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Memory Facilitation Produced by Dopamine Agonists: Role of Receptor Subtype and Mnemonic Requirements

MARK G. PACKARD[1] AND NORMAN M. WHITE

Department of Psychology, McGill University

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PACKARD, M. G. AND N. M. WHITE. *Memory facilitation produced by dopamine agonists: Role of receptor subtype and mnemonic requirements*. PHARMACOL BIOCHEM BEHAV **33**(3) 511–518, 1989.—The role of dopamine (DA) receptor subtypes in the acquisition of two memory tasks in the 8-arm radial maze was examined. The receptors were manipulated with posttraining, subcutaneous injections of an indirect DA receptor agonist (D-amphetamine), a selective D2 receptor agonist (LY171555), and a selective D1 receptor agonist (SKF-38393). On a win-stay task (sensitive to caudate nucleus lesions) a light cue signalled the location of food in 4 randomly selected arms on each trial. Rats were given one trial per day and injected after training on day 5. D-Amphetamine (2.0 mg/kg) and LY171555 (2.0 mg/kg) improved performance relative to controls; however SKF-38393 (1–4 mg/kg) had no effect on the acquisition of win-stay behavior. On a win-shift task (sensitive to fornix/hippocampal lesions) a delay of 18 hr was imposed between the first 4 and second 4 choices; drugs were injected after the first 4 choices. D-Amphetamine (1.0 mg/kg) and LY171555 (2.0 mg/kg) significantly improved retention relative to controls. SKF-38393 (1–4 mg/kg) had no effect on win-shift retention. These results suggest that the memory-improving properties of DA agonists on tasks sensitive to both hippocampal and caudate lesions are mediated by the D2 receptor.

SKF-38393 LY171555 D-Amphetamine Memory Radial maze Hippocampus Caudate nucleus

SEVERAL lines of evidence are consistent with the hypothesis that central dopaminergic neurotransmission is involved in learning and memory. Studies using the catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA) have implicated the nigrostriatal dopamine (DA) pathway in the acquisition of various learning tasks, including avoidance conditioning (21, 55, 84), Morris water maze behavior (79), and appetitive conditional discrimination (65). In the study of Zis *et al.* (84), for example, rats with 6-OHDA lesions that had failed to acquire an avoidance response learned it after treatments with L-Dopa, a dopamine precursor. They retained the learned behavior for several trials after the L-Dopa had ceased to be effective, suggesting that dopamine function was required for the acquisition, but not the retention of the behavior.

Further evidence for a role of the nigrostriatal DA pathway in memory comes from the demonstration that posttraining self-stimulation with electrodes in the nigrostriatal bundle (but not with electrodes in non-DA sites) improves memory (49). Moreover, the ability of posttraining self-stimulation of the nigrostriatal bundle to improve memory was blocked by administration of the DA antagonist, pimozide (82).

Direct pharmacological manipulation of DA activity by systemic administration of both agonist and antagonist drugs also provides evidence of a role for DA in learning and memory. For example, memory improving effects of posttraining injections of the indirect DA agonist D-amphetamine have been demonstrated in several studies (18, 20, 40, 61). Antagonism of DA function by posttraining administration of haloperidol impaired avoidance conditioning, an effect which was reversed by the DA agonist apomorphine (26). Similarly, administration of the DA antagonist spiroperidol impaired acquisition of a water Y-maze discrimination (64).

The discovery of multiple receptors for DA has led to research evaluating the role of receptor subtypes in various DA-mediated behaviors. DA receptors have generally been classified as D1 and D2 subtypes (36,69). The D1 receptor displays a low affinity for DA agonists, and has been linked to a stimulatory effect on adenylate cyclase activity (36,69). The D2 receptor has a higher affinity for DA agonists, and is uncoupled from or linked to adenylate cyclase in an inhibitory fashion (37,75).

Early research on the behavioral functions of the DA receptor subtypes focused on the motor behaviors known to be produced by nonspecific DA activation. For example, the selective D1 agonist SKF-38393 (71) has been reported to induce contralateral turning in rats with unilateral lesions of the substantia nigra (2, 22, 25), grooming (53), and oral dyskenisia (68). Blockade of D1 receptors produced by the D1 antagonist SCH-23390 attenuates the rewarding action of self-stimulation and food (41,54). In addition, recent

[1]Requests for reprints should be addressed to Mark Packard, McGill University, Dept. of Psychology, 1205 Dr. Penfield Ave., Montreal, P.Q., Canada H3A 1B1.

evidence suggests that D1 receptor stimulation may have an "enabling" synergistic effect on D2-induced behaviors (1, 5, 10, 80).

Activation of the D2 receptor has also been implicated in DA-mediated locomotion (2), stereotypy (1), and reward processes (32).

Although DA function has been implicated in memory consolidation, the role of DA receptor subtypes in this process is unknown. The investigation of this question was one purpose of the present study. Accordingly, we selectively manipulated DA receptor subtypes with injections of a D1 receptor agonist (SKF-38393), a D2 receptor agonist (LY171555), or an indirect DA agonist which causes stimulation of both D1 and D2 receptors (D-amphetamine) after training trials on two different memory tasks.

A second goal of the present study was to examine the effects of manipulating DA activity on two tasks the acquisition of which previous experiments (62) have suggested, may be mediated in different brain structures. One task is a variant of the standard win-shift radial maze task (57,60). It has been demonstrated many times that the ability of animals to acquire accurate win-shift performance in the radial maze is impaired by hippocampal/fimbria-fornix damage (17, 56, 58).

The second task was a win-stay radial maze task, in which a sensory cue (light) signalled the location of four randomly-selected reinforced maze arms on each trial. We found that lesions of the caudate nucleus severely impaired the ability of rats to acquire this task (62).

EXPERIMENT ONE: WIN-STAY RADIAL MAZE TASK

METHOD

Subjects

The subjects were 104 male Long-Evans rats (275–325 g). They were individually housed in a temperature-controlled 12-hr light/dark cycle, and given ad lib access to water. Lights were on in the colony room from 7 a.m. to 7 p.m. Animals were tested between 2 and 5 p.m.

Apparatus

The apparatus was a wooden eight arm radial maze (elevated 60 cm) painted flat gray. The diameter of the center platform was 40 cm, and each arm measured 60×9 cm. Food cups (1×2 cm) were drilled into the floor at the end of each arm. Small, 6-watt light bulbs were attached to a 3×9 cm wood strip above the entrance to each of the eight arms. The lights faced away from the center platform, and were controlled via a manual switchbox. A system of overhead tubes ran from the experimenter's location to the food cup at the end of each arm, allowing for rapid, unobtrusive rebaiting. The maze was surrounded by dark blue curtains, and was positioned so that opposing arms were equidistant from the curtains. A slanted overhead mirror was used to observe the animals. Dim illumination was provided by overhead lights.

Drugs

Dopamine agonists used were the selective D1 agonist SKF-38393 (Research Biochemicals Inc.), the selective D2 agonist LY171555 (quinpirole; Eli-Lilly, Co.) and the indirect-acting DA agonist D-amphetamine (Smith, Kline and French Canada, Ltd.). All drugs were dissolved separately in physiological saline. Drug injections were administered subcutaneously on the dorsal surface of the neck. Injection volume was constant at 1.0 ml per kg of body weight. Control animals were injected with an equal volume of saline.

TABLE 1

TREATMENT GROUPS FOR WIN-STAY TASK

Drug	Dose	Injection Time	N
Saline	0.0 mg/kg	0 Hr posttrial	8
D-AMP	1.0 mg/kg	0 Hr posttrial	6
D-AMP	2.0 mg/kg	0 Hr posttrial	13
D-AMP	4.0 mg/kg	0 Hr posttrial	6
D-AMP	2.0 mg/kg	2 Hr posttrial	6
Saline	0.0 mg/kg	0 Hr posttrial	8
LY171555	1.0 mg/kg	0 Hr posttrial	6
LY171555	2.0 mg/kg	0 Hr posttrial	13
LY171555	4.0 mg/kg	0 Hr posttrial	6
LY171555	2.0 mg/kg	2 Hr posttrial	6
Saline	0.0 mg/kg	0 Hr posttrial	8
SKF-38393	1.0 mg/kg	0 Hr posttrial	6
SKF-38393	2.0 mg/kg	0 Hr posttrial	6
SKF-38393	4.0 mg/kg	0 Hr posttrial	6

Procedure

Throughout the experiment, all animals were maintained at 85% of their ad lib feeding weights. On the first two days of training, animals were individually placed on the maze for 5 minutes with no food available. Food trials began on day 3. On each food trial, four of the eight maze arms were lit and baited. These four arms were randomly selected prior to each trial. After an animal visited a lit/baited arm, the arm was rebaited when the animal returned to the center platform. After an animal visited a lit/baited arm for the second time, the light was turned off and no further food was placed in that arm. Thus, animals were required to obtain eight food pellets within a trial by visiting each of four lit/baited arms twice. Animals were removed from the maze after obtaining all eight pellets, or 10 minutes had elapsed. Records were kept of the arms entered and the order of entry. Visits to unlit/unbaited arms were scored as errors. Food rewarded trials were run once a day for 10 days.

Animals were randomly assigned to the treatment groups shown in Table 1. The animals in all groups received a single drug injection following the training trial on Day 5 of the food rewarded trials. For all groups except two, the injections were given immediately after the animals were removed from the maze on Day 5. For two of the groups (D-amphetamine at 2.0 mg/kg and LY171555 at 2.0 mg/kg) the injections were given 2 hours after the animals were removed from the maze. The doses used for the delayed injections were selected after evaluating the effects of the three doses used for immediate posttraining injections. This accounts for the larger number of animals in the immediate posttraining injection groups (D-amphetamine 2.0 mg/kg, LY171555 2.0 mg/kg) since replication groups at these doses were run along with the delayed injection groups.

RESULTS

The effect of posttraining D-amphetamine treatment on the acquisition of win-stay radial maze behavior is shown in Fig. 1. A dose of 2.0 mg/kg D-amphetamine facilitated acquisition of this task. In contrast, doses of 1.0 mg/kg and 4.0 mg/kg of D-

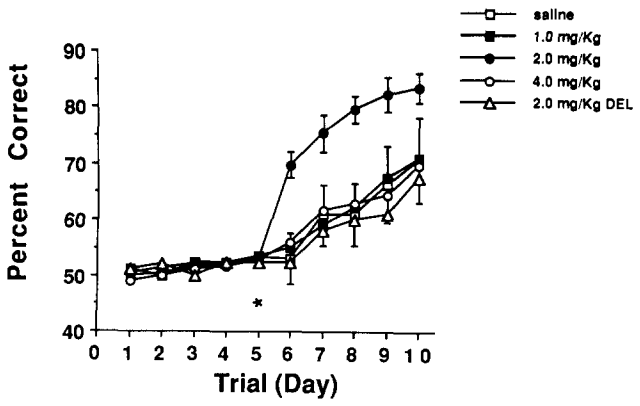

FIG. 1. Effect of posttrial D-amphetamine on acquisition of the win-stay task. Animals received a single posttrial injection of drug or vehicle after training on Day 5 (asterisk). Vertical bars on the data points in this and subsequent figures are standard errors of the means.

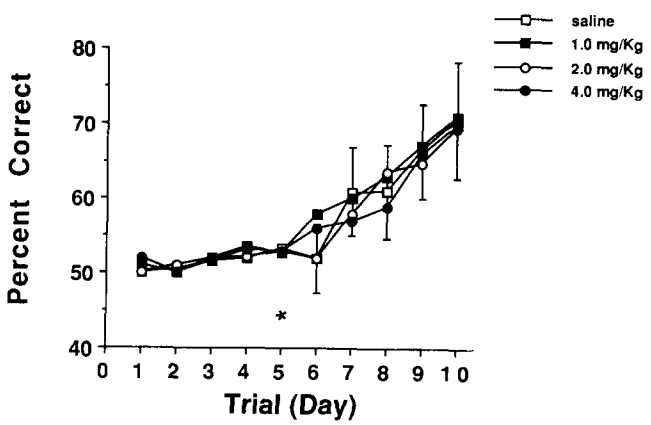

FIG. 3. Effect of posttrial SKF-38393 on acquisition of the win-stay task. Animals received a single posttrial injection after training on Day 5 (asterisk).

amphetamine had no effect; this was also true for the 2.0 mg/kg dose when treatment was delayed by 2 hours. A two-way one-repeated measure ANOVA computed on the first 5 trials (i.e., the preinjection trials) revealed no significant effect of either group, $F(4,34)=0.40$, n.s., or Trial, $F(4,34)=1.2$, n.s. In contrast, a two-way one-repeated measure ANOVA computed on trials 6–10 (i.e., the postinjection trials) revealed a highly significant effect of Group, $F(4,34)=28.3$, $p<0.01$. Newman-Keuls post hoc tests showed that the 2.0 mg/kg D-amphetamine group differed significantly from the saline group ($Q=4.79$). In addition, a significant main effect of Trial, $F(4,34)=40.9$, $p<0.01$, revealed that all groups improved over trials 6–10.

The effect of posttraining LY171555 treatment on the acquisition of win-stay radial maze behavior is shown in Fig. 2. The 2.0 mg/kg dose facilitated acquisition of this task, while both the 1.0 mg/kg and 4.0 mg/kg doses, as well as the 2.0 mg/kg delay treatment, were ineffective. A two-way one-repeated measure ANOVA computed on trials 1–5 (i.e., the preinjection trials) revealed no significant effect of either Group, $F(4,34)=0.884$, n.s., or Trial, $F(4,34)=2.2$, n.s. A two-way one-repeated measure ANOVA computed on trials 6–10 (i.e., the postinjection trials) revealed a significant effect of Group, $F(4,34)=17.2$, $p<0.01$. Newman-Keuls post hoc tests revealed that the 2.0 mg/kg LY171555 group differed significantly from the saline group ($Q=4.32$). A significant main effect of Trial, $F(4,34)=34.3$, $p<0.01$, showed that all groups improved over trials 6–10.

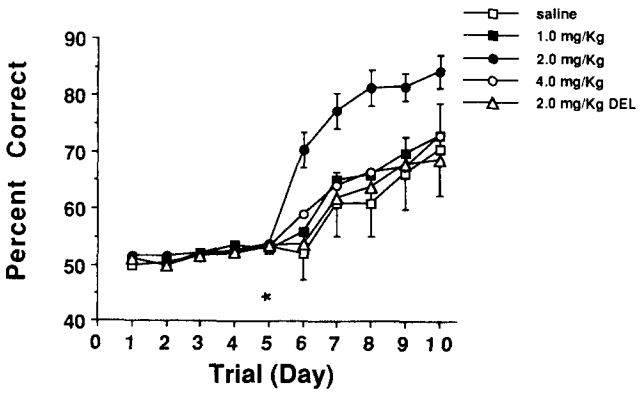

FIG. 2. Effect of posttrial LY171555 on acquisition of the win-stay task. Animals received a single posttrial injection of drug or vehicle after training on Day 5 (asterisk).

The effect of posttraining SKF-38393 on the acquisition of win-stay radial maze behavior is illustrated in Fig. 3. None of the three doses (1.0, 2.0, 4.0 mg/kg) had a significant effect on performance. A two-way one-repeated measure ANOVA computed on trials 1–5 (i.e., the preinjection trials) revealed no significant effect of Group, $F(3,22)=0.87$, n.s. A two-way one-repeated measure ANOVA computed on trials 6–10 (i.e., the postinjection trials) revealed no significant effect of Group, $F(3,22)=0.375$, n.s. A significant effect of Trial, $F(4,22)=18.0$, $p<0.01$, showed that all groups improved over trials 6–10.

DISCUSSION

The results of Experiment 1 demonstrate an improvement in the acquisition of win-stay radial maze behavior following posttraining administration of both D-amphetamine (2.0 mg/kg), and the selective D2 agonist LY171555 (2.0 mg/kg). In contrast, administration of the selective D1 agonist SKF-38393 (1.0, 2.0, or 4.0 mg/kg) had no effect on the acquisition of win-stay behavior.

When the injections of D-amphetamine and LY171555 were delayed until 2 hours after the completion of trial 5, they had no effect on subsequent performance. This suggests that the improvement in memory observed following an immediate posttraining injection was not due to any nonspecific proactive actions of the drugs such as effects on motivation, arousal, or sensory processes (47). Furthermore, the failure of delayed injections to affect performance suggests that a temporal gradient, consistent with consolidation theory (46) exists for the effect of these drugs on this task. Thus, posttraining injections must be administered within a critical period in order to facilitate memory consolidation.

Memory improvement following posttraining D-amphetamine treatment has been demonstrated in several studies (18, 20, 35, 40). In general, these studies have used aversively motivated tasks. The ability of posttraining D-amphetamine to improve win-stay radial maze acquisition in the present study generalizes these effects to appetitive tasks [see also (61)]. Since this is the first time that a posttraining, memory-improving effect of LY171555 has been reported, the effect of this drug on the acquisition of aversive tasks remains to be determined.

Given the finding that the acquisition of win-stay radial

maze behavior is impaired by lesions of the caudate nucleus (62), D-amphetamine and LY171555 may have exerted their memory enhancing effects through activation of DA function in the caudate nucleus in the present study. This suggestion is consistent with other evidence that DA receptor activation in the caudate nucleus may affect memory. This evidence includes the findings that lesions of the dopaminergic nigrostriatal neurons block the memory-improving effects of systemically administered D-amphetamine (83); and that posttraining intrastriatally injected D-amphetamine improves retention (15,78).

These findings suggest that striatal DA may function to improve, or "reinforce" the consolidation of memory for various tasks. However, it is important to note that the present data does not eliminate the possibility that DA release elsewhere in the brain may also be involved in consolidation of memory (13,72).

EXPERIMENT TWO: WIN-SHIFT RADIAL MAZE TASK

METHOD

Subjects

The subjects were 104 male Long-Evans rats (275–325 g), housed in conditions indentical to those described for Experiment 1.

Apparatus

The apparatus was a radial maze of the same dimensions as that used in Experiment 1. However, the overhead tubing system was not present, and the extramaze environment contained several cues. In addition, 4 Plexiglas doors were used to block the entrances to some of the maze arms as described in the Procedure section.

Drugs

The drugs used were identical to those used in Experiment 1.

Procedure

The delay win-shift procedure used was similar to that described in several previous reports [e.g., (60)]. Prior to training, all animals were reduced to 85% of their ad lib feeding weights, and were individually habituated to the maze for 5 minutes on two consecutive days with no food available. Rats were transported from the animal colony to a location in the testing room (which was visually secluded from the maze) by moving a rack which contained their home cages. The rack remained in the testing room for the duration of the experimental trials on each day. Food trials began on day 3. On each food trial 4 randomly selected arms were blocked and the other 4 were baited. Animals were allowed to obtain food from the four open arms. They were then removed from the maze and returned to their cages. After a delay the animals were returned to the maze for a retention test. During the retention test all eight arms were open; only those arms which had been blocked prior to the delay contained food. Animals were removed from the maze after the four baited arms had been chosen. Records were kept of the arms entered and the order of entry. Visits to unbaited arms were scored as errors.

There were two training phases followed by a test trial. For each of the training phases a criterion was established which required 4 correct responses in the first 5 postdelay choices on two consecutive days. Animals passed out of a phase by meeting this criterion. In phase 1 the delay was 5 minutes; in phase 2 the delay was 15 minutes. Once an animal had reached criterion at the 15-minute delay, the test (i.e., drug) trial was given on the following day. On this trial, animals were removed from the maze following the four predelay choices and injected either immediately, or after a 2-hour delay, and then returned to their cages. The retention test was given after a delay of 18 hours.

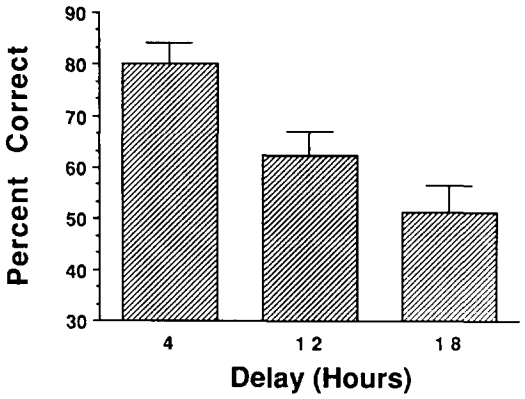

FIG. 4. Effect of varying the delay on retention in the win-shift task by untreated animals.

In a pilot study we established a temporal gradient of performance in this task by testing groups of animals that had reached the 15-minute training criterion at delays of 4, 12, and 18 hours. As shown in Fig. 4, when rats were exposed to a 4-hour delay, they responded at approximately 80% correct on the retention test. Choice accuracy declined following a 12-hour delay, and following an 18-hour delay choice behavior was essentially random. These data were the basis for selection of the 18-hour delay used in this study.

Animals were assigned to the treatment groups shown in Table 2. A rank-order method was used in assigning animals to treatment groups as each one reached the 15-minute criterion. Overall, animals progressed at an even rate of acquisition in this task, and animals in several drug groups were tested on any given drug trial.

The doses used for delayed injections were selected after evaluating the effects of immediate injections. This accounts for the larger number of animals in the immediate injection groups

TABLE 2

TREATMENT GROUPS FOR WIN-SHIFT TASK

Drug	Dose	Injection Time	N
Saline	0.0 mg/kg	0 Hr posttrial	8
D-AMP	0.5 mg/kg	0 Hr posttrial	6
D-AMP	1.0 mg/kg	0 Hr posttrial	13
D-AMP	2.0 mg/kg	0 Hr posttrial	6
D-AMP	1.0 mg/kg	2 Hr posttrial	6
Saline	0.0 mg/kg	0 Hr posttrial	8
LY171555	1.0 mg/kg	0 Hr posttrial	6
LY171555	2.0 mg/kg	0 Hr posttrial	13
LY171555	4.0 mg/kg	0 Hr posttrial	6
LY171555	2.0 mg/kg	2 Hr posttrial	6
Saline	0.0 mg/kg	0 Hr posttrial	8
SKF-38393	1.0 mg/kg	0 Hr posttrial	6
SKF-38393	2.0 mg/kg	0 Hr posttrial	6
SKF-38393	4.0 mg/kg	0 Hr posttrial	6

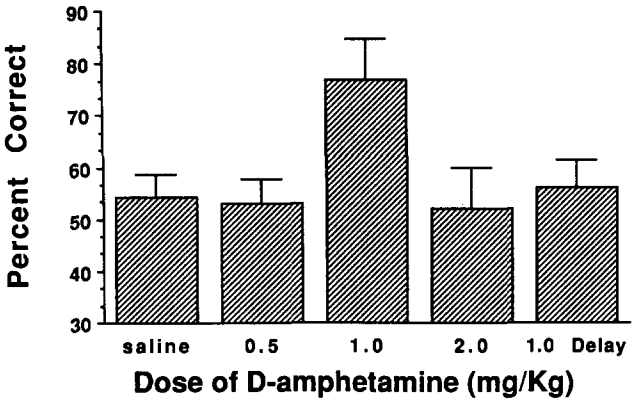

FIG. 5. Effect of posttrial D-amphetamine on retention test performance in the win-shift task (18-hr delay).

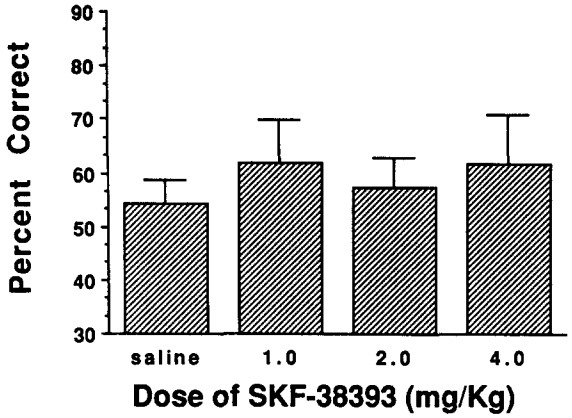

FIG. 7. Effect of posttrial SKF-38393 on retention test performance in the win-shift task (18-hr delay).

(D-amphetamine 1.0 mg/kg, LY171555 2.0 mg/kg), since replication groups were also run along with the delayed injection groups.

RESULTS

Performance on the postdelay retention test following administration of D-amphetamine is illustrated in Fig. 5. D-Amphetamine (1.0 mg/kg) improved performance, while doses of 0.5 mg/kg and 2.0 mg/kg, and the delayed injection of 1.0 mg/kg had no effect. A one-way ANOVA computed on the data in Fig. 5 showed a significant main effect of drug, $F(4,24) = 10.83$, $p<0.01$. Duncan's post hoc tests revealed that the 1.0 mg/kg dose of D-amphetamine significantly improved performance relative to saline controls ($Q = 3.22$).

The effects of LY171555 on the postdelay retention test are shown in Fig. 6. LY171555 (2.0 mg/kg) improved retention, while doses of 1.0 mg/kg and 4.0 mg/kg, and the delayed injection at 2.0 mg/kg had no effect. A one-way ANOVA computed on the data in Fig. 6 revealed a significant effect of drug, $F(4,27) = 6.74$, $p<0.02$. Duncan's post hoc tests showed that performance was significantly improved by the 2.0 mg/kg dose of LY171555 ($Q = 3.18$).

Retention following SKF-38393 (1.0, 2.0, 4.0 mg/kg) treatment is shown in Fig. 7. A one-way ANOVA computed on the data shown in Fig. 7 revealed no significant effects of drug treatment, $F(3,25) = 0.65$, n.s.

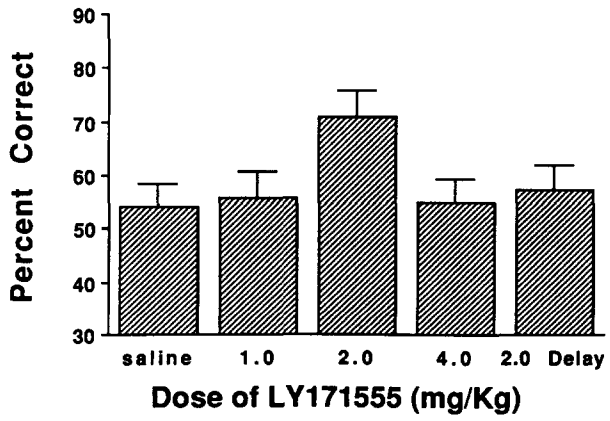

FIG. 6. Effect of posttrial LY171555 on retention test performance in the win-shift task (18-hr delay).

DISCUSSION

The results of Experiment 2 demonstrate an improvement in win-shift radial maze behavior following posttraining injections of both D-amphetamine (1.0 mg/kg), and the D2 agonist LY171555 (2.0 mg/kg). In contrast, injections of the D1 agonist SKF-38393 (1.0, 2.0, 4.0 mg/kg), had no effect on subsequent performance. This pattern of results is similar to that observed in Experiment 1.

When the effective injections were delayed until 2 hours after the predelay choices, neither D-amphetamine nor LY171555 improved retention. Thus, it is unlikely that the immediate injections of these drugs improved performance through nonspecific proactive effects, providing further evidence that the memory improving properties of DA agonists are mediated by the D2 receptor.

Two previous studies have examined the effects of D-amphetamine treatment on performance in the delay win-shift radial maze task (7,14). Although these studies reported a disruptive effect of D-amphetamine on postdelay retention, both used animals which were highly trained at the delay imposed. The use of highly trained control animals may preclude the possibility of observing memory improving effects. In addition, D-amphetamine impaired performance in both studies only when administered shortly (5–30 minutes) before the postdelay retention test. Thus, the impairments may have resulted from effects of D-amphetamine on motor activity and appetite (7).

It has been suggested that the "type" of memory process involved in the delay radial maze task may not involve "consolidation" of memory for the predelay choices (39). This suggestion was based on the finding that electrical stimulation of the hippocampus impaired retention in the delay radial maze task even when administered eight hours following the predelay choices (39). Therefore, it was suggested that the delay radial maze task may involve ongoing "maintenance" (39,59) of the required memory trace, as opposed to a "consolidation" (47) process.

The lack of a temporal gradient for the effectiveness of electrical stimulation in this task stands in contrast to the temporal gradients observed in several other tasks following posttraining electrical stimulation of the hippocampus [for review see (38)]. In the present study, when injections of effective doses were delayed until 2 hours after the predelay choices, no improvement in

retention was observed. This finding suggests that a temporal gradient does exist in the present delay radial maze paradigm, since drug treatments must be administered within a critical time period following the predelay choices in order to observe memory enhancing effects.

It is well established that accurate performance in the standard win-shift radial maze is dependent on a functional septo-hippocampal pathway (17, 56, 58). Therefore, the present facilitation of delay win-shift performance following D-amphetamine and LY171555 treatment may have involved an interaction with the septo-hippocampal system.

Evidence from previous studies is consistent with the hypothesis that DA activity can promote consolidation in the septo-hippocampal system. Posttraining intrahippocampal injections of the mixed DA agonist apomorphine facilitated the acquisition of a brightness discrimination task (28,33). In addition, 6-OHDA lesions of dopaminergic terminal areas of the lateral septum impaired the acquisition of radial maze behavior and spatial discrimination/reversal in a T-maze (72). Again, it should be noted that no evidence precludes the possibility that DA activity elsewhere in the brain participated in the facilitation of consolidation observed.

GENERAL DISCUSSION

Taken together, the results of Experiments 1 and 2 suggest that the memory improving properties of DA agonists are mediated by the D2 receptor. The use of systemic injections in the present study does not exclude the possibility that both D-amphetamine and LY171555 may have acted at a common anatomical site to improve memory in both the win-stay and win-shift radial maze tasks. However, given the evidence that the acquisition of the two tasks may be mediated by different brain structures (62), it is also possible that D2 receptor activation is a neurochemical characteristic common to the facilitation of consolidation in both the caudate nucleus and hippocampus.

In both experiments facilitation of retention was observed at an optimal dose of D-amphetamine and LY171555, while doses which were higher or lower were ineffective. The presence of such an inverted-U dose-response function is consistent with other reports of the memory improving properties of D-amphetamine (50), as well as those for epinephrine (23) and glucose (24,52). Similarly shaped functions have also been reported for the memory-improving effects of electrical stimulation of the brain (82). Although the precise physiological basis for the shape of these curves is not understood, they are often interpreted in terms of optimal level of arousal theory (23).

A difference between the two experiments was that the effective dose of D-amphetamine for the win-shift task (1.0 mg/kg) was lower than that for the win-stay task (2.0 mg/kg). In contrast, the effective dose for LY171555 (2.0 mg/kg) was the same in both tasks. It may be possible to understand this difference on the hypothesis that acquisition of win-shift and win-stay radial maze behavior are mediated by the hippocampus and caudate nucleus, respectively (62). The caudate nucleus receives its DA input via the nigrostriatal pathway originating in the substantia nigra (30), while the septo-hippocampal system is innervated by the mesolimbic DA pathway originating in the ventral tegmental area (44,45). Previous studies have revealed several differences in the regulation of these two DA pathways. For example, nigrostriatal and mesolimbic DA autoreceptors show a differential sensitivity to DA (77). In addition, system differences in DA turnover rates (3) and spontaneous firing (16) have been reported. Therefore, the finding that different doses of D-amphetamine improve memory in the two radial maze tasks may reflect a differential "sensitivity" of the two pathways to an indirect DA agonist.

The doses of SKF-38393 that produce grooming (53) and place aversion (32) (10.0 mg/kg) are generally considerably higher than the range (1–4 mg/kg) used in the present experiments. However, we have found that doses of 2.0 and 4.0 mg/kg of SKF-38393 produce place aversion (81). Although it is difficult to compare effective doses across different behavioral paradigms (i.e., motor activity, place preference and posttraining memory improvement), the doses of SKF-38393 used in the present study can produce behavioral effects in paradigms other than the ones used here.

One neurochemical model proposed to account for the role of striatal DA in learning and memory postulates that stimulation of DA-sensitive adenylate cyclase, an effect mediated by the D1 receptor (36) is a necessary concomitant of DA-induced memory improvement (8). The results of the present study provide no evidence for the hypothesis that D1 receptor stimulation promotes memory consolidation. It is possible that D1 receptor stimulation produced by endogenous DA release may have been involved in the facilitation of memory produced by posttraining D2 activation. However, in the striatum at least, D2 receptor stimulation has an inhibitory, not stimulatory effect on cyclic-AMP production (73,74).

Previous studies have implicated both striatal (63), and septo-hippocampal (6, 11, 27) cholinergic function in memory. In the caudate nucleus, the neurochemical and pharmacological interaction between DA and acetylcholine (Ach) has been studied extensively [for review see (42)]. Recent evidence suggests that the DA receptor modulating Ach function in the striatum is of the D2 subtype (19, 31, 70, 73). A DA-Ach interaction may also be involved in memory processes subserved by the hippocampus. Pharmacological data suggest that dopaminergic innervation of the lateral septum exerts a modulatory effect on hippocampal Ach function (66,67). In addition, acute administration of the cholinergic receptor blocker scopolamine reduced DA metabolism in the rat hippocampus and frontal cortex, an effect which paralleled the amnesic effect of scopolamine on retention of a passive avoidance task (51). Other studies have also begun to discern a possible Ach-DA link in memory processes (4, 34, 43, 48). Further research will be necessary to examine the hypothesis that dopaminergic modulation of cholinergic function is a common neurochemical characteristic of the memory functions subserved by the hippocampus and caudate nucleus (62).

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