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Scopolamine Injected Into the Rat Amygdala Impairs Working Memory in the Double Y-maze

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INGLES, J. L., R. J. BENINGER, K. JHAMANDAS AND R. J. BOEGMAN. *Scopolamine injected into the rat amygdala impairs working memory in the double Y-maze.* BRAIN RES BULL **32**(4) 339–344, 1993.—Recent neurochemical results suggest the hypothesis that the nucleus basalis magnocellularis (nbm) cholinergic projection to the amygdala may play a role in memory. The present study investigated the effects of intraamygdaloid injections of the cholinergic antagonist scopolamine on working and reference memory in the double Y-maze. Rats were pretrained until working and reference memory choice accuracy stabilized to a criterion of ≥86% correct. Bilateral cannulae were then surgically implanted in the basolateral amygdaloid complex. Rats (n = 9) received scopolamine in doses of 8.0, 24.0, and 72.0 μg/0.5 μl and saline (0.5 μl) in a counterbalanced order with retraining to criterion between injections. Intraamygdaloid scopolamine produced a dose-dependent and differential impairment of working and reference memory. A dose of 24.0 μg impaired working memory without significantly affecting reference memory; doses of 8.0 μg and 72.0 μg affected neither and both types of memory, respectively. Results implicate amygdaloid acetylcholine in memory.

Acetylcholine Amygdala Double Y-maze Nucleus basalis magnocellularis Reference memory Scopolamine Working memory

IN recent years the cholinergic projections of the basal forebrain have been strongly implicated in memory function (20,26). Excitotoxic lesions of the nucleus basalis magnocellularis (nbm), origin of cholinergic projections to the cortex and amygdala (6,34,35), produced large decreases in cortical cholinergic markers and impaired memory in rats in a variety of tasks (8). However, the magnitude of decrease in cortical cholinergic activity following excitotoxic lesions of the nbm appeared to be unrelated to the degree of cognitive impairment. Several studies (7,10–12,22,28,29,32) compared the effects of quisqualic acid to ibotenate and/or N-methyl-D-aspartate injected into the nbm and showed the latter two to produce greater impairments in memory in spite of similar depletions of cortical choline acetyltransferase by all three excitotoxins.

Because excitotoxins are not specific for cholinergic neurons, a differential loss of noncholinergic cells in the region of the nbm may have contributed to the discrepant neurochemical and behavioural results (12,13,22,29). Alternatively, corticipetal cholinergic projections of the nbm might not have been exclusively responsible for the behavioural deficits following nbm lesions (8). In support of this hypothesis we have found recently that different excitotoxins injected into the nbm differentially affected cholinergic activity in the cortex and amygdala. Studies of dose–response results showed that quisqualic acid was preferentially toxic to the cholinergic projections to the cortex, quinolinic acid was relatively more toxic to the cholinergic projections to the amygdala, and ibotenic acid and N-methyl-D-aspartate did not discriminate between the cortical and amygdaloid projections (3). These observations offer a possible explanation for the reported lack of correlation between cortical cholinergic deficits and behavioural impairments following excitotoxic lesions of the nbm: amygdalopetal projections of the nbm may play a role in memory.

There has been one paper reporting a nonsignificant correlation between cholinergic markers in the amygdala and maze acquisition following nbm lesions (18); however, performance may have been influenced by nonmnemonic variables. Many behavioural investigations have implicated the amygdala in memory (19,24,30). In one study rats received electrolytic lesions of the cortex or basolateral amygdala or ibotenic acid lesions of the nbm after being trained in a radial arm maze. Rats with the amygdala or ibotenic acid lesions displayed an order recognition

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memory deficit equivalent to that found in animals with nbm lesions. In contrast, animals with cortical lesions displayed no significant memory impairment (19). These results suggest that the nbm projection to the amygdala may play a critical role in memory. The purpose of the present study was to disrupt cholinergic neurotransmission by injecting the cholinergic antagonist scopolamine into the basolateral amygdala, a target of dense nbm cholinergic projections. Working and reference memory was evaluated in the double Y-maze, a task that allows for a relatively specific assessment of memory (2).

METHOD

Treatment of the rats in the present study was in accordance with the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care, and relevant University policy and was approved by the Queen's University Animal Care Committee.

Subjects

Nine experimentally naive male albino rats of the Sprague–Dawley Strain (Charles River, Canada), approximately 2 months old, weighed between 250–350 g at the start of the study. All rats were individually housed in a temperature-controlled environment (approximately 21°C) with a 12L:12D regime (lights on at 0700 h). Water was available ad lib in the home cages. Food was rationed daily to maintain the rats at 85% of their free-feeding level. Weights were increased by 7 g per week to allow for growth.

Apparatus

The double Y-maze was elevated 76 cm above the floor and consisted of a centre stem (55 cm long and 15 cm wide) with two arms extending 35 cm from each end of the stem at an angle of 120° [see (2)]. Removable wooden barriers could be inserted at the end of each arm and in the middle of the stem to provide 15 cm compartments. The maze walls (26 cm high) and barriers were painted light grey. The floor consisted of steel grids spaced approximately 1.0 cm apart except at the stem-arm junctions where there were triangular pieces of Plexiglas. Plastic food cups were located in the centre of the goal box adjacent to the end wall of each arm and in the centre of the stem adjacent to the second barrier. Froot Loops cereal was used as a reward and pieces of the cereal were scattered under the grid floor to mask possible reward odour cues. Testing was carried out in a small room in which several visually distinct cues (e.g., lights, door, window) were within sight of the rats in the maze.

Preoperative Training

Food deprivation began 5 days prior to training. During this time the rats were fed their ration of chow plus a small quantity of Froot Loops cereal in their home cages. Pieces of the cereal were subsequently used as food reward in the double Y-maze task.

Rats were given 3 days of habituation to the double Y-maze during which they were free to move throughout the maze for a 10-min period; five food cups containing Froot Loops cereal were placed throughout the maze. Following this period, the animals were given one training session per day of approximately 50 trials for 14 consecutive days. Following this massed training, as the rats began to acquire the maze task, the training was reduced to 24 trials per day, 7 days per week.

The double Y-maze required the rats to use both reference and working memory. Each trial began by placing the rat in one of the end arms of the first Y. Choice of the start location varied randomly with the condition that no more than half of the trials per day were given from the same side. The barrier was then removed and the rat was rewarded for going down the stem, the distal end of which was blocked by a removable barrier. Upon entering this region located in the middle of the stem, a barrier was dropped behind the rat preventing reentry into the first Y. This was the reference memory component of the task and it remained constant from trial to trial. The rat was always to go down the stem in the first Y and enter the box in the middle of the stem regardless of which end arm of the first Y was the starting position.

Following the correct reference memory choice the front barrier in the centre stem was removed to allow access into the second Y; this was the working memory component of the task. The correct working memory choice varied from trial to trial and was dependent upon the initial starting position of the rat. The rat was rewarded for entry into the arm of the second Y on the side of the maze diagonally opposite the side of the first Y from which that particular trial had begun.

When a rat made a reference memory error it was removed from the maze before it could make a working memory choice. In these instances the rat received fewer than 24 working memory trials. In all trials of the first 2 days and in the first 10 trials of the subsequent 12 days of the massed training period (50 trials per day) the rats were permitted to make working memory errors and then enter the correct arm to obtain the Froot Loop reward. During the rest of training and testing, if an incorrect working memory choice was made, the rat was removed from the maze and that trial ended. A working or reference memory choice was defined to have taken place when the hind legs crossed completely onto the grid floor of the arm.

The percent correct reference and working memory choices were recorded daily. Training continued at 24 trials per day until the rats reached a criterion of at least 86% choice accuracy on both memory components over a 3-day block.

Surgery

Rats were trained to criterion in the double Y-maze before surgery. Under sodium pentobarbital anaesthesia (Somnotol, 65 mg/kg interperitoneal) bilateral chronic guide cannulae (0.64 mm diameter) were implanted using standard stereotaxic techniques. The stereotaxic incisor bar was set at 3.3 mm below the horizontal plane passing through the interaural line. The following coordinates for the basolateral amygdaloid nucleus were used: 2.3 mm posterior to bregma, 4.6 mm lateral to the midline, and 8.4 mm ventral to the surface of the skull (27). The guide cannulae were aimed at a site 1.0 mm dorsal to the targeted amygdaloid nucleus so that the tips of the injection cannulae would be located in that nucleus at the time of injection. Animals were allowed free access to food for 5 days postsurgery and then a new 85% free-feeding weight level was determined and the rats were again food-deprived before the initiation of behavioural testing.

Central Drug Injections and Behavioural Testing

After cannulae implantation, training continued with 24 trials per day for approximately 10 days. Once the rats reached criterion, behavioural testing was initiated. A within-subjects design was used to examine the effects of scopolamine hydrobromide (Sigma Chemicals) injected bilaterally into the basolateral amygdaloid nucleus. Every rat received in a counterbalanced order four intraamygdaloid injections: three scopolamine doses (8, 24, 72 μg/0.5 μl) and saline (0.5 μl). The 24 μg dose of sco-

polamine was determined from pilot studies with three animals where it was seen to produce a significant decrease in working memory performance without significantly affecting reference memory performance. Animals were tested on working and reference memory in the double Y-maze immediately following each treatment with a minimum of 3 days of training between each administration of drug or vehicle to reestablish criterion level of performance. As in the training procedure, the percent correct working memory and reference memory choices were recorded.

Scopolamine (8, 24, 72 μg/0.5 μl) was dissolved in saline and delivered in a volume of 0.5 μl. The injection procedure involved administering substances into the amygdala via an injection cannula (0.31 mm diameter) extending 1.0 mm below the guide cannula and connected to a 10.0 μl Hamilton syringe with polyethylene tubing. The microliter syringe was mounted in an infusion pump (Sage Instruments, Model 355) and substances were administered at a constant rate of 1.0 μl/min. The two sides of each rat were injected in sequence. Injection cannulae were left in the amygdala for an additional 60 s following the injection to allow for diffusion of the drug or vehicle.

Histology

After the completion of behavioural testing the rats were anaesthetized with a lethal dose of sodium pentobarbital and then perfused intracardially with saline solution followed by a 4% formalin solution. The brains were extracted and stored in 4% formalin for 4 days before being frozen and sliced coronally into 50 μm sections with a freezing-stage microtome. The sections were mounted on glass slides and stained with thionin to verify cannulae placements.

RESULTS

Histological examination verified that the injection cannulae were located bilaterally within the amygdala in all animals (n = 9). Of these, six animals had bilateral cannula placements in the basolateral amygdaloid complex. Three rats had unilateral cannula placements in the basolateral complex. The cannulae placements for all animals are presented in Fig. 1.

The behavioural analyses were based on the data of the six animals with bilateral cannula placements in the basolateral amygdaloid complex. Mean percent correct responses as a function of the treatment conditions are shown for the reference and working memory components of the task in Fig. 2. The baseline performance measure was obtained from the mean of the percent correct responses during the four 3-day blocks at criterion accuracy, one prior to each drug injection.

To assess the effects of the treatment conditions on working and reference memory performance, two one-way repeated measures analyses of variance were performed. A significant effect of the treatment was found for both reference memory, $F(4, 20) = 7.02$, $p < 0.002$, and working memory, $F(4, 20) = 22.79$, $p < 0.0001$. Subsequent post hoc comparisons with Dunnett's t-tests of percent correct responses showed that the 72.0 μg scopolamine dose differed significantly from the saline control condition for reference memory, $F(4, 20) = 3.44$, $p < 0.05$, and working memory, $F(4, 20) = 7.09$, $p < 0.05$. The percent correct responses at the 24.0 μg scopolamine dose differed significantly from the saline condition only for the working memory component of the task, $F(4, 20) = 4.54$, $p < 0.05$.

In general, the response profile of the three animals with unilateral cannula placements in the basolateral amygdala did not differ from the animals with bilateral cannula placements in the basolateral amygdala. The mean ± SEM percent correct reference memory responses for the baseline, saline, and scopolamine 8.0, 24.0, and 72.0 μg/0.5 μl treatments were 96.2 ± 0.9, 98.0 ± 0.8, 82.0 ± 2.8, 95,8 ± 2.4, and 72.1 ± 4.2, respectively. As there were only three animals in this group, the low value at the 8.0 μg dose was probably due to sampling error. The respective values for working memory were 88.8 ± 0.8, 82.9 ± 2.8, 77.9 ± 0.3, 49.2 ± 5.0, and 46.7 ± 3.9, respectively.

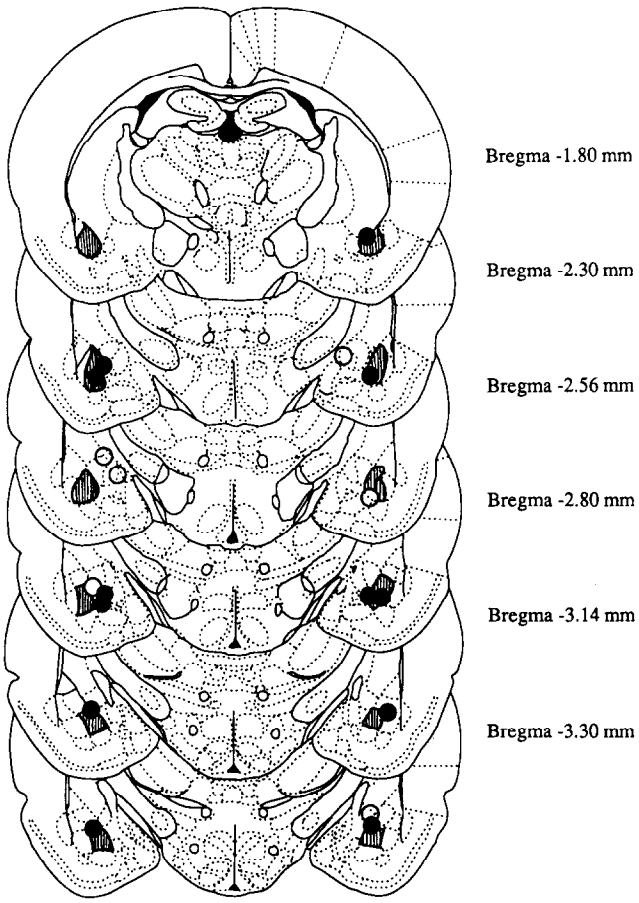

FIG. 1. Location of intracerebral injection sites. Basolateral amygdaloid nucleus is indicated by crosshatching. Solid circles represent placements from rats with bilateral cannulae in the basolateral amygdala (n = 6). Open circles represent placements from rats with only one cannula in the basolateral amygdala (n = 3). Coronal sections were taken from the atlas of Paxinos and Watson (22). Numbers beside each section indicate the distance (mm) posterior to Bregma.

DISCUSSION

Statistical analyses based on data from animals with bilateral cannula placement in the basolateral amygdala showed that intraamygdaloid injections of scopolamine produced a significant disruption in performance of the double Y-maze task. However, similar results were found in animals with only one cannula in the basolateral complex. This might suggest that unilateral blockade of scopolamine-sensitive cholinergic receptors is sufficient to impair behaviour. Previous studies have shown mnemonic deficits following unilateral lesions of the nbm (33).

One advantage of the double Y-maze over other paradigms previously used to assess working and reference memory is that the task demands of each component are identical, i.e., the animal must choose one of two identical arms each radiating at

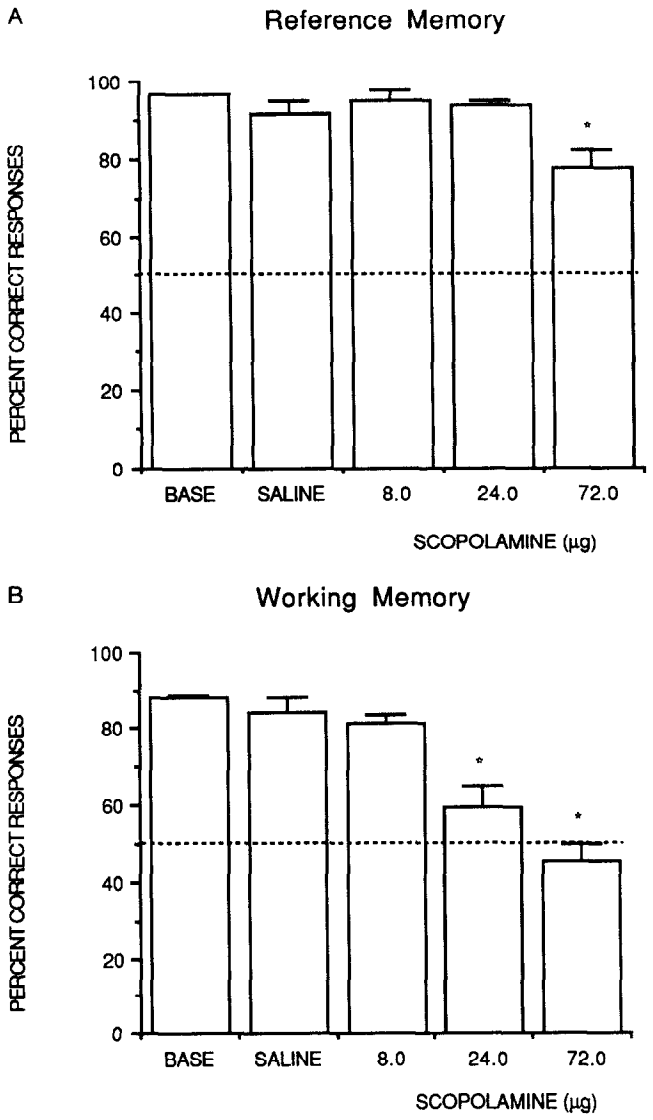

FIG. 2. Mean (±SEM) percent correct responses at baseline (BASE), saline, and scopolamine (8.0, 24.0, and 72.0 μg) conditions for (A) reference memory and (B) working memory components. The baseline measure was obtained from the mean of the percent correct responses during the four 3-day blocks at criterion accuracy prior to each injection. The broken line at 50% correct responses indicates chance performance. $n = 6$. *$p < 0.05$ versus saline injected controls by Dunnett's tests following significant treatment effects in one-way analyses of variance.

120° from the choice point. In this study the scopolamine dose of 24.0 μg caused a selective impairment in choice accuracy of the working memory component. It is unlikely that this dissociation would be produced by a nonmnemonic behavioural deficit, e.g., a motivational or perceptual impairment, because such an impairment would be expected to affect both task components equally. This implies that at the 24.0 μg dose the rats suffered a specific impairment in memory. With the 72.0 μg scopolamine dose this differential pattern of behavioural change was not observed; performance was disrupted in both the working and reference memory portions of the task, although the impairment was greater in the working memory component. It is, therefore, possible that at this dose the deficits were due to some nonmnemonic effects of the drug. The lack of a behavioural deficit following injections of saline or the 8.0 μg scopolamine dose suggests that the mnemonic impairments were due specifically to the dose-dependent effects of cholinergic receptor blockade.

It is possible that a drug-induced motor hypoactivity might have differentially affected working and reference memory. The correct working memory choice was contingent upon the initial starting position of the rat. If the animal was hypoactive, and it took longer to travel from the end compartment of the first Y-maze to the working memory choice point of the second Y-maze, working memory might have been impaired because of the lengthened retention interval. Although latency data were not systematically collected in the present study, the effects of scopolamine on working memory did not appear to result from a confounding effect of motor changes. Intraamygdaloid scopolamine administration appeared to have a dose-dependent excitatory effect on motor behaviour. This effect is consistent with previous reports that both systematic and central scopolamine induced transient hyperactivity (4,23). Thus, the behavioural impairments seen in rats followed bilateral intraamygdaloid injections of scopolamine most likely resulted from an effect on memory rather than changes in motor activity.

The present study seems to provide support for the differential involvement of cholinergic mechanisms in working and reference memory, where working memory was more sensitive to the disrupting effects of cholinergic receptor blockade. However, the magnitude of the behavioural impairments in each component of the task may have been related to the relative difficulty of the two components, because acquisition of the reference memory component was more rapid than acquisition of the working memory component [for a related discussion, see (25)]. Although this possibility cannot be ruled out, it is noteworthy that studies specifically controlling for this difficulty have observed differential effects of manipulations of cholinergic systems. When the demands of the working and reference memory components of a T-maze task were cleverly equated, leading to comparable acquisition rates, ibotenic acid lesions of the nbm selectively impaired working memory, suggesting a dichotomous classification of memory type with differential susceptibility to cholinergic manipulation (16). The present study is consistent with such an interpretation, but it is only demonstrated for the levels of mnemonic demand required in this particular task.

The present finding that intraamygdala injections of scopolamine produce mnemonic deficits is in good agreement with an extensive literature implicating acetylcholine in memory (1). Thus, others similarly have found mnemonic impairments following injections of cholinergic antagonists into the amygdala (9,14,31), dorsal hippocampus (4), and caudate putamen (15).

The notion that cholinergic input to the amygdala plays an important role in mediating working memory function is supported by the parallel detrimental effects on working memory performance of injections of scopolamine into the basolateral amygdala (observed here) and excitotoxic lesions to the nbm (2,10,16,22). Cholinergic activity in the basolateral amygdala is derived from the amygdalopetal projection of the nbm, projections from the nucleus tegmenti pedunculopontis, the subcoerulear region, the reticular formation (35), and intrinsic cholinergic neurons (5). However, compared to the nbm efferents, the brain stem projections and intrinsic cholinergic cells constitute a relatively small proportion of the total source of cholinergic activity in the amygdala. As much as 60% of choline acetyltransferase in the amygdala can be depleted by quinolinate-induced lesions of the nbm (3). Thus, mnemonic deficits following intraamygdaloid scopolamine may have resulted from antagonism of the amygdalopetal projection of the nbm. It fol-

lows that intraamygdaloid scopolamine may have approximated the neurochemical effects of nbm lesions. The degree to which these two manipulations are similar is critically dependent on the specific neurotoxin; different excitotoxins, when injected into the nbm, differentially affect cholinergic projections to the cortex and amygdala. Quisqualate is preferentially toxic to the cholinergic projections to the cortex; quinolinic acid is more potent in decreasing amygdaloid cholinergic activity; and ibotenic acid affects cholinergic projections to the two structures equally (3). This implies that the cholinergic disruption by nbm quinolinate or ibotenate lesions are the most comparable to the intraamygdaloid scopolamine injections.

If scopolamine injections to the amygdala and quinolinic or ibotenic nbm lesions are neurochemically similar, then analogous behavioural deficits should result following these treatments. Ibotenic acid lesions of the nbm or electrolytic lesions of the basolateral amygdala result in an order recognition (a complex working memory) deficit in the radial maze (19) providing support for this suggestion. Moreover, it was found that electrolytic lesions of the cortex produced no mnemonic impairment in the same task, implying that the nbm influences order recognition memory primarily through projections to amygdaloid but not neocortical targets. This is compatible with studies that have compared the effects of nbm quisqualate lesions (preferentially toxic to the cortex) to ibotenate lesions and have clearly shown the latter to produce greater mnemonic deficits (7,10–12,22,28,29,32).

Considerable evidence now suggests that the amygdalopetal nbm cholinergic system is involved in mnemonic function. In this study the relative significance of amygdaloid versus cortical cholinergic targets was not investigated. The cholinergic system is often regarded to have a multidimensional modulatory role, transmitting spatial and temporal patterns of activity to target areas, that then make their own contribution to a dimension of memory (34). The amygdala may have the general behavioural function of encoding emotional significance to ongoing sensory experiences (17), but a more detailed analysis of the respective roles in memory played by these two cholinoceptive regions would appear to be warranted.

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