the scopolamine and control conditions did not come from a higher number of RM errors under scopolamine. The difference resulted from a reduction in error scores in the control conditions. The higher level of motivation may have helped rats achieve a higher criterion of learning but did not seem to interfere with their performance.

It is now clear that animals make more RM errors, as well as more WM and WRM errors, under scopolamine relative to control conditions. The differential effects of scopolamine found in Experiment 1 were not a universal phenomenon. The failure to find a significant increase in RM errors under scopolamine in Experiment 1 can probably be attributed to the relatively high RM errors under control conditions. The means for RM errors under control conditions for the five studies are plotted from highest to lowest and shown in Fig. 2. It is noteworthy that the criteria of learning employed by the various investigators fall in inverse order to the plotted

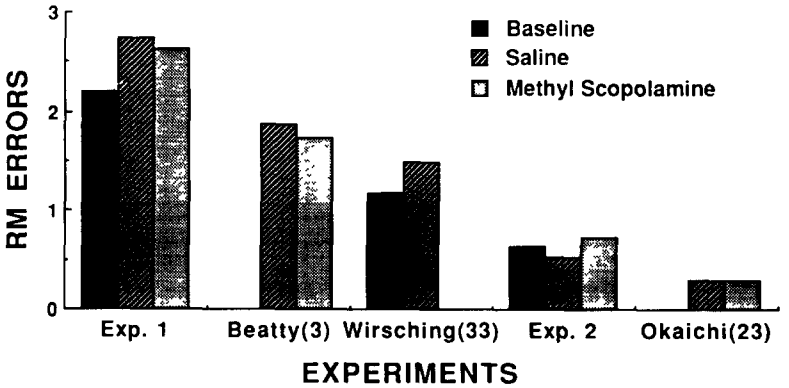

FIG. 2. Means of RM errors from highest to lowest under control conditions for five studies. Numbers in parentheses refer to reference citations.

means. The learning criteria were 75, 87, 92, and 95% for the present Experiment 1, Wirsching et al. (33), the present Experiment 2, and Okaichi et al. (23), respectively. Although Beatty and Bierley (3) did not employ a baseline for comparison purposes or a learning criterion per se, they did report that a change in reinforcement prior to their scopolamine study led to an increase in baseline errors in the RM but not the WM component of the task. (RM errors increased from 0.68 to 1.28 under food and liquid reinforcer, respectively.) The first three studies (Fig. 2) employing lower criteria of learning also found differential effects of scopolamine on the two types of memory.

GENERAL DISCUSSION

Scopolamine increased both WM and RM errors in rats trained to a high criterion of maze learning but appeared to increase WM errors selectively in rats trained to a lower criterion of learning. The results of Experiment 2, which employed the high learning criterion, are congruent with those of Okaichi et al. (23), who also employed a high criterion. The finding of selective impairment of working memory when lower criteria were used is similar to findings of studies where animals were not as well trained or showed a more variable baseline performance (3,33). The present experiments suggest that the critical variable underlying the discrepancy in investigations of anticholinergic effects on the two types of memory is the level of training.

It appears that there are substantial differences in baseline error rates for WM and RM. With animals trained to a lower criterion, these differences make it easier to detect an impairment in WM. With well-trained animals, baseline error rates decrease sufficiently to permit the deficit in RM to be manifest. It is likely that the relatively high baseline error rates for RM in the Beatty and Bierley (3) study masked the effect of scopolamine on reference memory. In the Wirsching et al. (33) study, chronological trials during baseline testing decreased significantly for RM but not WM. Had Wirsching and colleagues trained their rats until RM baseline scores stabilized to the score on the final day of training (which was similar to that for WM baseline), a difference between baseline and scopolamine conditions on the RM measure would probably have been found.

It is well documented that the effects of scopolamine on a wide range of performance variables are dose dependent (13). Nonetheless, it is doubtful that differences in dosage account for the inconsistencies in the working/reference memory studies. Whereas Wirsching et al. (33) found impairment in WM with 0.1 mg/kg, Beatty and Bierley (3) and Okaichi et al. (23) reported no disruption in performance with a similar dose. With higher doses (0.4–0.8 mg/kg), Beatty and Bierley (3) and the present Experiment 1 reported selective impairment in WM, while Okaichi et al. (23) and the present Experiment 2 found disruption of both WM and RM. Such contradictory results at similar dosages preclude attributing the aforementioned inconsistencies to dose levels.

Our results address the discrepancy in the literature regarding the effects of anticholinergics on the two types of memory. As Okaichi et al. (23) pointed out, studies with anticholinergics reporting both specific impairment of WM (5) and disruption of both WM and RM (26) continue to be published. A similar contradiction exists in the lesion literature. Selective impairment of the WM component of tasks on a T maze (4) and on a radial maze (16) has been reported after lesions to either the nucleus basalis or the hippocampus. On the other hand, deficits in both WM and RM have also been reported (20,21). Studies of spatial reference memory in isolation have indicated deficits after both anticholinergic treatment (29,32), and lesions to the nucleus basalis (32) or medial septum/diagonal band (14). Differences in baseline rates of responding or level of training, among other variables (13), may also account for some of the findings in those lesions studies that used the radial maze paradigm. It is worth mentioning that the paradigm, which affords the opportunity to refine an experimental question into effects on specific types of memory, has had heuristic value. The present research has underscored the need for future investigators using this paradigm to equate the baseline measures of the two memory components.

In the present study, interference from peripheral effects, motor or movement impairments, task difficulty, and motivational factors was ruled out. Despite these controls, the results of Experiment 2, in which scopolamine affected both WM and RM, undermine the exclusion of perceptual/attentional factors. Actually, our results question the validity of the argument made in Experiment 1 and in diverse other studies that the finding of differential effects on selective tasks within experimental conditions necessarily rules out confounds due to certain performance factors. With respect to possible interference from attentional mechanisms, it has been demonstrated that normal sensation and attention depend upon intact cholinergic transmission (10,30). Indeed, Dunne and Hartley (8) suggested that scopolamine acts to modulate selective attention rather than memory consolidation processes. The challenge of examining the effects of anticholinergics or lesions on attentional and memory processes independently awaits future research.

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