Retrieval enhancement in mice by pretest amphetamine injection after a long retention interval

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Mice were trained to avoid one compartment of a shuttlebox using the procedures of Pavlovian fear conditioning, and retention was measured 1 day later and 1 month later using an active avoidance test. Good retention was evident at 1 day, but substantial forgetting occurred after 1 month, performance levels in this group being equivalent to those exhibited by sham-conditioned animals. Treatment with d-amphetamine (2.0 mg/kg) before testing restored retention to levels shown by mice tested 1 day after conditioning. When retention was tested with a passive avoidance test, amphetamine increased rather than decreased latencies of animals tested 1 month after conditioning. Amphetamine did not decrease latencies of sham-conditioned mice tested in active avoidance and did not enhance the performance of those with strong memory tested 1 day following training in either active or passive tests. Amphetamine also enhanced retrieval in mice in which conditioning was weakened by a reduction in shock level rather than by imposition of a long retention interval. These findings add to the growing evidence that retention of weak memories can be facilitated by monoaminergic stimulation of retrieval mechanisms.

Many recent studies have shown that forgetting induced by treatment with amnesic agents can be alleviated by drugs administered before the retention test (see Quartermain, 1982, 1983, and Martinez, Jensen, & McGaugh, 1981, for reviews of these studies). For example, memory loss resulting from protein synthesis inhibition, inhibition of norepinephrine synthesis, disruption of catecholamine (CA) storage mechanisms, hypothermia, and electroconvulsive shock can all be attenuated by pretesting administration of pharmacological agents that increase activity in catecholamine neurotransmitter systems. These studies suggest that memory can be restored by pharmacological activation of retrieval mechanisms and, furthermore, that CA transmitter systems may have an important function in this process.

In order to securely establish the generality of the phenomenon it will be necessary to demonstrate that memory can be restored by CA stimulation following a wide variety of forgetting treatments. At the present time, support for CA involvement in retrieval processes is based principally on studies that use amnesic agents to induce forgetting. However, some recent studies suggest that CA stimulation may also alleviate other types of forgetting. For example,

Meyer and Meyer (1977) have shown that forgetting of a shock-motivated brightness discrimination induced by posterior cortical lesions could be ameliorated by d-amphetamine administered prior to testing. Recently, Sara and Deweer (1983) have demonstrated that forgetting of appetitively motivated discrimination learning induced by a long training-to-testing interval could be alleviated by d-amphetamine administered before testing. It is noteworthy that in both of the preceding experiments, the dose of amphetamine that facilitated retrieval failed to enhance performance when it was administered during acquisition. There is also some evidence that the forgetting that accompanies senescence can be attenuated by pharmacological agents. It has recently been shown that retention deficits in inhibitory avoidance present in senescent Swiss Webster mice can be reversed by pretest administration of lisuride (Quartermain, Judge, & Friedman, 1983) or d-amphetamine (Judge & Quartermain, 1983). The studies reviewed above indicate that pharmacological activation of CA systems prior to the retention test may alleviate forgetting resulting from quite diverse sources.

The purpose of the present experiment was to attempt to strengthen this conclusion by determining whether administration of amphetamine prior to testing could alleviate forgetting of fear conditioning resulting from a long retention interval. Previous studies had shown that Pavlovian fear conditioning was forgotten quite rapidly in rats and, in addition, that pretest exposure to the CS and UCS could result in substantial alleviation of this forgetting (Spear, 1978). We had previously shown that forgetting of

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fear conditioning induced by depletion of biogenic amines could be attenuated by pretest stimulation of CA systems (Quartermain & Judge, 1983). The present study attempted to determine whether forgetting of fear conditioning induced by a 1-month retention interval could be attenuated by treatment with amphetamine before the retention test.

GENERAL METHODS

Behavioral Task

Fear was conditioned to stimuli of one side of a mouse shuttlebox, using the procedures of Pavlovian fear conditioning. Retention was tested 1 day or 1 month later by measuring latencies to escape from the shock compartment under extinction conditions. Previous studies had shown that substantial forgetting occurs in this task over a 1-month interval, and also that this forgetting could be alleviated by behavioral reactivation treatments, such as brief presentation of the CS and UCS (Spear, 1978).

Animals

The subjects for this study were 200 male Swiss Webster mice (West Jersey Biological Supply), approximately 11 weeks old at the time of training and weighing between 35 and 45 g. The mice were housed 4 per cage with ad-lib food and water after 1 week of adaptation to the laboratory in group cages (13-15 per cage). The vivarium was maintained at $22^{\circ} \pm 2^{\circ}\text{C}$, and the lights were on from 0700 to 1900 h.

Apparatus

Fear conditioning was conducted in one side of a two-compartment mouse shuttlebox (LVE MSC-022). The shock side, which was 9 cm wide, 11 cm high, and 23 cm long, had black Plexiglas walls and a black lid. The floor consisted of stainless steel rods (0.3-cm diameter, 7 cm between rods), through which a scrambled shock (0.2 mA ac) could be delivered from a Coulbourn constant-current shocker. The conditioned stimulus (CS) was a 24-V dc light flashing on for 0.5 sec at a frequency of 1 Hz. The CS was positioned on the lid above the shock compartment. The non-shocked (safe) side of the compartment had the same dimensions as the shock side, white Plexiglas walls, and a white cardboard floor; it was covered with a white Plexiglas lid. The two sides were separated by a partition that contained a guillotine door, 4 cm wide $\times$ 4 cm high. Sham training was carried out in an adjacent room in a chamber of the same dimensions as the training shock chamber, but having a V-shaped aluminum floor with a separation of 1 cm between the two sides at the floor of the trough. Each side was connected to one pole of a constant-current shock source set to the same intensity (0.2 mA) as the UCS used in fear conditioning. The shock source was yoked to the training apparatus so that the sham-trained mice received shocks at the same time as their classically conditioned counterparts. Testing took place in the training apparatus at approximately the same time of day as the training session, between 1000 and 1800 h. All apparatus were kept in temperature-controlled rooms adjacent to the vivarium. Training and testing took place in a dimly lit room, whereas the sham procedure was carried out under normal illumination.

Procedure

Pavlovian fear conditioning. Individual mice were first placed in the white ("safe") side of the conditioning chamber, where they remained for 90 sec. No shock was administered. The door was then opened, and the animal was gently pushed with a Plexiglas panel into the black side of the apparatus, where three fear conditioning trials were administered. Each trial consisted of a 13-sec presentation of the CS accompanied, for the final 3 sec, by the UCS. CS and UCS terminated together. The three trials were given on a variable interval 30-sec schedule. Following the third shock, the door was raised and the mice were gently pushed into the white side, where they remained for 90 sec; after this they

were again returned to the shock side for another three conditioning trials. The conditioning procedure thus consisted of a total of six CS-UCS pairings and exposure to the stimuli of the safe (nonshocked) compartment for an equal time period. Conditioned mice from each cage were kept in a holding cage and returned to their home cage after all cagemates were trained.

Sham conditioning. Animals scheduled for sham conditioning were yoked to a mouse receiving classical conditioning. Thus, the number, intensity, and timing of shocks was identical for the two groups, but no formal CS-UCS pairing occurred for the yoked controls.

Retention testing. Retention was tested either 1 day or 1 month following conditioning, using the following procedures. *Active avoidance*—Mice were placed in the shock compartment facing away from the door. After 5 sec, the door was raised and the CS initiated. When the mouse crossed into the safe compartment (entry of $>50\%$ of the body), the CS was terminated, the door was closed, and the response latency was automatically recorded. Between trials, the mice remained in the safe side for 60 sec. If an animal failed to respond within 60 sec, the door was closed and the mouse was lifted into the safe side by the experimenter and given 60 sec as a test score. Each animal received five trials. No shock was administered. *Passive avoidance*—Some animals were tested with a passive avoidance procedure to evaluate the contribution to retention performance of drug-induced alterations in activity. The animals tested with this procedure were placed in the safe side facing away from the door. After 5 sec, the guillotine door was raised, allowing access to the shock chamber in which the CS was continuously present. During the 5-min test period, the initial latency to enter the shock compartment, the total number of entries, and the total time spent in the shock compartment were recorded. Mice failing to leave the safe side within 5 min were given the maximum latency score of 300 sec. No shock was given during testing.

Drug administration. The mice were injected 30 min prior to the retention test with either saline or different doses of d-amphetamine sulfate (Sigma) dissolved in saline. All injections were given subcutaneously in a volume of 0.01 ml per gram of body weight.

Data analysis. For multiple-trial tests, latency scores were transformed into log-seconds and evaluated with repeated-measures analyses of variance. When appropriate, these data were also subjected to linear trend analysis (Kepple, 1973) to confirm group differences. Passive avoidance data were analyzed with *t* tests. In all figures, untransformed latency data were used in order to facilitate visual evaluations.

EXPERIMENT 1

The purposes of Experiment 1 were: (1) to determine the amount of forgetting of fear conditioning that occurred over a 1-month retention interval in untreated mice, and (2) to determine whether forgetting of fear conditioning could be alleviated by treatment with various doses of d-amphetamine administered prior to the retention test.

Method

Controls. In order to evaluate the possible contribution of non-specific effects of amphetamine, two control conditions were included in this experiment. In one, mice were given sham conditioning and treated with either the highest dose of amphetamine or with saline to determine the effects of the drug on animals without memory of fear conditioning. The saline-injected sham-trained group also served as a baseline against which to assess performance of the trained animals. The other control consisted of testing retention with a passive rather than active procedure. Conditioned mice were injected with either 2.0 mg/kg amphetamine or saline 30 min before the test. With this procedure, enhanced

retention would be indexed by increased rather than decreased latencies. This would provide a convincing demonstration that amphetamine was influencing performance by its effects on memory rather than by alterations in such nonmemorial processes as general activity.

Procedure. Eighty-eight mice were conditioned and 67 were given sham training, using the procedures described in General Methods. Testing was organized into four parts:

(1) One day following training, 16 sham-treated and 12 conditioned mice were selected randomly and tested using the active retention test. All animals were injected with saline 30 min before testing. After the 1-month interval had elapsed, 17 conditioned and 13 sham-treated mice were selected randomly and tested 30 min following a saline injection. A comparison of the performance of the 1-day and the 1-month groups provides the basic reference conditions for establishing the amount of forgetting attributable to the 1-month retention interval. (See Figure 1.)

(2) Three groups of conditioned mice were injected with 0.1 (N=10), 1.0 (N=10), or 2.0 mg/kg (N=13) d-amphetamine sulfate 30 min before testing. (See Figure 2.)

(3) Mice in one sham-conditioned group (N=13) were injected with 2.0 mg/kg d-amphetamine to evaluate the effects of the drug on animals without memory of fear conditioning. (See Figure 2.)

(4) Two groups of conditioned mice and two groups of sham-treated mice were tested using the passive measure. One of each pair of conditioned and sham groups was injected with 2.0 mg/kg d-amphetamine (N=13/group), and the other two groups were injected with saline (conditioned, N=13; sham, N=12). (See Figure 3.)

Results

Effects of a 1-month retention interval on test performance. Repeated-measures analyses of variance (two-way) of log-transformed latency scores confirmed the following group differences and characteristics apparent in Figure 1:

(1) Mice in Group CD (conditioned, 1-day retention interval) enter the safe side significantly faster than mice receiving sham training (SD), indicating that a strong memory of training exists 1 day after training [groups, $F(1,26)=16.39$, $p \leq .01$]. There was a significant interaction of training treatment and trials [$F(4,104)=5.95$, $p \leq .01$], but no overall

trials effect due to the diverging latency scores of both groups after Trial 1 [$F(4,104)=2.24$, n.s. (not significant), $p > .05$]. Linear trend analyses confirmed the difference in the response of these groups to the test trials, indicating that there was a significant positive slope for the SD group [mean trend coefficient = $+0.79$, $F(1,15)=8.91$, $p \leq .01$] and that the trend for conditioned mice was in the opposite direction (mean trend coefficient = -0.89) but not significantly different from zero slope [$F(1,11)=3.67$, n.s.].

(2) After a 1-month retention interval (RI = M), an ANOVA confirms that the avoidance behavior of conditioned mice (CM) was not different from that of a sham group tested after the same interval (SM) [groups, $F(1,28)=0.29$, n.s.]. However, trend analyses suggest that there was some residual memory in conditioned mice at 1 month, since the slope of their average response latencies was not significantly different from zero [mean trend coefficient = $+0.03$, $F(1,16)=0.01$, n.s.]; the sham group exhibited a significant positive trend equivalent to that of shams tested after 1 day [mean trend coefficient = $+0.84$, $F(1,12)=8.75$, $p \leq .05$].

(3) An ANOVA comparing the two sham groups (SD and SM) indicated that there was no effect of retention interval on their performance [Groups, $F(1,27)=0.62$, n.s.] and no interaction of RI and trials [$F(4,108)=0.10$, n.s.]. There was, however, a significant trials effect [$F(4,108)=6.90$, $p \leq .01$], confirming the results of the trend analyses. This effect seems to be attributable to the fact that the 60-sec intertrial interval is spent in the safe side, and therefore increasing latencies to enter this compartment over successive trials represent a trend towards equalization of the amount of time spent in each compartment.

(4) Comparison of the two conditioned groups by ANOVA confirms the detrimental effect of a long retention interval on memory. There was a significant groups difference [$F(1,27)=11.11$, $p \leq .01$] and a trials effect [$F(4,108)=2.85$, $p \leq .05$] attributable primarily to the negative trend in the latencies of the CD group. There was no significant groups $\times$ trials interaction [$F(4,108)=1.98$, n.s.].

Effects of amphetamine on active retention test performance. Pretest amphetamine produced a dose-dependent enhancement of performance (see Figure 2). In an overall ANOVA of the four dose groups [A (amphetamine) 2.0=2.0 mg/kg, A 1.0=1.0 mg/kg, A 0.1=0.1 mg/kg, A 0.0=0.0 mg/kg = saline], there was a significant effect of drug treatment [groups, $F(3,46)=3.77$, $p \leq .05$] as well as a strong trials effect [$F(4,184)=12.48$, $p \leq .01$] and a significant drug dose $\times$ trials interaction [$F(12,184)=2.48$, $p \leq .01$]. Comparisons of individual amphetamine groups to the saline reference group revealed that the 2.0-mg/kg dose was principally responsible for the overall groups difference [groups, $F(1,28)=8.31$, $p \leq .01$], while

Figure 1. Active avoidance test performance of conditioned (C) or sham-trained (S) mice tested after a retention interval of 1 day (D) or 1 month (M).

Figure 2. Active avoidance test performance of conditioned mice tested after a 1-month retention interval. Groups received pretest injections of saline (SAL) or d-amphetamine sulfate in doses of 0.1 (A 0.1), 1.0 (A 1.0), or 2.0 (A 2.0) mg/kg. One sham-trained group was injected with 2.0 mg/kg of amphetamine.

the lower doses are essentially ineffective [A 1.0, groups, $F(1,25)=2.71$, n.s.; A 0.1, groups, $F(1,28)=0.01$, n.s.]. In each of these comparisons, there was a significant trials effect [A 2.0, $F(4,112)=6.62$, $p \leq .01$; A 1.0, $F(4,100)=2.65$, $p \leq .05$; A 0.1, $F(4,100)=2.76$, $p \leq .05$], and the drug treatment interaction with trials was significant between saline and A 2.0 [$F(4,112)=5.99$, $p \leq .01$] and A 0.1 [$F(4,100)=2.78$, $p \leq .05$], but not between saline and A 1.0 [$F(4,100)=1.5$, n.s.].

A linear trend analysis of the data from the most effective drug dose (A 2.0) indicates a significant negative slope for the test latencies of this group [mean trend coefficient = -1.87 , $F(1,12)=28.15$, $p \leq .01$].

Effects of amphetamine on active test performance of sham-conditioned mice. Mice receiving sham conditioning and 2.0 mg/kg of amphetamine before testing at a 1-month retention interval (SM-A 2.0, see Figure 2) exhibited performance comparable to that of saline-injected mice [SM-A 2.0 compared with SM-SAL; groups, $F(1,24)=0.08$, n.s.], although their test scores did not exhibit the positive trend seen in saline sham groups [mean trend coefficient (SM-A 2.0) = $+0.14$, $F(1,12)=0.17$, n.s.]. An ANOVA confirmed that there was a significant effect of training treatment on the active test performance of amphetamine-treated mice [SM-A 2.0 compared with CM-A 2.0; groups, $F(1,24)=10.81$, $p \leq .01$; trials, $F(4,96)=5.92$, $p \leq .05$; interaction, $F(4,96)=7.26$, $p \leq .01$].

Effects of amphetamine on passive avoidance test performance. When tested with a passive avoidance procedure after a 1-month retention interval, mice injected with amphetamine (2.0 mg/kg) before testing demonstrated enhanced retention by (1) waiting longer than saline mice to enter the shock compartment [comparison of mean latencies: $t(24)=3.01$, $p \leq .01$], (2) making fewer entries into it [$t(24)=$

3.04 , $p \leq .01$], and (3) spending a smaller percentage of the test-session time in the shock compartment [$t(24)=4.03$, $p \leq .001$] (see Figure 3). Amphetamine-injected sham controls were indistinguishable from saline mice in all three measures: latency [$t(23)=0.82$, n.s.], number of entries [$t(23)=1.47$, n.s.], and percent time in the shock side [$t(23)=1.25$, n.s.].

EXPERIMENT 2

A major question raised by the results of Experiment 1 concerns the specificity of the enhanced retention induced by pretest amphetamine treatment. Did amphetamine act as a nonspecific enhancer facilitating all memories indiscriminately regardless of their strength or experimental history. The hypothesis that amphetamine facilitates retrieval processes would predict that pretest administration would facilitate performance of a weakened habit and only minimally influence strong memories when the retrieval system was operating close to maximum efficiency. A related question concerns the specificity of drug effects on weak memories. Is retrieval of all weak memories enhanced by pretest amphetamine or is facilitation restricted only to memories that were initially strong and subsequently degraded by a forgetting treatment? Experiment 2 addressed these issues by determining (1) whether pretest amphetamine treatment could enhance performance of a strong memory tested 1 day after conditioning, and

Figure 3. Passive avoidance test performance of conditioned (C) or sham-trained (S) mice tested after a 1-month retention interval and injected with saline (SAL) or d-amphetamine sulfate, 2.0 mg/kg (A 2.0) before testing.

(2) whether amphetamine could facilitate retrieval of a 1-day memory that had been weakened by reduction of the intensity of the UCS during conditioning.

Method

A group of 28 mice were conditioned using the procedures described in General Methods and tested 1 day following training. Seven mice were injected with amphetamine (2.0 mg/kg) 30 min before being tested in the active procedure. To determine whether amphetamine administration could enhance retrieval of a strong memory, the performance of this group (CD-A 2.0) was compared with that of the 1-day group injected with saline (CD-SAL). The remaining mice were tested with the passive procedure 30 min after being injected with saline ($N=12$) or amphetamine 2.0 mg/kg ($N=9$).

A second group of 17 mice were trained with the conventional procedures, except that the UCS duration was 0.5 sec rather than the standard 3.0 sec. Pilot experiments had shown that this procedure resulted in weaker fear conditioning, as indexed by escape latencies. One day after conditioning, the mice were injected with either 2.0 mg/kg amphetamine (WD-A 2.0, $N=7$) or with saline (WD-SAL, $N=11$) 30 min before the retention test. A comparison of the performance of these two groups would indicate whether amphetamine could enhance retrieval of weak fear conditioning as well as strong fear conditioning weakened by forgetting.

Results

An ANOVA comparing test latencies of normally conditioned saline- (CD-SAL) and amphetamine-injected (CD-A 2.0) mice indicates that there was no significant effect of amphetamine [groups, $F(1,17) = 0.45$, n.s.] and no drug $\times$ trials interaction [$F(4,68) = 1.84$, n.s.] in the active test. The tendency for the latencies of both groups to decrease over successive trials was significant [$F(4,68) = 7.52$, $p \leq .01$] as would be expected for well-conditioned subjects (see Figure 4A). It is possible that these results are simply due to the inability of animals to escape the shock compartment any faster than the conditioned saline mice do, although this seems unlikely. If, however, amphetamine produces memory enhancement that is masked by response-speed limitations, the enhancement should be revealed by a passive test, in which improved memory is indexed by a longer first-entry latency, fewer entries into the shock compartment, and a reduction in the amount of time spent there, as in Experiment 1. The results of the passive test indicate that this is not the case. Pretest treatment with amphetamine did not result in a significant enhancement of memory in any of these measures (see Table 1). There is a slight, but not significant, trend for amphetamine to increase activity, with mice entering the shock side somewhat faster and making more entries during the test session, but the distribution of time spent in the two compartments is identical for saline- and amphetamine-treated subjects.

The weak training procedure produced significantly less conditioning than the normal procedure, as indicated by significant groups [$F(1,21) = 5.34$,

Figure 4. Active avoidance test performance of mice tested 1 day (D) after conditioning and receiving pretest injections of saline (SAL) or d-amphetamine sulfate, 2.0 mg/kg (A 2.0). Panel A: Subjects given strong conditioning (C), as in Experiment 1. Panel B: Subjects given weak conditioning (W).

$p \leq .05$] and interaction [$F(4,84) = 3.31$, $p \leq .05$] effects in an ANOVA comparison of saline-treated mice trained under each condition (compare Figure 4A, CD-SAL with Figure 4B, WD-SAL). An ANOVA comparing mice receiving weak conditioning and injected before testing with saline (WD-SAL) or amphetamine (WD-A2.0) indicates that there is a significant drug treatment effect [groups, $F(1,15) = 7.04$, $p \leq .05$] and a significant drug $\times$ trials interaction [$F(4,60) = 5.10$, $p \leq .01$]. The trials effect is also significant [$F(4,60) = 2.53$, $p \leq .05$], but trend analyses confirm that this is attributable mainly to the amphetamine group, which has a significant negative slope [mean trend coefficient = -1.78 , $F(1,5) = 13.50$, $p \leq .05$], as compared with that of the saline group, which has a slope not significantly different from zero [mean trend coefficient = $+0.57$, $F(1,10) = 2.50$, $p > .05$]. An interpretation of this effect as being due to "new learning" produced by the amphetamine treatment is ruled out by the failure of amphetamine to influence sham groups in Experiment 1.

Table 1
Passive Avoidance Test Data

Condition	Pretest Drug						t test	
	Saline			Amphetamine			Saline vs. Amphetamine	
	N	Mean	SE	N	Mean	SE	t	p
Latency to Enter Shock Side*	12	202.9	31.3	9	146.3	34.5	1.21	n.s.
Entries into Shock Side	12	3.3	1.3	9	5.1	1.9	0.81	n.s.
Percent Time in Shock Side	12	11.0	4.5	9	10.3	5.6	0.10	n.s.

Note—Training = 6 shocks at 0.2 mA, 3.0 sec each. Retention interval = 1 day; saline or amphetamine, 2.0 mg/kg 30 min pretest. Comparisons of group means by *t* test, n.s. = not significant, *p* > .05. *In seconds.

DISCUSSION

The results of this study have demonstrated that pretest administration of the general CA stimulant d-amphetamine can alleviate forgetting of fear conditioning induced by a long retention interval. Control experiments ruled out alterations in motor activity as an explanation for these findings by showing that amphetamine (1) failed to influence performance in sham-conditioned mice, and (2) resulted in either increased or decreased response latencies, depending on whether retention was indexed by an active or a passive test. In addition, these results establish boundary conditions for the enhancement of retention by amphetamine. Animals that have experienced either no conditioning or those that are tested 1 day following training do not show enhanced performance relative to controls following an amphetamine injection. In the former instance, no memory of specific fear conditioning exists to be facilitated, and in the latter case, little forgetting has occurred and retrieval processes are functioning close to maximum capacity, so that the addition of amphetamine stimulation does not result in significant improvement of performance.

The results of Experiment 2 indicate that amphetamine-induced enhancement of retention is not restricted to strong habits which have been weakened by a forgetting treatment. Conditioned responses that are below maximum strength as a result of the use of suboptimal conditioning parameters can also be enhanced by amphetamine treatment. The facilitation of both types of poor memory in Experiments 1 and 2, when considered in combination with the failure of amphetamine to produce any signs of enhanced learning in sham-conditioned animals, suggests that the general effect of amphetamine is interactive rather than additive, facilitating the utilization of existing memory rather than producing independent new learning.

It is of interest to consider the possible consequences of memory facilitation by amphetamine on the subsequent retrieval of the same memory. The pharmacological effects of the drug would not be

expected to persist, but the aftereffects of utilizing a facilitated memory should be apparent at later testing if reprocessing occurs following its reactivation. The demonstration of a facilitating effect of memory retrieval on later recall in both animals and humans supports the hypothesis that such reprocessing does occur (see Spear, 1981, for a review). Furthermore, although we have no data on the weak training condition, we have recently shown that when strong training is weakened by forgetting, the facilitation of retention induced by amphetamine is still apparent when subjects are retested 24 h following drug treatment (Judge & Quartermain, 1983)—a finding that would not be expected unless amphetamine produced a genuine enhancement of memory and associated reprocessing during the original test. Studies are currently in progress to investigate the durability characteristics of amphetamine-induced enhancement in greater detail.

This study supports the conclusions of previous experiments on reversal of drug-induced amnesias (e.g., Quartermain & Altman, 1982; Quartermain & Botwinick, 1975) that amphetamine can facilitate retention by its action on retrieval processes. Alterations in activity levels cannot account for the findings, and one of the earlier studies (Quartermain & Altman, 1982) showed that it is unlikely that amphetamine-induced enhancement of retention can be accounted for in terms of new learning based on fear or stress. The present findings, which demonstrate facilitated retention 1 month following training, can most plausibly be explained in terms of the effects of amphetamine on retrieval processes.

Taken in conjunction with our previous studies, the present findings indicate that distinctly different types of forgetting can be alleviated by activating a common system. The observation that forgetting due to protein synthesis inhibition, catecholamine depletion, senescence, or a long retention interval can all be alleviated by pretest administration of CA stimulating agents (Quartermain, Judge, & Friedman, 1983) suggests that monoamine systems play a fundamental role in mediating retrieval processes in animals.

The means by which pharmacological agents facilitate retrieval mechanisms is at present unknown. A promising direction for research into this issue is provided by Spear's (1978) hypothesis that treatments that increase similarity between conditions present at training and those existing in the test environment are likely to facilitate retrieval. Agents that stimulate monoamine systems may enhance this similarity by providing internal cues closely related to those present during conditioning. In addition, these agents may sharpen selective attention (Mason, 1980) or neuronal network feature extraction mechanisms (Woodward, 1974) in such a way that critical stimuli are more discriminable in the retrieval environment. It is well established that brief exposure to some component of the training situation, such as the CS, the UCS, and certain contextual stimuli, can alleviate forgetting when they are presented prior to the retention test (Spear, 1978; Spear & Parsons, 1976). The close similarity between the effects of these treatments on retention and those produced by pharmacological agents suggests that the monoamine neurotransmitter systems may be the common mechanism through which reactivation treatments are working. The evaluation of this hypothesis is one of our current research goals.

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