Pharmacology Biochemistry & Behavior, Vol. 15, pp. 673–676, 1981. Printed in the U.S.A.

Short-Term Memory: The Role of d-Amphetamine[1]

RAYMOND P. KESNER,[2] REX A. BIERLEY AND PAT PEBBLES

University of Utah, Salt Lake City, UT 84112

Received 17 June 1980

KESNER, R. P., R. A. BIERLEY AND P. PEBBLES. *Short-term memory: The role of d-amphetamine.* PHARMAC. BIOCHEM. BEHAV. **15**(5) 673–676, 1981.—d-Amphetamine injections produce a dose-dependent disruption of performance within a discrete delayed alternation and a spatial delayed matching-to-sample task. Since d-amphetamine in the doses used had no deleterious effects on discrimination performance (no delay condition), it is suggested that d-amphetamine disrupts neuronal activity representing short-term memory. The data provide support for an independence model of short- and long-term memory.

d-Amphetamine Short-term memory Arousal

THE recent expansion of research and theory in human short-term memory (STM) has led to the development of interest in animal models of STM. This has resulted in a revival of tasks such as delayed response, delayed alternation, and delayed matching-to-sample. It is often assumed that performance on these tasks reflects the operation of processes associated with STM [6, 11, 19, 20, 22, 25]. With current theories of animal memory a distinction is often made between STM, working, or active memory and LTM or reference memory [10, 16, 28].

There are differences among theories as to the hypothesized relationship of STM to LTM. Certain theories propose that the amount of information stored in LTM is a direct function of the duration of processing of information within STM [16,28]. One prediction from this sequential model is that any treatment that is capable of altering STM should also alter LTM.

Other theories propose that STM and LTM can operate in parallel and that information can be processed independently in each system even though some form of sequential processing might also occur [13]. One prediction from this independent model is that treatments could alter STM without producing comparable changes in LTM and vice versa. Support for this latter model has come from studies in humans, which show that manipulations, that presumably enhance arousal, disrupt retention at short time delays, but facilitate retention at long time delays [4, 14, 27]. Also, diethyldicarbamate (DDC) injected in rats prior to passive avoidance training results in facilitation of short-term and complete disruption of long-term retention for the aversive experience [18]. DDC blocks norepinephrine biosynthesis and presumably decreases the level of arousal. Based on the above mentioned observations, Kesner [13] has suggested that for STM arousal acts to accelerate the rate of decay of activated neural traces and for LTM arousal facilitates consolidation.

Based on the observation that amphetamine (an arousal inducing agent) injected in rats facilitates long-term memory [15], the sequential model would predict that this LTM facilitation is a function of an enhancement of STM [16]. In contrast, the independence model would predict that this LTM facilitation could also emerge as a function of a disruption of STM [13]. There is no previous work that has directly investigated the effects of amphetamine on STM in rats, but in monkeys amphetamine disrupts performance in delayed matching-to-sample tasks [1,7], thus presumably amphetamine has a disruptive effect on STM. Because of the difficulty in comparing dose levels between monkeys and rats, it would be of interest to examine the effects of amphetamine in rats within tasks that measure STM and test the differential predictions of the two above mentioned models, namely that low doses of amphetamine either disrupts STM (independence model) or facilitates STM (sequential model).

EXPERIMENT 1

In the first experiment animals were tested in a discrete delayed alternation task. Bierley and Kesner [2] have shown that correct performance in this task is directly related to the length of the delay interval (seconds) reflecting a function characteristic of STM.

METHOD

Subjects

Three male Long-Evans rats (weight 325–400 g) served as subjects. Animals were maintained at 70–80% of their ad lib body weight but allowed continuous access to water.

Apparatus

The experimental chamber contained two retractable bars

[1]Support for this research was provided by Biomedical Research Support Grant. NIH RR07092-12.

[2]Requests for reprints should be sent to Raymond P. Kesner, Department of Psychology, University of Utah, Salt Lake City, UT 84112.

placed symmetrically on either side of a liquid reinforcement device. The entire assembly was housed in a sound attenuating chamber with an exhaust fan for cooling and masking external noises. Correct responses were reinforced with a 30% w/v sucrose solution. Each reinforcement contained 0.01 ml of the solution. The operation of the bars and dipper was accomplished with standard relay circuitry.

Procedure

Rats were trained to barpress and then advanced to progressively more difficult schedules over a period of 5–6 months. Training was considered complete when animals displayed stable performance on the discrete trial-delayed alternation (DA) task. Briefly, the task was as follows. On a given trial either the right or left bar was extended (study phase). Pressing the bar initiated both the retraction of the bar and the start of one of five randomly presented delay conditions (0, 5, 15, 30, and 40 sec). At the end of the delay, both bars were extended (test phase) and the rat had to press the bar opposite the one it pressed last in order to receive reinforcement. Since no correction procedure for incorrect responses was used, responding to either bar during the test phase initiated retraction of the bars and began a 20 sec intertrial interval (ITI). This task differs from most delayed alternation tasks [8] in that the bar extended to start a trial is programmed independently of the bar pressed during the test phase of the preceding trial. Each daily session lasted approximately 30 min and consisted of four 0-sec warm-up trials plus six trials at each of the five randomly presented delay conditions.

Animals received one of three dosages of d-amphetamine sulfate (0.33, 1.0, or 2.0 mg/kg) or saline injected IP 30 min prior to testing. Each animal received a total of five sessions for each drug dosage. The order of injections was counterbalanced across animals with the stipulation that a single dose was used consecutively for five drug sessions. At least three saline injection sessions separated d-amphetamine sessions. Performance on the previous saline injected day was used as a baseline. There were 30 observations for each experimental condition. The number of correct or incorrect responses was measured for each delay and each treatment. Percentage of correct responses was used as an index of retention. The data were analyzed using analysis of variance techniques.

RESULTS

Observation of the animals in the home cages during the 30 min following injection of d-amphetamine revealed some signs of hyperactivity in rats at the higher drug doses (1.0 and 2.0 mg/kg) but not at the low doses (0.33 mg/kg). However, observation of the rats during testing in the DA apparatus indicated little remaining behavioral effects of the drug. That is, no measurable differences in latency to respond or time to complete sessions were detectable between saline and drug conditions.

Baseline responding (saline injections) was typified by near perfect performance at the short delays with a gradual decline to slightly less than 90% correct at the longest delay. The relatively accurate performance even at the longest delay reflects considerable overtraining of the subjects on the DA task. No differences between saline and any of the three drug doses were observed at the 0 sec delay indicating the absence of any drug effect on performance per se. No differences between saline and the 0.33 mg/kg dose of

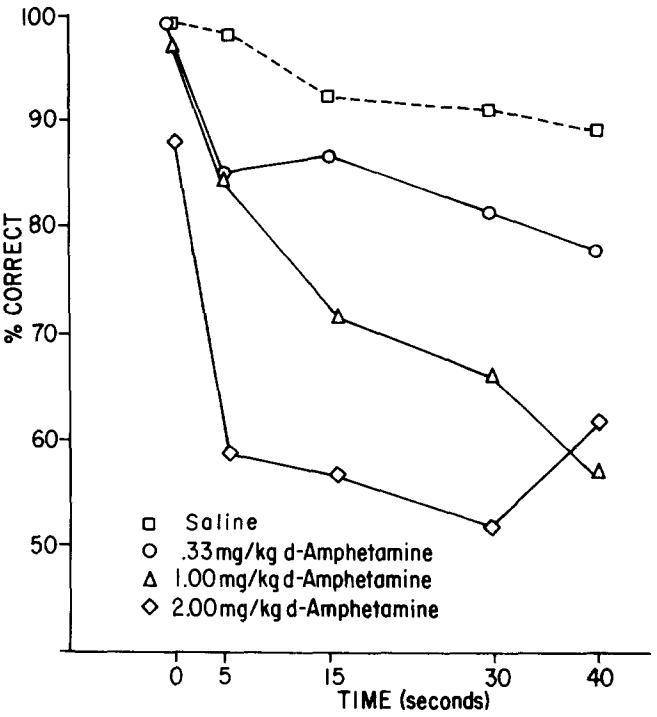

FIG. 1. Effects of 0.33, 1.0 or 2.0 mg/kg of d-amphetamine upon percentage correct performance in the discrete-trial delayed alternation task as a function of time of retention test delay. (Fifty percent correct responding reflects chance performance.)

d-amphetamine were observed at any delay, but a significant reduction in performance, relative to the saline condition, was observed at the 1.0 and 2.0 mg/kg doses. As can be seen by examining Fig. 1, these reductions in performance occurred at progressively earlier delays at higher doses.

The data were subjected to an analysis of variance for two repeated measures (4 drug levels × 5 delays) [12]. Analyses for differences in baseline performance (saline injections) for each of the three drug levels failed to reach significance, $F(2,4)=3.28$, $p>0.10$, so that these data were combined in the main analysis. Differences between drug levels at each of the five delays were tested using a Newman-Keuls analysis.

Results of the main analysis indicated significant effects due to drug level, $F(3,6)=28.86$, $p<0.001$, and delay, $F(4,8)=57.10$, $p<0.001$. The drug level × delay interaction was marginally significant, $F(12,24)=1.99$, $p=0.073$. Newman-Keuls analysis indicated (a) no differences between any drug dose at the 0 sec delay, (b) significant differences between saline and the 1.0 mg/kg dose at the 30 and 40 sec delays (both $p<0.05$) and (c) significant differences between saline and the 2.0 mg/kg dose at all delays 5 sec and longer (all $p<0.05$).

EXPERIMENT 2

Often the time course for decay of active traces within STM has been assumed to be in the order of minutes rather than seconds. Thus, a different task was selected in which retention can be measured at longer delays (30 min).

METHOD

Subjects

Five male Long-Evans rats (weight 325–400 g) served as subjects. Animals were maintained at 80% of their ad lib body weight but allowed continuous access to water.

Apparatus

The apparatus consisted of an eight arm maze similar to that described by Olton and Samuelson [17]. The central platform was 27 cm in diameter. Eight arms radiated from the center platform at equidistant points. Each arm was 10 cm wide and 86 cm long. The entire apparatus was constructed of wood painted white and was elevated 47 cm above the floor. The testing room was well lighted with fluorescent lights and with many pictures on the surrounding walls.

Procedure

Animals were initially trained using the standard eight arm procedure with all arms reinforced. Reinforcement consisted of small pieces of Froot Loops cereal. Once the animals were familiar with the apparatus and rapidly retrieved the food from each of the reinforced arms they were switched to a spatial matching-to-sample task. A single arm was randomly chosen for reinforcement each day and the animal was allowed to explore the maze until that arm was chosen. The animal was then momentarily restrained on the center platform inside a translucent cover while the correct arm was rebaited. The restraining cover was immediately removed and the animal was allowed to remain on the maze until the correct arm was traversed and the Froot Loops reinforcement was consumed. The animal was allowed 10 sec on the reinforced arm before being returned to the home cage and fed the daily maintenance ration of standard laboratory chow. The number of incorrect arms entered was used as measure of retention.

Once the task was learned with few errors, progressively longer retention intervals were imposed on the animal. At this stage of training, and throughout the testing, animals were allowed 10 sec exposure on the baited arm and then were removed from the end of the arm and returned to a holding cage during the retention period (out of sight of the maze). Errors were determined as in previous training by requiring all four legs to cross an imaginary line between center platform and the chosen arm before scoring the response as incorrect [17]. Care was taken never to place the animal on the center platform from the same location or with the same orientation. Final performance for data collection consisted of delays of 1 and 30 min.

Animals then received either one of two doses of amphetamine (2.0 or 3.0 mg/kg) or saline injected IP 30 min prior to testing. Higher doses of amphetamine were used because pilot data had indicated that 1.0 mg/kg amphetamine had no effect on retention measured at 1 or 30 min delays. Each animal received four sessions for each drug condition for each retention delay. The order of amphetamine and saline injections was counterbalanced across animals with the stipulation that each drug dose was used for a total of four sessions.

RESULTS

The effects of 2.0 or 3.0 mg/kg amphetamine or saline upon total number of errors as a function of retention test delay are shown in Fig. 2.

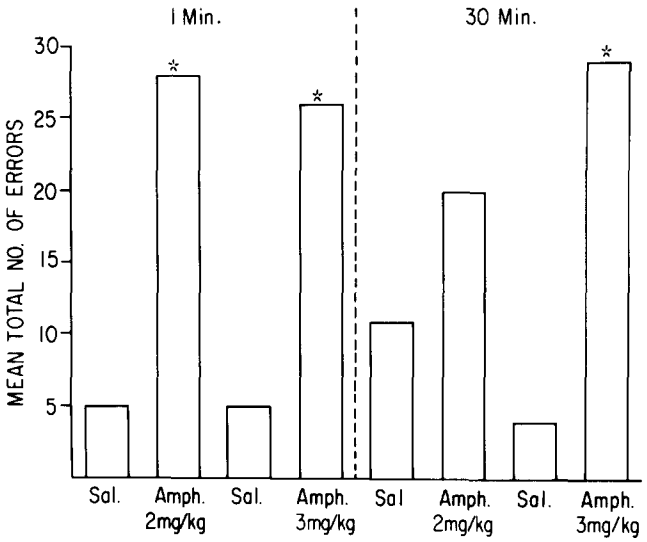

FIG. 2. Effects of 2 or 3 mg/kg of d-amphetamine upon mean total number of errors in the spatial delayed matching-to-sample task as a function of time of retention test delay. *Amphetamine is significantly different from saline $p<0.05$ using Newman-Keuls tests.

As can be seen both 2 and 3 mg/kg of amphetamine had a disruptive effect at the 1 min retention test, but only the higher dose resulted in a disruptive effect at 30 min.

A one-way analysis of variance on all eight conditions revealed that there was a significant treatment effect, $F(7,28)=5.43$, $p<0.05$. Further analyses using Newman-Keuls indicated that 2 mg/kg amphetamine injections resulted in significantly more errors than saline injections at both 1 and 30 min delays ($p<0.05$). At a dose of 3 mg/kg amphetamine injections resulted in significantly more errors than saline injections at only the 30 min delay ($p<0.05$). No other comparisons were significant.

GENERAL DISCUSSION

The results of both experiments indicate that amphetamine produces a disruption of delayed alternation and spatial delayed-matching-to-sample performance.

In both the delayed alternation task and delayed matching-to-sample task it appears that a 2 mg/kg dose of amphetamine had a large disruptive effect at all retention delays (5–30 sec, 1–30 min, respectively), whereas 1 mg/kg dose of d-amphetamine either had no effect or a disruptive effect only at long delays. At the 3 mg/kg d-amphetamine dose there appeared to be a disruption only at a 30 min but not a 1 min delay. However, this apparent lack of effect at 1 min might have been due primarily to an unexplained increase in errors in the control group. Amphetamine injections still resulted in a large number of errors at the 1 min delay.

These data are consistent with the findings of Bauer and Fuster [1] and Glick and Jarvick [7], who demonstrated that

d-amphetamine injections in monkeys disrupted performance in a delayed-matching-to-sample task.

Thus, given that performance in these tasks is a reflection of the efficiency of STM, the data suggest that d-amphetamine disrupts STM, perhaps via an arousal mediated enhancement in the rate of inactivation of neural traces representing STM. Alternative explanations implicating changes in motor activity can be ruled out, because in the delayed alternation task amphetamine had no deleterious effect on performance at zero sec delay, (i.e., discrimination performance). Consistent with the suggestion that enhanced arousal might lead to the disruption of STM are the findings in both humans and rats that manipulations that enhance arousal disrupt memory, while manipulations that reduce arousal facilitate memory at short retention delays [4, 14, 18, 26, 27]. Furthermore, amphetamine disrupts FI and DRL performance and interferes with the development of short-term habituation (tasks that also involve the operation of a STM system) [3, 5, 9, 21, 22, 23].

The observation in the present study that amphetamine disrupts performance on tasks using retention delays that presumably involve the operation of STM in conjunction with findings that comparable doses of amphetamine facilitate performance on tasks using retention delays that presumably require the operation of LTM [13,15] support the independence model [13]. Furthermore, if one assumes that d-amphetamine enhances arousal, the data are consistent with the effects of manipulations that presumably enhance arousal on short- and long-term memory in humans [4, 14, 27].

In summary, low doses of amphetamine disrupt performance in a discrete delayed alternation and a delayed spatial-matching-to-sample task, suggesting that amphetamine might alter processes (e.g., arousal) associated with efficient operation of short-term memory. The data support the independence rather than the sequential STM-LTM model.

REFERENCES

1. Bauer, R. H. and J. M. Fuster. Effects of d-amphetamine and prefrontal cortical cooling on delayed matching-to-sample behavior. *Pharmac. Biochem. Behav.* **8:** 243–249, 1978.
2. Bierley, R. A. and R. P. Kesner. Short-term memory: The role of the midbrain reticular formation. *J. comp. physiol. Psychol.* **94:** 519–529, 1980.
3. Branch, M. N. and L. R. Gollub. A detailed analysis of the effects of d-amphetamine on behavior under fixed interval schedules. *J. exp. Analysis Behav.* **21:** 519–539, 1974.
4. Eysenck, M. W. Arousal, learning and memory. *Psychol. Bull.* **83:** 389–404, 1976.
5. File, S. E. Effects of parachlorophenylalanine and amphetamine on habituation of exploration. *Pharmac. Biochem. Behav.* **6:** 151–156, 1977.
6. Fletcher, H. J. The delayed response problem. In: *Behavior of Nonhuman Primates*, edited by A. M. Schrier, H. F. Harlow and F. Stollnitz. New York: Academic Press, 1965.
7. Glick, S. D. and M. E. Jarvick. Impairment by d-amphetamine of delayed matching performance in monkeys. *J. Pharmac. exp. Ther.* **169:** 1–6, 1969.
8. Heise, G. A. Discrete trial analysis of drug action. *Fedn Proc.* **34:** 1898–1903, 1975.
9. Heise, G. A. and N. L. Lilie. Effects of scopolamine, atropine, and d-amphetamine on internal and external control of responding on non-reinforced trials. *Psychopharmacology* **18:** 38–49, 1970.
10. Honig, W. K. Studies of working memory in the pigeon. In: *Cognitive Processes in Animal Behavior*, edited by S. H. Hulse, H. Fowler and W. K. Honig. Hillsdale, NJ: Lawrence Erlbaum Assoc., 1978.
11. Jarrard, L. E. and S. L. Moise. Short-term memory in the monkey. In: *Cognitive Processes of Nonhuman Primates*, edited by L. E. Jarrard. New York: Academic Press, 1971.
12. Keppel, G. *Design and Analysis: A Researcher's Handbook*. Englewood Cliffs, NJ: Prentice-Hall, 1973.
13. Kesner, R. P. A neural system analysis of memory storage and retrieval. *Psychol. Bull.* **80:** 177–203, 1973.
14. Kleinsmith, L. J. and S. Kaplan. Paired-associate learning as a function of arousal and interpolated interval. *J. exp. Psychol.* **65:** 190–193, 1963.
15. Krivanek, J. A. and J. L. McGaugh. Facilitating effects of pre and post-trial amphetamine administration on discrimination learning in mice. *Agents Actions* **1:** 36–42, 1969.
16. McGaugh, J. L. and R. G. Dawson. Modification of memory storage processes. In: *Animal Memory*, edited by W. K. Honig and P. H. R. James. New York: Academic Press, 1971.
17. Olton, D. S. and R. J. Samuelson. Remembrance of places passed: Spatial memory in rats. *J. exp. Psychol: Animal Behav.* **2:** 97–116, 1976.
18. Randt, C. T., D. Quartermain, M. Goldstein and B. Anagnoste. Norepinephrine biosynthesis inhibition: Effects on memory in mice. *Science* **172:** 498–499, 1971.
19. Roberts, W. A. Spatial separation and visual differentiation of cues as factors influencing short-term memory in the rat. *J. comp. physiol. Psychol.* **78:** 284–291, 1972.
20. Rosvold, H. E. and J. M. R. Delgado. The effect on delayed alternation test performance of stimulation or destroying electrically structures within the frontal lobes of the monkey's brain. *J. comp. physiol. Psychol.* **47:** 173–178, 1954.
21. Sanger, D. J. Effects of d-amphetamine on temporal and spatial discrimination in rats. *Psychopharmacology* **58:** 185–188, 1978.
22. Sanger, D. J. and D. E. Blackman. Rate-dependent effects of drugs: A review of the literature. *Pharmac. Biochem. Behav.* **4:** 73–83, 1976.
23. Sanger, D. J., M. Key and D. E. Blackman. Differential effects of chlordiazepoxide and d-amphetamine on responding maintained by a DRL schedule of reinforcement. *Psychopharmacology* **38:** 159–171, 1974.
24. Stamm, J. S. Electrical stimulation of frontal cortex in monkeys during learning of an alternation task. *J. Neurophysiol.* **24:** 414–426, 1961.
25. Stamm, J. S. Retardation and facilitation in learning by stimulation of frontal cortex of monkeys. In: *The Frontal Granular Cortex and Behavior*, edited by T. M. Warren and K. Akert. New York: McGraw-Hill, 1964.
26. Terry, W. S. and S. G. Anthony. Arousal and short-term memory: Effects of caffeine and trial spacing on delayed-alternation performance. *Anim. Learn. Behav.* **8:** 368–374, 1980.
27. Uehling, B. S. Arousal in verbal learning. In: *Human Memory: Festschrift for Benton J. Underwood*, edited by C. P. Duncan, L. Sechrest and A. W. Melton. New York: Appleton-Century-Crofts, 1972.
28. Wagner, A. R., J. W. Rudy and J. W. Whitlow. Rehearsal in animal conditioning. *J. exp. Psychol.* **97:** 407–426, 1973.