Enhancement of win-shift radial maze retention by peripheral posttraining administration of *d*-amphetamine and 4-OH amphetamine

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We examined the effect of posttraining subcutaneous injections of *d*-amphetamine and 4-OH amphetamine on acquisition of a win-shift task in an eight-arm radial maze. On each day, rats were allowed to obtain food from four randomly selected maze arms and were then removed from the maze. After a delay, the rats were returned to the maze for a retention test in which all eight arms were open and only the four arms that were not visited (i.e., win-shift) prior to the delay contained food. On the experimental day, rats were injected with drug or vehicle after completion of the first four choices, and a retention test was given after a delay of 18 h. Posttraining injections of 1.0-mg/kg *d*-amphetamine enhanced win-shift retention relative to the performance of saline-injected controls, while doses of 0.5 mg/kg and 2.0 mg/kg were ineffective. Posttraining injections of 4-OH amphetamine (2.0 mg/kg), an analogue that does not readily cross the blood-brain barrier, also enhanced win-shift retention, while doses of 0.5, 1.0, and 4.0 mg/kg had no effect. Injections of memory-enhancing doses of *d*-amphetamine and 4-OH amphetamine administered 2 h posttraining were ineffective. The memory enhancement observed following administration of 4-OH amphetamine suggests that peripheral actions of amphetamine may be sufficient for improving retention. However, the difference in effective doses of the two amphetamines suggests that *d*-amphetamine may enhance win-shift retention by either a direct central action or a dual action on the brain and periphery.

Peripheral posttraining injections of the indirect catecholamine agonist *d*-amphetamine have been shown to enhance memory in several aversively motivated learning and memory tasks (Doty & Doty, 1966; Evangelista & Izquierdo, 1971; Martinez, Jensen, et al., 1980; Martinez, Vasquez, et al., 1980). Studies of the mechanism by which *d*-amphetamine improves memory for aversive events suggest that the drug may exert its effect in part by acting on peripheral mechanisms. For example, the retention-enhancing effects of peripherally administered *d*-amphetamine obtained with inhibitory avoidance training are attenuated by adrenal medullation, and peripheral sympathectomy induced by 6-hydroxydopamine (6-OHDA) shifts the effective dose of *d*-amphetamine to a lower value (Martinez, Jensen, et al., 1980; Martinez, Vasquez, et al., 1980). In addition, intraventricular posttraining injection of a wide range of doses of *d*-amphetamine failed to enhance retention of one-trial inhibitory avoidance training (Martinez, Jensen, et al., 1980).

Another approach to investigating the mechanism by which peripherally administered *d*-amphetamine improves memory involves the use of 4-OH amphetamine, an analog that does not readily cross the blood-brain barrier (Weiner, 1980). Peripheral posttraining injections of 4-OH amphetamine enhance retention of one-trial inhibitory avoidance (Martinez, Vasquez, et al., 1980b) and active avoidance (Martinez et al., 1983) tasks in doses that are similar to the effective doses of *d*-amphetamine. As with *d*-amphetamine, the retention-enhancing effects of 4-OH amphetamine are attenuated by adrenal medullation, and 6-OHDA-induced sympathectomy shifted the effective dose of the drug to a lower value (Martinez et al., 1983; Martinez, Vasquez, et al., 1980). Thus, several lines of evidence suggest a peripheral action for the memory-enhancing effect of peripherally administered *d*-amphetamine.

While many of the studies demonstrating memory improvement following posttraining injection of *d*-amphetamine have used aversively motivated tasks (Doty & Doty, 1966; Evangelista & Izquierdo, 1971; Martinez, Jensen, et al., 1980; Martinez, Vasquez, et al., 1980), comparable findings have also been obtained in studies using appetitively motivated learning tasks (Krivanek & McGaugh, 1969; Oscos, Martinez, & McGaugh, 1988; Packard & White, 1989; Strupp, Bunsey, Levitsky, & Kesler, 1991). However, the contribution of the peripheral effects of *d*-amphetamine to the memory improvement observed in appetitive tasks is unknown. To address

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this issue in the present study, we examined the effect of postraining injections of either *d*-amphetamine or 4-OH amphetamine on retention in a win-shift radial maze task (Packard & White, 1989). In this task, animals are first allowed to obtain one food pellet from each of four arms in a radial maze. Following a delay, animals are returned to the maze and given access to all eight arms, but only those arms that were not entered prior to the delay contain food. Thus, the task requires animals to remember which maze arms were visited prior to the delay. On the test day, drugs are injected immediately following the first four choices, and retention is measured after a delay of 18 h. Previous work indicates that peripheral postraining injections of *d*-amphetamine enhance retention in this win-shift radial maze task (Packard & White, 1989).

METHOD

Subjects

The subjects were 70 male Sprague-Dawley rats (Charles River Laboratories, 250–275 g), housed individually in a temperature (70°F) controlled room on a 12:12-h light:dark cycle (lights on from 7 a.m. to 7 p.m.). Prior to the beginning of behavioral procedures, all animals were adapted to the laboratory with ad-lib food and water for 4 days following their arrival. Behavioral testing was conducted between 1 p.m. and 5 p.m. daily.

Apparatus

The apparatus was an elevated (60 cm) wooden eight-arm radial maze painted flat gray. Each arm measured 60×9 cm. The center platform was 40 cm in diameter. Recessed food wells (1×2 cm) were located at the end of each arm. The maze was surrounded by several extramaze cues, including horizontal and vertical striped wall posters, a 15-W lamp, a table, an animal cage rack, and the seated experimenter.

Drugs

The drugs used were *d*-amphetamine (Sigma) and dl-4-hydroxy-amphetamine (Smith, Kline, & French). The drugs were dissolved in 0.9% physiological saline prior to injection. The injections were administered subcutaneously on the dorsal surface of the neck in a volume of 1.0 ml/kg. Control animals were injected with an equal volume of saline.

Behavioral Procedures

Prior to training, the animals' weights were reduced to 85% of their ad-lib feeding weights over a 5-day period. On each day, the rack of home cages was moved from the animal colony to a location in the testing room that was visually secluded from the maze; the rack remained in the testing room for the duration of the day's experimental trials. On 2 consecutive days, each animal was placed in the maze and allowed to explore for 5 min. No food was available in the maze during the 2 habituation days, but the animals were allowed to consume 10 Noyes Formula A food pellets in their home cages on each day. Food-rewarded trials began on Day 3. On each food trial, four randomly selected arms were blocked by removable Plexiglas doors and the other four were baited with a single food pellet placed in the wells of the arms. On the initial food trial only, food pellets were also placed on the center platform and on the edge of the food wells. The rat was allowed to obtain food from the four baited arms and was then removed from the maze and returned to its cage. After a delay, the animal was returned to the maze for a retention test. For the retention test, all eight arms were open and food was placed in the food wells of only the arms that had been blocked prior to the delay. The rat was removed from

Table 1

Group	Dose (mg/kg)	N	Mean Trials to Criterion
Saline		20	10.3
<i>d</i> -amphetamine	0.5	7	10.1
	1.0	10	10.4
	2.0	6	9.8
<i>d</i> -amphetamine (delayed injection)	1.0	5	11.0
4-OH amphetamine	0.5	7	10.7
	1.0	7	11.0
	2.0	20	9.9
	4.0	7	11.2
4-OH amphetamine (delayed injection)	2.0	6	9.8

the maze after the four baited arms were entered. An arm was recorded as entered when the rat reached the food cup. Records were kept of the arms entered and of the order of entry. Visits to unbaited arms on the retention test were scored as errors. The type of behavior required for accurate performance in this task has been termed *win-shift* since animals win by obtaining food, and must then shift to a new maze arm in order to obtain food.

There were two training phases followed by a single test (i.e., drug) trial. The delay in Phase 1 was 5 min. The delay in Phase 2 was 15 min. To pass from one phase to the next, a rat had to make at least four correct responses on the first five retention test choices (i.e., arm entries) on 2 consecutive days. When an animal reached criterion at the 15-min delay, the test (i.e., drug) trial was given on the following day. On this trial, the animals were removed from the maze following the four pre-delay choices, injected immediately with drug or vehicle solutions, and then returned to their cages. The retention test was given after a delay of 18 h. Previous findings indicate that in untreated animals trained to criterion with a 15-min delay, retention test errors increased as the test trial delay is extended from 4 h to 18 h, and at the 18-h delay, the performance of control animals is essentially random (Packard & White, 1989). This finding was the basis for the selection of the 18-h delay used on the test trial in the present study.

The treatment groups are shown in Table 1. The animals were assigned to treatment groups by using a rank-order method as each rat reached the 15-min criterion (i.e., 1st rat to reach criterion, saline; 2nd rat, *d*-amphetamine; 3rd rat, 4-OH amphetamine; 4th rat, 4-OH amphetamine; etc.). In general, rats acquire this task at an even rate, so that several animals are tested on any given drug trial. The use of a rank-order method in assigning animals to treatment groups ensured that the mean number of trials to criterion was consistent across groups (see Table 1). An additional group of animals received a postraining injection of *d*-amphetamine ($n = 5$, 1.0 mg/kg) or 4-OH amphetamine ($n = 6$, 2.0 mg/kg), 2 h after the first four choices on the test trial. These doses were selected on the basis of the behavioral effects found with the immediate postraining injections.

RESULTS

The effect of postraining injections of *d*-amphetamine on performance on the win-shift retention test is shown in Figure 1. A one-way analysis of variance (ANOVA) of the number of errors on the retention test showed a significant group effect [$F(4,33) = 6.18$, $p < .001$]. Scheffé's post hoc tests indicated that the 1.0-mg/kg dose of *d*-amphetamine significantly improved win-shift retention relative to saline injected controls ($F = 4.53$, $p < .05$), while doses of 0.5 and 2.0 mg/kg had no effect. In-

Figure 1. Effect of posttraining injection of *d*-amphetamine on win-shift retention. Animals received a posttraining injection after the first four choices in an eight-arm radial maze. The retention test was given after an 18-h delay. Percent correct = number of baited arms chosen/total number of arms chosen $\times$ 100%. Vertical bars represent the standard errors of the mean.

jections of 1.0-mg/kg *d*-amphetamine administered 2 h posttraining did not affect retention (Figure 1). This finding shows that the effect of the posttraining injection of *d*-amphetamine is time dependent, indicating that the improvement in retention produced by the immediate posttraining injection was not due to a proactive effect of the drug on sensory, motoric, or motivational processes (McGaugh, 1966, 1989).

The effect of posttraining injection of 4-OH amphetamine on performance on the win-shift retention test is shown in Figure 2. In an initial experiment, a 2.0-mg/kg dose of 4-OH amphetamine ($n = 10$) produced a trend toward enhancement of retention, while doses of 0.5, 1.0, and 4.0 mg/kg had no effect. Therefore, we examined the effect of a 2.0-mg/kg dose of 4-OH amphetamine in an additional experiment by testing animals treated with saline ($n = 10$) and 4-OH amphetamine ($n = 10$). A one-way ANOVA on the number of errors on the retention test revealed a significant group effect [$F(1,18) = 4.20, p < .05$]. The 2.0-mg/kg dose of 4-OH amphetamine significantly enhanced retention. There were no significant differences between the two saline groups or the two 4-OH amphetamine groups in the two experiments, and therefore their data were combined for analysis. This accounts for the higher number of rats in these two groups (Table 1). A one-way ANOVA of the number of errors on the retention test using the combined data also showed a significant group effect [$F(4,55) = 3.04, p < .05$]. Scheffé's post hoc tests indicated that the 2.0-mg/kg dose of 4-OH

amphetamine significantly improved win-shift retention relative to that of saline injected controls ($F = 2.67, p < .05$), while doses of 0.5, 1.0, and 4.0 mg/kg had no effect. Injections of 2.0-mg/kg 4-OH amphetamine administered 2 h posttraining did not affect retention (Figure 2). Thus, as is the case with *d*-amphetamine, the enhancement of retention observed following immediate posttraining administration of 4-OH amphetamine is not due to a proactive effect of the drug on nonmnemonic processes.

DISCUSSION

The results indicate that peripheral posttraining administration of *d*-amphetamine enhanced retention in a win-shift radial maze task. In addition, peripheral posttraining injection of 4-OH amphetamine, an analogue with a limited capacity to cross the blood-brain barrier, also produced a significant improvement in win-shift retention.

The finding of enhancement in win-shift retention following *d*-amphetamine injection is consistent with those in previous studies using this task (Packard & White, 1989; Strupp et al., 1991). In each of the previous studies (Martinez et al., 1983; Martinez, Jensen, et al., 1980; Martinez, Vasquez, et al., 1980; Williams & Jensen, 1990) in which the effect of 4-OH amphetamine on memory was examined, the tasks were aversively motivated. The enhancement of win-shift retention following 4-OH amphetamine injection indicates that this effect generalizes to performance in appetitive tasks. Posttraining administration

Figure 2. Effect of posttraining injection of 4-OH amphetamine on win-shift retention. Animals received a posttraining injection after the first four choices in an eight-arm radial maze. The retention test was given after an 18-h delay. Percent correct = number of baited arms chosen/total number of arms chosen $\times$ 100%. Vertical bars represent the standard errors of the mean.

of *d*-amphetamine has also been shown to be effective in enhancing memory in both aversive (e.g., Doty & Doty, 1966; Martinez, Jensen, et al., 1980) and appetitive (Krivanek & McGaugh, 1969; Oscos et al., 1988; Packard & White, 1989, 1991; Strupp et al., 1991) learning tasks.

Peripheral Actions of Amphetamine on Memory

The enhancement of win-shift retention produced by 4-OH amphetamine suggests that the peripheral effects of amphetamine are *sufficient* to produce memory enhancement in this task. However, the precise nature of the peripherally initiated signal by which *d*-amphetamine and/or 4-OH amphetamine may act to improve memory is not well understood. One possible mechanism involves the stimulation of the adrenal medulla by 4-OH amphetamine and *d*-amphetamine, and the subsequent release of adrenal catecholamines such as epinephrine. This action appears to contribute in part to the memory-enhancing effects of both *d*-amphetamine and 4-OH amphetamine in a one-trial inhibitory avoidance task, since these effects are attenuated by adrenal medullation (Martinez, Jensen, et al., 1980; Martinez, Vasquez, et al., 1980). Furthermore, several studies have shown that posttraining administration of epinephrine, as well as endogenous release of epinephrine from the adrenal medulla, regulates memory storage (for a review, see Gold, 1991). Increases in circulating levels of glucose, produced by epinephrine release (Ellis, Kennedy, Eusebi, & Vincent, 1967), has been proposed as an intermediate step by which epinephrine may act, at least in part, to modulate memory

storage (Gold, 1991). Consistent with this hypothesis, posttraining administration of glucose enhances memory in both aversive (Gold, 1986; Messier & White, 1984, 1987) and appetitive (Messier & Destrade, 1988; Packard & White, 1990) learning tasks. Moreover, unlike the effects of epinephrine (Introini-Collison, Saghafi, Novack, & McGaugh, 1992; Sternberg, Korol, Novack, & McGaugh, 1986), the memory-enhancing effects of glucose are not blocked by adrenergic antagonists (Hall, Vogt, & Gold, 1986). Thus, one possible peripheral mechanism by which *d*-amphetamine and 4-OH amphetamine may enhance memory involves the release of epinephrine from the adrenal medulla, with a subsequent modulatory action of glucose on memory storage.

Recent evidence indicates that the memory enhancement induced by 4-OH amphetamine in an inhibitory avoidance task is attenuated by vagotomy (Williams & Jensen, 1991). Vagotomy has also been shown to block the memory enhancement produced by posttraining injections of the neuropeptide CCK-8S (Flood, Smith, & Morley, 1987). Furthermore, lesions of the celiac ganglion, which remove afferents of the right branch of the vagus nerve, block the memory-enhancing effects of posttraining administration of glucose (White, 1991). Thus, the vagus nerve is a putative pathway by which neural signals initiated in the periphery may be transmitted to regions of the central nervous system involved in memory processing.

In the present study, the dose (2.0 mg/kg) of 4-OH amphetamine required to enhance retention was higher than the effective dose (1.0 mg/kg) of *d*-amphetamine. This

finding contrasts with previous reports indicating that both drugs enhance memory at similar doses (Martinez, Jensen, et al., 1980; Martinez, Vasquez, et al., 1980). One possible explanation for this difference is that aversively motivated tasks were used in previous studies, and a higher dose of 4-OH amphetamine may be required to enhance memory in an appetitive task. Alternatively, the difference in effective doses of the two amphetamines may reflect the possibility that *d*-amphetamine enhances win-shift retention by either a central or a dual action on the periphery and brain. In support of the latter alternative, it should be noted that due to the presence of the *l* isomer, the racemic mixture of 4-OH amphetamine used in the present study has a slightly more potent cardiovascular action than that of *d*-amphetamine (Weiner, 1980). Thus, if *d*-amphetamine enhanced win-shift retention solely through the same peripheral mechanism as that activated by dl-4-OH amphetamine, and if this mechanism involved amphetamine effects on cardiovascular function, one would expect that a *higher* dose of *d*-amphetamine would be required to enhance retention. However, the effective dose of *d*-amphetamine (1.0 mg/kg) was *lower* than that of dl-4-OH amphetamine (2.0 mg/kg), suggesting a possible difference in mechanism of action.

Central Actions of Amphetamine on Memory

While the ability of 4-OH amphetamine to improve retention suggests that the peripheral effects of amphetamine may be *sufficient* to produce memory enhancement, the findings do not rule out the possible *participation*, or even *necessity*, of the central actions of *d*-amphetamine. Although posttraining intraventricular injection of *d*-amphetamine failed to enhance retention of inhibitory avoidance training (Martinez, Jensen, et al., 1980), several recent studies have demonstrated that memory can be enhanced by intracerebral posttraining injections of *d*-amphetamine. For example, posttraining injections of *d*-amphetamine infused into the caudate nucleus improved memory in a conditioned emotional response (CER) task (Carr & White, 1984; Viaud & White, 1989) and in a simultaneous visual discrimination task (Packard & White, 1991). Interestingly, the retention enhancing effect of peripheral injections of *d*-amphetamine in a CER task is blocked by 6-hydroxydopamine lesions of nigrostriatal neurons (White, 1988). One interpretation of this finding is that peripherally injected *d*-amphetamine affects memory by acting directly on dopaminergic neurons innervating the caudate nucleus. Alternatively, *d*-amphetamine may initiate a peripheral signal that subsequently acts on nigrostriatal neurons.

The findings from a previous experiment with training and test procedures identical to those of the present experiment indicate that posttraining intrahippocampal injections of *d*-amphetamine enhance win-shift retention in a radial maze task (Packard & White, 1991). Furthermore, lesion studies have shown that the functional integrity of

the hippocampal system is necessary for the acquisition of win-shift radial maze behavior (e.g., Olton, 1983). Therefore, the peripheral neural signal initiated by 4-OH amphetamine may ultimately act on the hippocampus to produce its memory-enhancing effect. In this regard, it is interesting to note that peripheral injection of a behaviorally effective dose (0.82 mg/kg) of 4-OH amphetamine has decreased regional brain concentrations of dopamine, but not norepinephrine, in the hippocampus, amygdala, and hypothalamus (Martinez et al., 1983).

Finally, as an indirect catecholamine agonist, *d*-amphetamine releases both dopamine and norepinephrine (Weiner, 1980). Available evidence suggests that the memory-enhancing effect of *d*-amphetamine following central administration may be due primarily to its action on dopaminergic neurons. For example, posttraining intracerebral injection of dopamine D1 (SKF-38393) and D2 (LY 171555) receptor agonists produces memory-enhancing effects comparable to those induced by *d*-amphetamine injected into the same brain regions (Packard & White, 1991). However, further research using selective dopaminergic and noradrenergic antagonist drugs is necessary in order to evaluate the noradrenergic contribution to *d*-amphetamine-induced memory improvement.

In summary, the findings from these experiments indicate that peripheral posttraining injection of *d*-amphetamine and 4-OH amphetamine enhance retention in a win-shift radial maze task and suggest that the peripheral actions of amphetamine are *sufficient* to enhance memory in this task. However, the possibility that the two amphetamines act through independent mechanisms to enhance win-shift retention remains viable and is supported by the difference in effective doses of the two drugs.

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