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Scopolamine Degrades Spatial Working Memory but Spares Spatial Reference Memory: Dissimilarity of Anticholinergic Effect and Restriction of Distal Visual Cues[1]

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BEATTY, W. W. AND R. A. BIERLEY. *Scopolamine degrades spatial working memory but spares spatial reference memory: Dissimilarity of anticholinergic effect and restriction of distal visual cues.* PHARMACOL BIOCHEM BEHAV 23(1) 1–6, 1985.—The influence of the centrally active anticholinergic, scopolamine hydrobromide, on working and reference memory was studied in rats tested in a 12-arm radial maze. Both 0.25 and 0.5 mg/kg doses of the drug increased the number of working memory (WM) errors but had no effect on reference memory (RM) errors. A lower dose (0.125 mg/kg) was ineffective, as was the peripherally active anticholinergic, scopolamine methylbromide (0.5 mg/kg). Some of the behavioral effects of anticholinergics on spatial memory are mimicked by blindess or eliminating distal visual cues. If distal visual cues were more important for maintaining accurate WM than for RM, the selective effect of scopolamine on WM could be easily explained. But surrounding the maze with a curtain to eliminate extramaze cues increased RM errors without significantly increasing WM errors. Thus, the selective effect of anticholinergies on spatial memory in the radial maze is qualitatively different from the effect of restricting distal visual cues and must arise from some other action of the drug.

Scopolamine Anticholinergic drugs Spatial memory Working memory Reference memory Distal visual cues Rats

TREATMENT with centrally active forms of the anticholinergic drugs, scopolamine and atropine, 10–30 minutes before testing consistently disrupts spatial working memory as assessed in the radial maze. Impaired performance has been observed during acquisition [24,29] by naive subjects as well as in animals that are already proficient in remembering the win-shift rule required for successful performance on the task [3,6]. In the aforementioned studies all arms of the maze were initially baited so the task can only measure working memory. However, if only a subset of arms (usually half) are baited, the subject must learn not to enter the unbaited arms (a reference memory [RM] task) as well as to enter each of the baited arms only once during the session (the working memory [WM] component). In this test treatment with anticholinergics clearly disrupts the WM component [11, 17, 30].

Left unresolved by the available data is the effect of anticholinergics on RM performance in the radial maze. Using rats, Okaichi and Jarrard [17] reported that scopolamine disrupted both the working and reference memory components equivantly for both cue and place problems. By contrast, Wirsching, Beninger, Jhamandas, Boegman and El-Defrawy [30] found that scopolamine increased only WM errors reliably. The increases in RM errors they observed after drug treatment were not statistically significant. Levy, Kluge and Elsmore [11] also observed that atropine, but not methylatropine, increased working but not reference memory errors in mice. But they also noted that the drug increased the number of repeated visits into never baited arms (i.e., repeated reference memory errors). The authors interpreted this latter kind of error as a type of WM error, but it is just as reasonable to consider it as a class of RM errors.

Because the effects of anticholinergic treatment on RM in the radial arm maze remain unclear, the present study was performed to reexamine the effects of scopolamine on both working and reference memory components of spatial memory under conditions in which an assessment of the peripheral as well as the central actions of the drug could be made.

EXPERIMENT 1

METHOD

Animals

The subjects were 11 male albino rats that were experi-

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mentally naive when they were obtained from the Holtzman Co., Madison, WI at 2.5 months of age. They were caged singly in an air-conditioned animal room that was illuminated from 0800–2000 by overhead fluorescent fixtures. Water was freely available in the home cage; Purina Lab Chow pellets were given in an amount sufficient to maintain body weight at 80–85% of the free feeding level adjusted for growth.

Apparatus

A symmetrical 12 arm radial maze constructed of wood painted white was mounted on a pedestal 60 cm above the floor in the center of a 3.4×4.7 m room. Each arm of the maze measured 9×74 cm and contained a small plastic food cup (0.7 cm deep × 3 cm diameter) at the end. Black plastic side walls (13 cm high) ran the length of both sides of each arm. A single 23 cm h × 30 cm l clear Plexiglas barrier was placed on each arm to prevent animals from crossing arms outside the central platform. The arms extended from a central hub (diameter=36 cm) like spokes from a rimless wheel. Clear plastic guillotine doors (8 cm w × 31 cm h) located at the junction of the hub and the arms were remotely controlled by an overhead system of nylon lines to regulate access to the arms of the maze. Illumination was provided by a 150 W light bulb mounted 1.8 m above the center of the maze. Surrounding the maze were a rich variety of extramaze stimuli including 2 shuttleboxes, 3 relay racks, several large wooden chambers, a large metal cabinet, a table and a chair where the experimenter sat, a blank wall and a doorway.

Procedure

For each rat the 6 arms to be baited were selected at random. During preliminary training a single 190 mg Noyes pellet was placed in the food cup at the end of each designated baited arm. The animals were adapted to the maze by raising the doors to the 6 baited arms. When the rats entered and ate from all 6 arms in 20 min (which required 5–7 sessions), pretraining began. During pretraining the rat was placed on the center hub and the doors to all 12 arms were raised. Testing continued until the rat entered all 6 baited arms or 20 min elapsed. A choice was recorded when the rat walked close enough to the end of an arm such that its nose touched an imaginary cylinder over the food cup. Entries into arms that were never baited were considered RM errors while reentries into baited arms that had already been visited on that session were considered working memory errors. During the 50 pretraining sessions the average number of WM errors per session dropped from a mean of 1.84 during the first 5 sessions to a mean of 0.24 during the last 5 sessions (i.e., sessions 46–50). Over the same training interval RM errors dropped from a mean of 4.66 per session to a mean of 0.68 per session. By the end of pretraining all rats consistently completed the session in 5 min or less.

For the next 36 sessions the rats participated in experiments concerned with the effects of amphetamine on working and reference memory. In these experiments the rats received a total of 6 injections each of 0, 0.5 or 1.0 mg/kg d-amphetamine sulfate([1], Experiments 1 and 2). During these tests, which were conducted using 190 mg Noyes pellets as the rewards for correct choices, performance under the saline control condition remained at the levels achieved by the end of pretraining for both working and reference memory error rates.

Previous experience in this laboratory [8] as well as in many other laboratories indicates that the peripheral anticholinergic properties of scopolamine make it nearly impossible for rats to ingest large dry food pellets. Accordingly rats were shifted to a liquid reinforcer (0.25 cc of an 8% sucrose solution) over the next 33 sessions. Otherwise the testing procedures remained unchanged. Surprisingly performance on the RM component of the task deteriorated and the excellent performance displayed when Noyes pellets served as the rewards was never regained. On the last 5 sessions for surcrose, RM errors averaged 1.28 errors/session. By contrast, the rats made comparatively few WM errors while running for sucrose and averaged 0.34 WM errors/session over the last 5 sessions.

Since there was no indication that additional training with sucrose would lower the RM error rate, the formal experiment began at this point using 0.25 cc of 8% sucrose as the reward for correct choices. For the next 15 days, the rats received IP injections (1 ml/kg) of 0, 0.125, 0.25 or 0.5 mg/kg scoplamine hydrobromide or 0.5 mg/kg scopolamine methylbromide 20 min prior to testing. Both drugs were purchased from Sigma Chemical Co., St. Louis, MO and were prepared by dissolving the drug in physiological saline. Doses are expressed as the weight of the salt. The order of drug treatment was counterbalanced within and between subjects according to a block randomized replicated Latin Square design. Thus each animal was tested 3 times at each dose of each drug with the constraint that each rat was tested with every dose of each drug before it received a subsequent test with any dose of either drug. On a given session testing continued until the rat entered and consumed the sucrose from all 6 baited arms or 10 min elapsed. For unknown reasons 1 rat failed to complete 2/3 of its sessions under all treatment conditions including saline. Its data were excluded from the analysis.

Data Analysis

Initial analyses of the data indicated that there were no reliable effects of blocks of testing on either working or reference memory errors. Hence the data for each drug condition were averaged over the 3 blocks.

At the highest dose of scopolamine hydrobromide (0.5 mg/kg) failures to complete the session occurred in about 25% of the tests. These failures arose either because the rat failed to enter any arms or because it made many errors. (If rats entered baited arms they consumed the reward.) To deal with this problem the data were analyzed in 2 different ways: (1) considering only those sessions in which all baited arms were entered and (2) considering all sessions on which at least 4 baited arms were entered. Since both analyses yielded comparable results, only the latter data are reported. The latter is the more conservative estimate of scopolamine disruption because of the higher error rate by many rats who failed to visit all arms in the allotted 10 minutes. Comparison of performance under the saline and methylscopolamine control conditions revealed that there were no reliable differences for either working or reference memory error rates. Consequently performance under these two conditions was averaged for both dependent variables. The number of repeated entries into arms that were never baited (i.e., repeated reference memory errors) was so low as to preclude a meaningful statistical analysis. Over all subjects and all tests only 3 such errors occurred during saline tests while no such errors occurred when the rats were injected with methylscopolamine. For the 0.125, 0.25 or 0.5 mg/kg doses of scopolamine hydrobromide the total number of repeated reference memory errors was 2, 1, and 0 respectively.

TABLE 1

MEAN NUMBER OF ERRORS/SESSION

Drug		Methyl-scopolamine	Scopolamine HBr (mg/kg) 0	0.125	0.25	0.5
Working Memory	Mean	0.27 (0)	0.27 (1)	0.33 (1)	0.77 (3)	0.69 (7)
	SEM	0.16	0.17	0.21	0.19	0.16
Reference Memory	Mean	1.73	1.87	1.37	1.83	1.72
	SEM	0.28	0.33	0.30	0.40	0.28

Numbers in parentheses are the number of sessions (out of 30) that were not completed within 10 min.

RESULTS AND DISCUSSION

As seen in Table 1 scopolamine hydrobromide increased the number of WM errors but did not affect the number of RM errors. Within-subjects analyses of variance confirmed the apparent effect of drug treatment on the WM error rate, $F(327)=2.98$, $p<0.05$, and the absence of drug effect on RM errors ($F < 1$). Subsequent tests indicated that both the 0.25 and 0.5 mg/kg doses of the centrally active form of scopolamine increased the rate of WM errors relative to the combined control condition, $ts(9)>2.99$, $p<0.02$, but the modest effect of the lowest dose was not statistically significant.

Although we did not record choice or session time, the apparent dose-dependent increase in the number of times scopolamine-treated animals failed to complete the session within 10 min is in good agreement with earlier studies [6, 11, 17] suggesting that centrally active anticholinergics slow speed of responding.

It might be argued that because large baseline differences exist in the error rates for working and reference memory errors, it is therefore easier to detect an impairment in WM. This explanation is improbable for the following reasons: (1) While the RM error rate (1.80 errors/session) was certainly high relative to the WM error rate, it was low relative to the RM error rate (4.66 errors/session) for the same subjects early in training. (2) If one examines RM error rates for the five most proficient subjects, the average number of RM errors per session was 1.07 for the combined control conditions versus 1.13 and 1.10 for 0.25 and 0.5 mg/kg scopolamine hydrobromide conditions. (3) In a subsequent study ([1], Experiment 3) using the same rats and sucrose reinforcement for correct choices we found that 2 mg/kg d-amphetamine sulfate increased both WM and RM error rates (from 0.5 to 1.8 and 1.3 to 2.7 errors per day respectively) while a lower 1 mg/kg dose was ineffective on either measure. Clearly the failure to observe a significant increase in RM errors cannot have arisen because of a ceiling effect.

EXPERIMENT 2

Wirsching *et al.* [30] suggested that scopolamine selectively affects WM because this agent disrupts the cholinergic inputs to the hippocampus which Olton [18] has suggested is critically important to the integrity of normal WM.

Although this idea has considerable empirical support [18, 20, 21, 28], other workers have reported [9,14] that large hippocampal lesions cause persistent deficits in both WM and RM, an observation that may raise difficulties for the interpretation advanced by Wirsching *et al.* [30].

In the present experiment we tested an alternative hypothesis regarding the differential effects of scopolamine on WM and RM. The hypothesis essentially postulates that in the radial maze distal visual cues are more important in controlling WM than RM. The idea arises from our own unpublished observations that at least with some training procedures, WM errors are reduced to nearly 0 levels in 10–15 sessions while RM errors remain at much higher levels, and decline only after much more extensive training. Furthermore, in some tests of spatial behavior the effects of anticholinergics are quite similar to those of blindness. For example, in the Morris water maze rats treated with the centrally active anticholinergic, atropine sulfate, or rats that were peripherally blinded by enucleation never improved their initial heading errors, despite extensive training. On this measure, their behavior approximated that of normal rats for whom the target was randomly moved from day to day (i.e., for whom improvement in initial heading was impossible.) On the other hand both atropinized and blinded rats did learn to escape from the maze more rapidly with training [25].

Although much evidence demonstrates that distal visual cues from the extramaze environment provide the major sensory inputs essential to accurate WM, other stimuli can clearly guide behavior when these visual cues are unavailable. Blinded rats eventually acquire accurate performance in the radial maze, and if they are trained preoperatively, their performance is only transiently impaired by blinding [5]. Moreover, in the parallel-arm maze, an apparatus designed to make spatial coding by distal visual cues very difficult, sighted and blinded rats learn at similar rats which are appreciably slower than rates of learning by sighted animals in the radial maze [4]. Finally thirsty rats can learn to return to the one of 8 identical bottles from which they have drunk if they are passively transported more than 1 m away from the target through a route that involves one 90° turn. Following blinding accurate performance on this task can be relearned [22].

These considerations indicate that accurate spatial behaviors occur without visual guidance although learning is slow in the absence of visual cues. If elimination of RM errors proceeds slowly because distal visual cues are less important for controlling RM than they are for WM, then eliminating such cues should differentially affect WM and RM, preferentially increasing WM errors.

METHOD

The same 11 rats and apparatus were used. By the time of the present study the rats were 11 months old and had received a total 215 sessions in the maze. Subsequent to Experiment 1 they were tested in an amphetamine study (referred to above) and an experiment concerned with the effects of ECS on WM and RM. In the latter experiment they were tested for about 1 month with a delay of 4 hr imposed between their 3rd and 4th choices. Each rat received 3 ECS treatments identical to the low intensity ECS described in [23].

About one week after the completion of the ECS experiment the rats were readapted to the maze using the same testing procedures as in Experiment 1 except that each baited arm contained a single 190 mg Noyes pellet instead of the sucrose solution. Because of their extensive prior training only two adaptation sessions were required. On alternate days for the next 4 sessions the animals were tested in the usual way with unrestricted view of the rich variety of extramaze cues (control sessions) or with their view of these stimuli restricted by a curtain. The curtain was made of white king size bedsheets hung from a circular rod (285 cm diameter) which completely surrounded the maze. The rod was mounted 244 cm above the floor of the room. Because the floor of the room was stained in one place, providing another potential extramaze cue, on the experimental sessions of the floor was covered with a layer of brown wrapping paper upon which white sheets were laid. It was not practical to cover the top of the maze, so the edges of 2 parallel fluorescent fixtures to which the circular rod was attached were visible to the rats.

RESULTS AND DISCUSSION

Restricting access to distal visual cues increased RM errors (Mean errors per experimental session=2.55 ± 0.71 versus 0.55 ± 0.14 per control session; $t(10)=3.03$, $p<0.01$ but did not reliably affect WM errors (Mean errors per session=0.86 ± 0.42 on experimental sessions versus 0.23 ± 0.16 on control sessions; $t(10)=1.29$,ns). Only 3 of the rats averaged more than 1 WM error per session under conditions of visual restriction (Range: 1.5–4.5) while 7 of the 11 rats averaged more than 1 RM error per session under the experimental condition (Range: 2–7). Four rats were completely unaffected by the experimental manipulation; they averaged no more than 0.5 WM or RM errors per session during both control and experimental tests.

It is important to note that the rats did not solve the WM component of the task by employing any obvious response algorithm, either on experimental or control sessions. Use of a rigid response pattern (e.g., always turn sharply to the right) was precluded by the random distribution of baited arms and we saw no evidence of other consistencies in the sequence of choices from test to test. Finally, in the experiment these rats completed just prior to the present tests, ECS selectively increased WM errors but did not affect RM errors.

Since restricting distal visual cues degraded RM but did not reliably affect WM, exactly the opposite pattern from that caused by scopolamine, our hypothesis regarding the mechanism of anticholinergic action on spatial memory must be rejected.

Given the importance of vision and of distal visual cues for WM in the radial maze our failure to detect a reliable impairment in WM requires some comment. First, 3 animals were cleary impaired. That the remaining 8 animals were unaffected (in terms of their WM error rates) suggests that they were able to use some sort of internal guidance system or some other external cue that we did not restrict to support accurate WM. Their extensive prior experience, which included more than 100 sessions on which their first 3 choices were randomly selected from the set of baited arms, may have facilitated the development of parallel input pathways each with some access to the spatial WM storage system. Since it is clear that following blinding rats can relearn many "spatial" tasks to high levels of proficiency [5,22], the existence of such alternate guidance systems is not in question although their nature is far from clear. Furthermore, while it is clear that rats with extensive training in radial mazes will choose on the basis of extramaze (presumably distal visual) cues if these cues are available [12], O'Keefe [16] reported that some of his rats were able to find the goal in a 3-arm maze even when the lights were turned off. Their performance was accurate even on the first such test. Hence, while it is somewhat surprising that both WM and RM in 4 of the rats were completely undisturbed by restricting distal visual cues, such an observation is not unprecedented.

GENERAL DISCUSSION

The present findings confirm and extend earlier reports [11,30] that treatment with centrally active cholinergic antagonists degrades spatial WM without disrupting RM. The present data make this point more strongly because unlike previous studies RM error rates under scopolamine hydrobromide treatment were actually slightly lower than under control conditions. There is one minor discrepancy between the present findings and those of Levy *et al.* [11]. They reported that atropine increased the number of repeated visits to arms that were never baited while we did not observe such an effect. The most likely explanation of this discrepancy is the number of training sessions prior to the start of drug tests. Our animals had received 128 sessions before their first exposure to anticholinergics while their subjects had received only 20 sessions. Species differences (rats versus mice) as well as differences in the anticholinergic drug used (scopolamine versus atropine) may also be important.

How then could Okaichi ajd Jarrard [17] have observed (apparently) equivalent increases in working and reference memory errors following scopolamine treatment? First, it is important to note that these investigators did not present their data for working and reference memory errors separately. Further, in their statistical analysis they combined working and reference memory error rates in a complex statistical analysis which also evaluated the variables drug dose and type of problem. The inference that working and reference memory were equally disrupted by scopolamine rests on the reported absence of a drug dose × type of memory error interaction. Obviously in this sort of analysis a large drug effect on working memory errors combined with a small drug effect on reference memory errors might lead to the absence of a detectable interaction. Considering that the lowest dose used by Okaichi and Jarrard [17] was the highest dose employed in the present study as well as the fact that reference memory errors were increased, albeit insignificantly at the highest scopolamine dose (0.8 mg/kg) employed by Wirsching *et al.* [30], the appropriate conclusion is readily apparent: At low doses central muscarinic blockade selectively disrupts working memory. At higher doses both working and reference memory may be affected.

Assume for the moment that the foregoing analysis is cor-

rect, namely that the neural mechanisms that subserve spatial working memory are more dependent upon "normal" cholinergic innervation than those that mediate spatial reference memory. Why might this be so?

One possibility is that cholinergic systems are essential to the normal storage of spatial working memories. To test this idea Godding *et al.* [8] imposed a 5 hr retention interval between the first 4 and subsequent choices in an 8 arm maze and administered scopolamine at various times after the first 4 choices. When given immediately after the first 4 choices were completed doses as high as 5 mg/kg did not disrupt the accurate performance (88% correct) seen under control conditions. Hence, the notion that anticholinergics impair the mechanism that maintain storage of spatial working memories can be dismissed. The possibility that scopolamine disrupts WM simply by interferring with the programming of movement sequences also seems unlikely since scopolamine does not interfere with radial maze performance of rats that employ response patterns [29].

A more promising possibility is that cholinergic receptor blockade interferes with the operation of some neural systems that are essential to the normal encoding of spatial WM. Reports from Olton's laboratory [20, 21, 28] that fimbria-fornix lesions cause profound and persistent disruption of WM but only temporary impairment of RM in both spatial and certain nonspatial tasks properly directs attention to the cholinergic input to the hippocampus that arises in the septum since this pathway would be interrupted by these lesions. Likewise the finding [2] that intrahippocampal injections of scopolamine cause greater disruption of spatial delayed alteration than of a visual brightness discrimination is consistent with this view. As noted previously the observation that large hippocampal lesions degrade both WM and RM in the radial maze [9,14] is potentially troublesome for this interpretation although not necessarily devastating. More difficult to reconcile with the view that fimbria-fornix lesions selectively affect WM are data from Morris' laboratory. Using the water maze that he developed Morris [13] reports that both hippocampal and fornix lesions interfere with spatial localization and these deficits are persistent. Finding the location of a hidden platform which is not moved from day to day should engage RM but not WM, so these findings are quite damaging to the view that the hippocampus is principally concerned with WM. Sutherland, Whishaw and Kolb [28] have replicated Morris' findings with large hippocampal lesions and in addition they found that lesions that were restricted to cell fields CA3–CA4 or to the dentate gyrus also disrupted spatial behavior in the water maze. Finally, Oades and Isaacson [15] observed that large hippocampal lesions disrupted learning to avoid unbaited sites in an open field-like arena, another RM task. Given these inconsistencies in the empirical base for the "working memory" theory of hippocampal function it is clearly premature to conclude that centrally active anticholinergies exert their selective effect on spatial WM by blocking cholinergic inputs to the hippocampus.

Instead it seems prudent to consider other cholinergic pathways as possible loci for the selective effect of anticholinergics on spatial WM. In particular, the intrinsic and extrinsic cholinergic pathways of the cerebral cortex merit attention. Complete decortication profoundly disturbs place learning on a variety of tasks, but leaves cue learning undisturbed [31]. In the radial maze lesions restricted to the parietal cortex lead to transient impairment in the acquisition of accurate WM without affecting the development of RM [10]. The similarity to the effects of scopolamine is, at least, intriguing. Furthermore, unlike fimbria-fornix lesions, damage to the parietal cortex leaves behavior in the Morris water maze relatively unaffected.

It has recently been reported that neurotoxic lesions of the nucleus basalis magnocellularis (NBM) interfere with retention of a passive avoidance response [7]. Since the NBM is a major origin of cholingergic fibers to the cortex including the parietal area, it would be interesting to determine the effects of selective interruption of cholinergic inputs to parietal cortex on spatial memory in the radial maze.

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