Pharmacology Biochemistry & Behavior, Vol. 18, pp. 7–12, 1983. Printed in the U.S.A.

Spatial Working Memory in Rats: Effects of Monoaminergic Antagonists

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Received 17 May 1982

BEATTY, W. W. AND J. R. RUSH. *Spatial working memory in rats: Effects of monoaminergic antagonists.* PHARMACOL BIOCHEM BEHAV **18**(1) 7–12, 1983.—To assess the possible involvement of the monoaminergic neurotransmitters norepinephrine, dopamine and serotonin in the maintenance of spatial working memory rats were treated with antagonists 0 or 2 hr after completing the first 4 choices in an 8 arm maze. Haloperidol (0.25–1 mg/kg), when administered 2 hr after Choice 4, produced a small but consistent impairment in performance on retention tests given 5 hr after the first 4 choices. This deficit closely resembled natural forgetting in terms of the type of errors committed. By contrast, haloperidol in the same doses given 0 hr after Choice 4 or 3 hr before the first 4 choices did not affect retention. Likewise treatment with propranolol (10–20 mg/kg), phentolamine (5–20 mg/kg) or methysergide (5–15 mg/kg) did not impair spatial memory, regardless of when these drugs were injected within the session. Evidently dopaminergic neuronal systems are important in the maintenance of normal spatial working memory.

Working memory Short term memory Catecholamines Serotonin Haloperidol Methysergide Phentolamine Propranolol

WHEN tested in an 8 arm radial maze, the spatial memory of rats remains highly accurate for as long as 8 hr [3]. This working memory system is also very resistant to disruption by a wide range of physiological and environmental treatments introduced during the retention interval [3, 4, 11, 23]. Because of these properties spatial memory in rats provides a unique arena for assessing the influence of pharmacological and other reversible physiological treatments on the neurochemical mechanisms that maintain this form of temporary memory.

Administration of electroconvulsive shock (ECS) degrades spatial working memory in a time-dependent manner. If ECS was given 2 or 4 hr after the to-be-remembered event (choosing 4 of the 8 arms in the maze), retention was severely impaired, but if ECS was given within 15 min after the rat completed its first 4 choices, memory was unaffected [25]. It is reasonable to suppose that the effect of ECS represents a reasonably selective influence on working memory since the type of errors made after ECS closely approximated the error pattern observed during control sessions. Moreover, ECS treatments prior to the to-be-remembered event were ineffective.

More recently we examined the effects of scopolamine, varying the dose and time of administration of the drug with respect to the rat's first 4 choices in the maze [9]. High doses of scopolamine did modestly disrupt retention, but since memory was equally affected by treatment prior to the to-be-remembered event as by treatment during the retention interval, there was no reason to suppose that the drug affected mechanisms essential to the maintenance of memory.

In the present experiments we assessed the possible importance of the monoaminergic neurotransmitters norepinephrine (NE), dopamine (DA) and serotonin (5HT) for spatial working memory. The vast literature relating these neurotransmitters to both long and short term memory has been reviewed elsewhere [14,29].

More recent work raises the possibility that NE, 5HT, and DA may be specifically involved in spatial memory. For example, Mason and Fibiger [16] reported that rats with selective 6-hydroxydopamine lesions of the dorsal NE bundle were profoundly impaired to the acquisition of a delayed alternation problem. Further, lesions of the median raphe nucleus, the origin of the 5HT input to the hippocampus, disrupt spatial reversal learning and performance in radial mazes [1,28]. Finally, damage to the central DA systems is associated with deficits in delayed alternation [6] and memory for spatial avoidance responses [26]. Moreover, the DA antagonist haloperidol disrupts both working and reference memory components of a search task [19].

To provide more precise information about the role of monoaminergic systems in spatial memory we exploited the unusually long time span of working memory in the radial maze which made it possible to administer antagonists at various times after the to-be-remembered event.

METHOD

Animals

The subjects were 16 male albino rats originally obtained from the Holtzman Co., Madison, WI at about 3 months of age. All had previously served in an experiment concerned with the effects of scopolamine on spatial memory [9]. The present study began when the rats were about 13 months old and continued for 5 months. Throughout the experiment the rats were caged singly with free access to water in an air-conditioned animal room (22±3°C) that was illuminated from 0700–2100 by overhead fluorescent lights. They were maintained on a restricted feeding schedule of Purina Lab chow

pellets designed to maintain body weight at 80–85% of the free-feeding level adjusted for growth. Behavioral tests occurred during the daylight portion of the L:D cycle.

Apparatus

Behavioral testing was conducted in an elevated 8 arm maze made of wood painted white which was shaped like rimless wagon wheel. Each arm (74×9 cm) extended from an octagonally shaped central hub (36 cm across). Black plastic sidewalls (3.5 cm high) extended the length of each arm. Small metal cups, mounted at the end of each arm, served as receptacles for reinforcers. Guillotine doors surrounded the hub and controlled access to each arm. The room housing the maze (3 m^2) was cluttered with running wheels, a steam line with valves and hoses and other surplus equipment which provided a rich variety of extra-maze cues.

Behavioral Procedures

By virtue of their extensive prior training the rats were already quite proficient at performing in the maze at the 5 hr-long retention interval used throughout the present study. Hence it was only necessary to test them for about 2 weeks to reestablish baseline performance. At the start of each session a single 190 mg Noyes pellet was placed into the food cup at the end of each alley. The rat was placed into the central hub and the guillotine doors were raised, permitting access to any of the arms. The animal was allowed to choose 4 arms in any order that it wished. It was then returned to its home cage for the duration of the 5 hr interval. Since food was never replenished during a session, the rat was required to learn a win-shift food-searching strategy. The retention test continued until the rat succeeded in finding all of the pellets or 10 min elapsed. Reentries into an arm previously visited on that test day were counted as errors. Since testing continued until the rat collected all of the pellets, the total number of errors was potentially unlimited. Retention errors (reentries into arms previously visited during the retention test) were also recorded.

Drug Treatments

Propranolol, phenoxybenzamine and phentolamine were dissolved in saline and administered IP at a volume of 1 ml/kg. Methysergide was dissolved in saline and administered IP at a volume of 2 ml/kg. Haloperiodol was given IP at a volume of 1 ml/kg. The stock solution (5 mg/kg) was diluted with saline to the appropriate concentration. For all experiments drug treatments were given 0 or 2 hr after the rat completed the first 4 choices or 3 hr before the first 4 choices. The latter condition was included as a control for possible proactive effects on performance. Each rat was tested once under each treatment condition and within each drug experiment treatments were counterbalanced among subjects. Drug treatments occurred every third day. On the intervening days (No Trt) the rats were simply tested in the usual way. The retention interval was 5 hr in all cases.

First the effects of the β antagonist, propranolol HCl (0, 10 or 20 mg/kg, Inderal, Ayerst Labs) were studied. Next we attempted to employ phenoxybenzamine HCl (Dibenzyline, Smith Kline), a relatively specific α_1 antagonist. However, when 10 mg/kg of this agent was injected 0 hr after Choice 4, 6 of the 16 rats failed to complete the retention test. (The rats that completed the test exhibited normal retention). Accordingly we switched to phentolamine HCl (Regitine, Ciba-Geigy), which blocks both α_1 and α_2 receptors. Initially the effects of 0, 5 or 10 mg/kg doses were examined. Subsequently 20 mg/kg of phentolamine was administered 0 or 2 hr after Choice 4. Since neither of these treatments had any discernable effect, the influence of the 20 mg/kg dose given 3 hr before the first 4 choices was not determined.

Subsequently the effect of the DA antagonist haloperidol (0, 0.5 or 1.0 mg/kg, Haldol, McNeil Labs) was examined. Just before the start of this study one rat broke one of its upper incisors. Consequently it was not tested in the study. The animal recovered and was tested in subsequent studies. Next the influence of the 5HT antagonist methysergide maleate (0, 5 or 15 mg/kg, Sansert, Sandoz Pharmaceuticals) was studied. Since the initial experiment with haloperidol suggested that the drug might have a selective effect on spatial working memory but only when administered 2 hr after Choice 4, a follow-up experiment was performed. In this study haloperidol (0.25 or 0.5 mg/kg) was given 2 hr after or 3 hr before the first 4 choices using a counterbalanced within subjects design similar to that employed throughout the sequence of studies. Two No Trt control days were interposed between the drug test days. No saline control was conducted in this phase.

To assess the possibility that another CNS depressant might also degrade spatial memory 30 mg/kg of methohexital Na (Brevital, Lilly, 3 ml/kg) was administered 2 hr after Choice 4 and performance under this condition was compared to concurrent performance without treatment. Because previous research [3] demonstrated that treatment with Brevital and other barbiturates did not disrupt spatial memory when administered immediately after the first 4 choices, the 0 hr condition was not included in the present study. Throughout the experiment the rats were tested 7 days a week except that 4–10 days without testing were interposed after tests with each drug were completed.

Data Analysis

For each major drug experiment statistical analyses on two dependent variables, percent correct on choices 5–8 and total number errors per day, were conducted. As the conclusions were identical only the results for percent correct are reported. The data from No Trt sessions were initially examined for evidence of systematic changes in performance over time and testing. No such trends were apparent so the data were pooled to yield a single value for the No Trt condition on each measure. One way repeated measures analyses of variance were performed on each measure. In rare instances animals failed to complete a scheduled run after drug treatment. Such missing data was accounted for by recording the condition mean and correcting the *df* and error variance appropriately. One rat failed to complete each of the following conditions: propranolol, 20 mg/kg 3 hr before the first 4 choices (−3 hr); phentolamine, 20 mg/kg, 0 hr; phentolamine, 5 mg/kg, 0 hr; phentolamine, 10 mg/kg, −3 hr; haloperidol, 1 mg/kg, −3 hr; haloperidol, 1 mg/kg, 0 hr; haloperidol, 1 mg/kg, 2 hr. In addition in the second haloperidol study one rat failed to complete 3 of the 4 drug tests; its partial data were excluded from the analysis.

The number of retention errors (i.e., reentering an arm already visited during the retention test) was too small to permit a detailed quantitative analysis, but none of the agents appeared to increase the proportion of these errors relative to the No Trt condition.

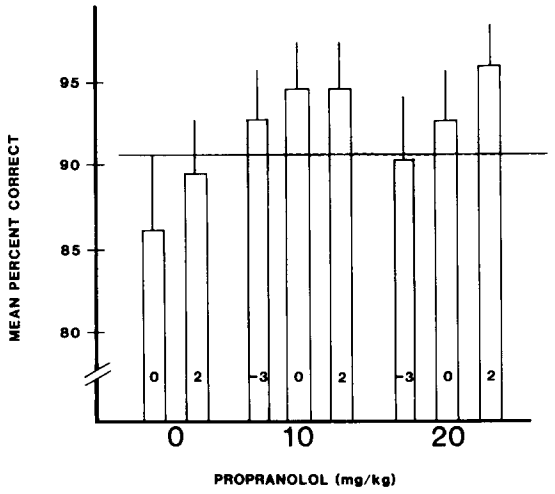

FIG. 1. Mean percent correct on choices 5–8 at varying doses of propranolol. Vertical bars=1 SEM. Numbers on the histograms indicate the time in hours of drug treatment in relation to the first 4 choices. Solid horizontal line and shaded area indicate the mean±1 SEM for the No Trt condition.

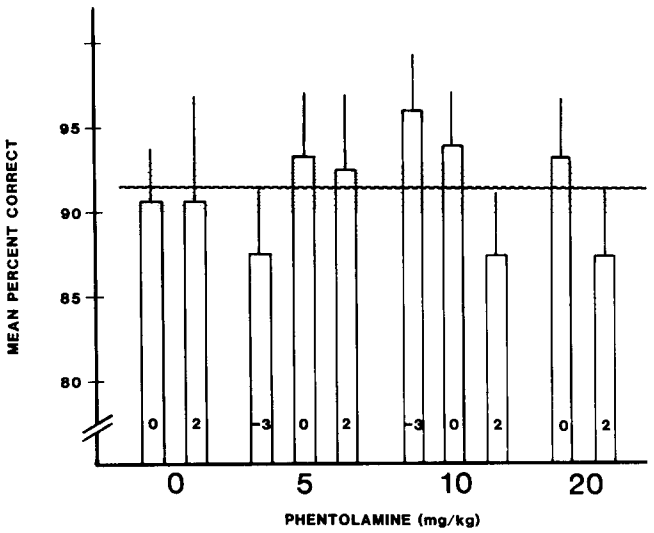

FIG. 2. Mean percent correct on choices 5–8 at varying doses of phentolamine. Vertical bars=1 SEM. Numbers on the histograms indicate the time in hours of drug treatment in relation to the first 4 choices. Solid horizontal line and shaded area indicate the mean±1 SEM for the No Trt condition.

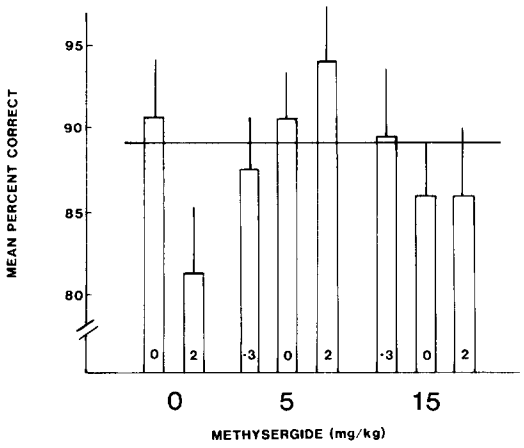

FIG. 3. Mean percent correct on choices 5–8 at varying doses of methysergide. Vertical bars=1 SEM. Numbers on the histogram indicate the time in hours of drug treatment in relation to the first 4 choices. Solid horizontal line and shaded area indicate the mean±1 SEM for the No Trt condition.

RESULTS

As seen in Fig. 1, treatment with propranolol did not disrupt the spatial memory. In fact there was a tendency for the drug to improve the accuracy of performance, but this effect was not reliable ($F<1$). Phentolamine was also ineffective at all doses examined ($F<1$, see Fig. 2). The same was true of methysergide ($F=1.15$, see Fig. 3).

Among the monoamine antagonists examined, only haloperidol disrupted spatial memory. In the first study the omnibus analysis failed to reveal a reliable effect, $F(8,108)=1.62$, $p>0.05$, but it appeared that administration of the drug 2 hr after choice 4 caused a modest impairment which was not greater at the higher dose. Treatment with haloperidol at either dose immediately after or 3 hr before the first 4 choices clearly did not affect performance (see Fig. 4). To inspect the possibility that haloperidol treatment had a time-dependent effect, performance on the No Trt and saline conditions was pooled to form a single control condition and the 2 doses of haloperidol were pooled at each temporal interval. The resulting data are replotted in Fig. 5. Statistical analysis revealed a reliable treatment effect, $F(3,42)=5.50$, $p<0.03$, and subsequent tests indicated that retention was impaired by haloperidol treatment 2 hr after Choice 4, but not at any other time. Performance when haloperidol was given 2 hr after Choice 4 differed from all other conditions, $F(1,14)>5.61$, $p<0.05$. Since all of the errors made under this condition involved repetitions of arms visited during the first 4 choices, the decrement in retention mimicked natural forgetting.

The apparent effect of haloperidol on spatial working memory was confirmed in the follow up study (See Table 1). Again there was no effect of dose so performance under the 0.25 and 0.5 mg/kg doses was pooled to yield a single value at each time interval. Statistical analysis revealed a reliable treatment effect, $F(2,28)=5.94$, $p<0.01$, and subsequent analysis showed that haloperidol treatment 2 hr after Choice 4 disrupted retention relative to the No Trt or proactive control conditions, $F(1,14)>5.82$, $p<0.05$. Analysis of the total number of errors revealed an identical pattern. Retention errors (i.e., reentries into arms already visited during the retention test) were infrequent in all conditions, accounting for 10.8% of all errors under No Trt, 0% of errors when haloperidol was given 3 hr before the first 4 choices and 15.6% of errors made when haloperidol was injected 2 hr after Choice 4.

When the barbiturate methohexital was administered 2 hr after Choice 4, retention was not impaired; rather, it was significantly improved. On the No Trt days the rats averaged

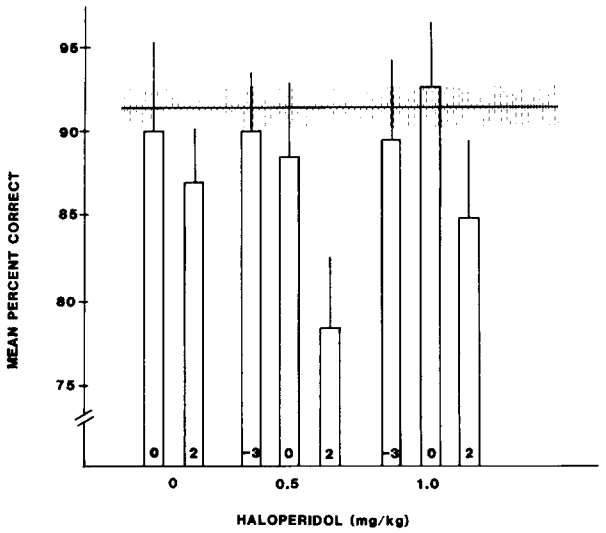

FIG. 4. Mean percent correct on choices 5–8 at varying doses of holoperidol. Vertical bars=1 SEM. Numbers on the histograms indicate the time in hours of drug treatment in relation to the first 4 choices. Solid horizontal line and shaded area indicate the mean±1 SEM for the No Trt condition.

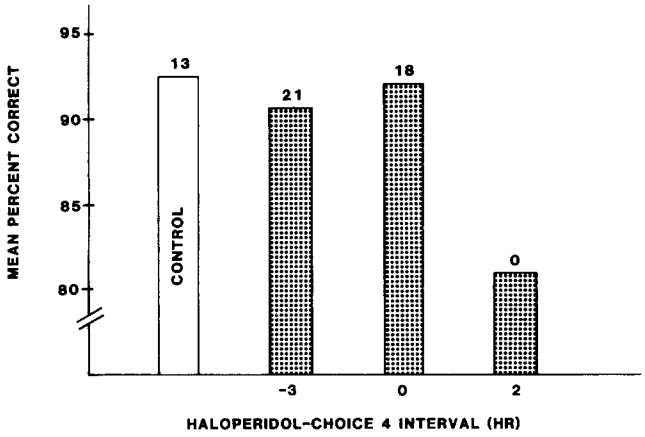

FIG. 5. Mean percent correct on choices 5–8 as a function of time of haloperidol administration. At each time interval data from the 0.5 and 1.0 mg/kg haloperidol doses were averaged. The control is the weighted average of the No Trt and saline conditions. Numbers above the histograms are the percent of total errors that were retention errors.

89.8% correct on choices 5–8 while after methohexital performance improved to 98.4% correct, $F(1,15)=8.41, p<0.02$.

DISCUSSION

Among the monoaminergic antagonists examined only haloperidol disrupted spatial working memory. The influence of haloperidol appears to involve an action upon mechanisms necessary to maintain working memory or to permit successful retrieval since doses of the drug that were effective when administered during the retention interval were ineffective if given prior to the to-be-remembered event. Moreover, a reduction in the accuracy of spatial memory was not accompanied by an increase in retention errors. Both the normal pattern of retention errors as well as the absence of proactive effects argue against explanations of the data in terms of impairments in attention, changes in motivation, general confusion or impairments in reference memory (i.e., the memory for the general win-shift rule). In this respect our findings differ somewhat from recent work by Oades [19]. Using haloperidol treatments prior to testing in a different food searching task, Oades found that the drug disrupted both working and reference memory. Our findings suggest that working memory may be especially sensitive to the effects of haloperidol at least when the drug is administered 2 hr after the to-be-remembered experience. On the other hand, the effects of haloperidol on short term memory may be task-specific since Bartus [2] did not observe increased rates of forgetting after haloperidol treatment in monkeys in a delayed response task.

TABLE 1

MEAN PERFORMANCE (±SEM)

Haloperidol Dose (mg/kg)	Hr after Choice 4	Percent Correct Choices 5–8	Total Errors
No Trt		90.2 ± 1.4	0.53 ± 0.10
0.25	−3	91.7 ± 3.1	0.33 ± 0.13
0.25	2	81.7 ± 5.2	0.87 ± 0.29
0.5	−3	91.1 ± 3.1	0.36 ± 0.12
0.5	2	81.7 ± 3.8	1.27 ± 0.43

The influence of haloperidol on spatial working memory was clearly time-dependent. Administration of haloperidol immediately after Choice 4 had no effect on retention while treatment with the drug 2 hr later caused a small but consistent decrement. In earlier work [25] we observed a similar time-dependent influence of ECS on spatial working memory, although the amnestic effects of ECS were considerably more pronounced than those of haloperidol. Whether or not the similarity in the time-dependent nature of the amnestic effects of ECS and haloperidol is more than coincidental is not at present clear.

Alternatively, the time-dependent nature of the amnestic effect of haloperidol might be considered an instance of asymmetrical state-dependent forgetting. This explanation requires that one make very specific assumptions about the duration of drug action. To explain the present data in terms of a state-dependency hypothesis one must presume that haloperidol was present in sufficient amounts to cause a change in physiological state for at least 3 hr, but was reduced to ineffective levels in less than 5 hr. Considering that doses as high as 1 mg/kg were ineffective in causing amnesia if given immediately after choice 4, but much smaller doses were effective when administered 2 hr after choice 4, the asymmetric state-dependency hypothesis, while plausible, is not especially appealing.

Regardless of the resolution of the state-dependency issue it is likely that the disruptive effects of haloperidol on memory arise from its principal pharmacological action as a DA

antagonist. Haloperidol is weakly anticholinergic, antiserotonergic, antihistaminergic and can act as an α antagonist, but it is not likely that any of these effects are responsible for its influence on spatial memory. Previous work [9] indicates that the powerful antimuscarinic, scopolamine, does not disrupt spatial working memory in a way that mimics natural forgetting. The failure of the α antagonist, phentolamine, or the 5HT antagonist, methysergide, to affect performance in the present study suggests that these actions of haloperidol are probably not responsible for its effect on spatial memory.

And while we did not study any agents that are primarily antihistamines, both phentolamine and methysergide are known to act as antihistamines in some tissues [7,27], suggesting that this property of haloperidol is probably not responsible for its influence on spatial memory either. While antagonism of DA appears to be the property of haloperidol that is essential for its amnestic action, the effects of the drug on other aminergic systems may contribute to this effect. Zornetzer [29], among others, has suggested that it is unlikely that complex behaviors such as spatial memory are regulated by a single neurotransmitter. Subsequent studies utilizing other DA antagonists with varying potencies to affect other neurochemical systems should help to clarify these possibilities. Finally, since the barbiturate methohexital did not impair retention when administered 2 hr after Choice 4, the time-dependent effect of haloperidol cannot be simply the result of nonselective depression of the CNS. That methohexital facilitated spatial memory is surprising but not totally unexpected since we observed a similar trend in earlier work [3]. The implications of this effect are not presently clear, but the effects of barbiturates on spatial memory clearly merit additional study.

Granting for the moment that the effects of haloperidol most likely depend upon blockade of normal traffic in brain DA pathways, existing data offer little clue as to which DA pathway is most likely to be important to maintaining normal spatial working memory. Lesion experiments suggest impairments in various spatial tasks may accompany damage to the substantia nigra, or the ventral tegmental area [20,26], as well as to their targets, the neostriatum and the prefrontal cortex ([6, 7, 20, 26], but see [5]). And recent data make it highly likely that DA is a neurotransmitter in the hippocampus [10,24], a structure long known to play a pivotal role in processing spatial information [18, 21, 22]. Of interest in this connection is the fact that dorsal hippocampal lesions block the disruptive effects of haloperidol on working and reference memory in a food searching task [19].

The present findings that propranolol, phentolamine and methysergide, even in relatively high doses, were all ineffective in degrading spatial memory implies that neither noradrenergic nor serotonergic systems are crucial to the maintenance of spatial working memory.

Earlier findings that dorsal NE bundle lesions interfere with the acquisition of delayed alternation [16] and median raphe lesions profoundly disrupt acquisition of efficient radial maze behavior [28] may reflect influences of these systems on the development of reference memory or, alternatively, nonspecific behavioral changes such as inattention or hyperactivity [15,17]. These inferences must be made cautiously in light of the uncertain penetration of phentolamine into the CNS when administered peripherally. However, the importance of central NE pathways to memory is at best uncertain and many of the facilitatory effects of catecholamine (CA) agonists on memory are mediated, at least in part, by the release of CAs from peripheral stores, especially the adrenal medulla [12, 13, 14]. The present work, together with earlier findings [9,25], make it clear that marked alterations in the functioning of the autonomic nervous system have little if any effect on spatial working memory.

Finally, while the present data imply that DA plays a role in maintaining normal working memory, at the same time it is clear that DA circuits are only one component of the rat's robust long-lived spatial memory system.

ACKNOWLEDGEMENTS

We thank Ayerst Laboratories, Smith Kline, Ciba Geigy, McNeil Laboratories, and Sandoz Pharmaceuticals for donating the supplies of propranolol, phenyoxybenzamine, phentolamine, haloperidol and methysergide used in this research.

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