Pharmacology Biochemistry & Behavior, Vol. 24, pp. 1539–1542, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Amphetamine and the Overtraining Reversal Effect

I. WEINER, E. BEN HORIN AND J. FELDON

Department of Psychology, Tel-Aviv University, Ramat-Aviv, Tel-Aviv, Israel

Received 17 December 1985

WEINER, I., E. BEN HORIN AND J. FELDON. *Amphetamine and the overtraining reversal effect.* PHARMACOL BIOCHEM BEHAV **24**(6) 1539–1542, 1986.—Rats were trained in a Y-maze on a two choice simultaneous brightness discrimination with light as S+ and dark as S− (position irrelevant). Animals in the Mastery group were trained until they reached criterion and were then switched to reversal, where the reinforcement contingencies of the original training were reversed. Animals in the Overtraining group received a further 110 trials before being switched to reversal. The administration of 1 mg/kg d-amphetamine facilitated dramatically reversal learning in Mastery group. Overtraining improved reversal in saline injected animals and slowed down reversal in amphetamine-treated animals. The drug also facilitated the acquisition of the initial brightness discrimination.

d-Amphetamine Simultaneous brightness discrimination Reversal learning Overtraining reversal effect Rat

IN a recent experiment [36], we found that the administration of 1 mg/kg d-amphetamine dramatically facilitated reversal learning of a Y-maze simultaneous brightness discrimination. This finding is of interest for several reasons. First, it is one of the few reported improvements in discrimination produced by d-amphetamine in animals [2, 3, 11], as opposed to the typically obtained disruption of discrimination performance (e.g., [1, 4, 7, 9, 10, 19, 21, 22]). Second, although the facilitation of reversal is in line with reports by Calhoun and Jones [2] and Kulig and Calhoun [11], it is inconsistent with findings of Ridley *et al.* [27,28], who obtained a disruption of reversal learning under amphetamine in monkeys. Third, the effects of amphetamine on reversal learning may provide important clues as to the "cognitive" actions of the drug. Thus, the course of reversal learning provides a measure of changes in the associative strength of S+ and S− as well as changes in attention to the discriminative stimuli [15, 16, 35]. The elucidation of the effects of amphetamine on attentional learning is of particular interest in view of (a) the proposition that amphetamine treatment in animals may provide an analogue to schizophrenia [8, 30, 31] and (b) the suggestion that attentional dysfunction is one of the central characteristics of schizophrenia [17].

The purpose of the present experiment was twofold: first, to replicate our previous result of reversal facilitation by amphetamine and second, to compare the facilitatory effect of amphetamine to the overtraining reversal effect (ORE). The ORE refers to the finding that overtrained animals learn reversal more rapidly than animals trained to a criterion [6, 15, 16, 24, 26, 33], although the effect is not readily obtained under all conditions. This phenomenon has provided important information regarding the processes occurring in discrimination learning and reversal, and we felt that the comparison between the ORE and the effects of amphetamine may enhance our understanding of the drug action on reversal. Amphetamine or saline treated rats were trained on simultaneous brightness discrimination until they reached a criterion (Mastery condition) or received additional 110 trials (Overtraining condition) before being switched to reversal.

METHOD

Subjects

Twenty-five male Wistar rats (Tel-Aviv University Medical School, Israel) approximately 3 months old were used. They were housed one to a cage under a reverse cycle lighting and given water for 30 min a day, about 15 min after the daily session.

Apparatus

The rats were tested in a Y-maze made of opaque Plexiglas. The floor consisted of metal grid composed of equally spaced rods. The walls were 17.5 cm high. The startbox was 27 cm long and 10 cm wide, and had a manually operated black guillotine door. The choice section was pentagonal with 10 cm long sides. The two goal arms were 14 cm long and 10 cm wide, and were set at an angle of 90 degrees to one another. They had manually operated perspex side-opening doors that separated them from the rest of the maze. The startbox and choice section had clear perspex lids, and the goal arms had white, opaque perspex lids. Each goal arm contained an automated Campden Instruments dipper mechanism, attached outside the rear wall of each goalbox, which delivered 0.15 ml water to the box. A 24 V electric bulb, located above each dipper 12.5 cm from the floor, provided the light serving as S+ or S−.

Procedure

All animals were handled for a week and given 5 days of

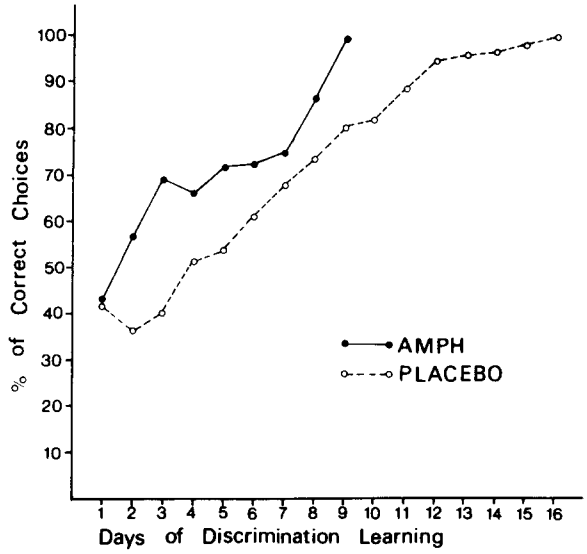

FIG. 1. Mean of percent correct choices during the initial brightness discrimination (training to criterion) in the Placebo and Amphetamine groups.

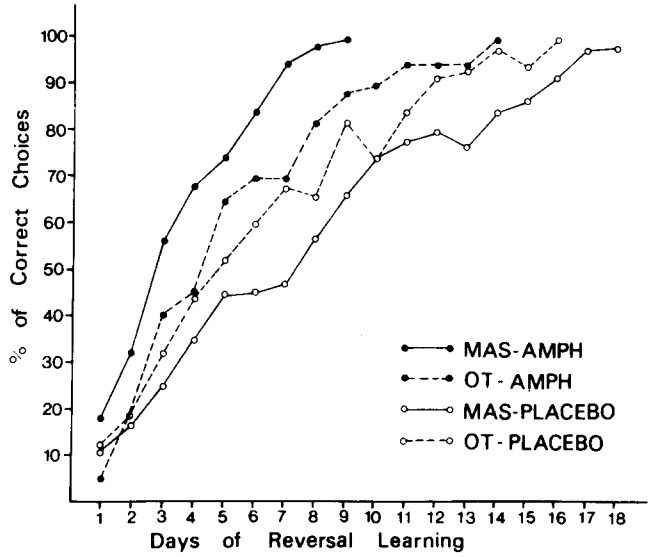

FIG. 2. Mean of percent correct choices during reversal training in the Mastery-Amphetamine, Overtraining-Amphetamine, Mastery-Placebo and Overtraining-Placebo groups.

pretraining. On each day, each animal was placed in the Y-maze for 10–15 min. All Y-maze doors were open and water was available in both arms of the maze. The experimenter ensured that the animal drank the water before being removed from the maze. Following pretraining, animals acquired a simultaneous dark-light discimination, with light as the S+. They were run for 10 trials a day. Upon the termination of each trial, the animal was immediately taken out of the goal arm and replaced into the startbox. On each daily session, S+ was in the right arm of the maze on 5 trials and in the left arm on the other 5 trials. The placement of S+ and S− was randomly determined with the provision that they did not remain in the same arm of the maze for more than 2 consecutive trials. The criterion of learning was at least 17 correct responses in 20 consecutive trials on two consecutive daily sessions. Two response measures were taken: percent correct choices and mean days to criterion. The Mastery group was trained to a criterion and immediately switched to reversal on the next session. The Overtraining group received an additional 110 trials (11 days) and was then switched to reversal. In reversal training, animals were trained on the same discrimination with the former S− (dark side) now S+. The criterion of learning was the same as in the initial discrimination.

The animals were randomly assigned to one of four groups in a 2×2 factorial design consisting of type of training (Mastery or Overtraining) and drug (amphetamine or saline). In the Mastery-Placebo condition there were 10 animals, 5 of which were used later in a different experiment. In all other groups, n=5.

Drug Injections

The appropriate drug, either 1 mg/kg d-amphetamine sulfate dissolved in 1 ml of saline, or an equivalent volume of saline, was administered IP 10 min prior to the daily session throughout the experiment.

The data were analyzed using 2×2 ANOVAs and where appropriate, a repeated measurements factor of days was included. One animal from Amphetamine-Overtraining group was dropped from the experiment because of apparatus failure. Thus, the final analysis was performed on 24 animals.

RESULTS

Initial Discrimination

Figure 1 presents the mean of percent correct choices in the initial brightness discrimination for the Placebo and Amphetamine groups. As can be seen, amphetamine-treated animals reached criterion faster than saline controls. This was supported by a significant main effect of drug, $F(1,22)=10.67$, $p<0.005$, as well as by the significant interaction of drug × days, $F(17,374)=2.71$, $p<0.01$. A similar result was obtained in the analysis of mean days to criterion: Amphetamine injected animals (mean number of days=7.6, SD=1.9) required significantly, $F(1,22)=6.43$, $p<0.02$, fewer days to reach criterion than Placebo animals (mean number of days=10.2, SD=2.7).

Reversal

Figure 2 presents the mean of percent correct choices in reversal for the Placebo-Mastery, Placebo-Overtraining, Amphetamine-Mastery and Amphetamine-Overtraining groups. An ANOVA with main factors of drug (placebo, amphetamine) and type of training (mastery, overtraining) and a repeated measurements factor of days yielded a significant main effect of drug, $F(1,20)=7.35$, $p<0.02$, as well as a significant interaction of drug × days, $F(17,340)=2.18$, $p<0.05$. As can be seen in Fig. 2, these outcomes reflected improved reversal performance of the amphetamine groups. In addition, the interaction of drug × type of training approached significance, $F(1,20)=3.00$, $p<0.10$, and the linear component of the drug × type of training × days interaction was significant, $F(1,370)=3.87$, $p<0.05$. As can be seen in Fig. 2, these outcomes reflect the fact that whereas in placebo injected animals, overtraining improved reversal, the opposite pattern was evident in amphetamine injected

animals, i.e., overtrained animals were slower than animals trained to criterion. The same results were obtained in the analysis of mean number of days to criterion. The main effect of drug was significant, $F(1,20)=10.57$, $p<0.05$, and the interaction of drug × type of training approached significance, $F(1,20)=3.38$, $p<0.09$. The mean days to criterion in Reversal were: Placebo-Mastery—14.2, SD=3.7; Placebo-Overtraining—11.00, SD=3.3; Amphetamine-Mastery—7.0, SD=2.0; Amphetamine-Overtraining—9.0, SD=3.3.

DISCUSSION

In line with other reports (e.g., [6, 14, 24, 26, 33]) overtraining improved reversal in placebo animals. In comparison to overtraining, amphetamine produced a far more dramatic facilitation of reversal.

As can be seen in Fig. 2, Mastery-Amphetamine animals shifted their choices to the new S+ very rapidly and indeed, reached 100% correct performance in 9 days, whereas other groups took 14–18 days. Such a rapid shift to the new S+ indicates that amphetamine does not affect the associative values of S+ and S−, since the latter would lead to greater persistence in selecting the former S+ at the outset of reversal. In contrast, the drug dramatically enhances the attention to, or the associability of, these stimuli, i.e., their rate of conditioning under changed contingencies of reinforcement [15, 16, 35]. It should be noted that the rapid switch to the new S+ occurred in spite of the fact that amphetamine enhanced original discrimination, which would be expected to lead to a greater persistence in choosing the former S+ at the outset of reversal. This suggests that already in the original discrimination, improved performance under amphetamine is due to increased associability of the discriminative stimuli rather than to increments in their associative strength, and strengthens the conclusion that amphetamine-produced facilitation of reversal results from enhanced associability. The present pattern of results is incompatible with the proposition that amphetamine enhances the reinforcing impact of reward [34] or stimuli associated with reward [5], and selectively stimulates dominant responses [13]. All of these actions would be expected to enhance the associative strength of S+ and lead to increased persistence in responding to S+ in reversal. However, if the drug enhances in general the reinforcing effect of feedback stimuli from the environment so that there is increased discrimination between different degrees of reinforcing feedback [29], it would indeed be expected to increase the associability of the discriminative stimuli.

The facilitatory effect of amphetamine on reversal was attenuated by overtraining. At first sight, this finding is surprising, since overtraining is assumed to facilitate reversal by enhancing the associability of the relevant stimuli and this effect would be expected to combine with the enhancing effect of amphetamine, yielding a further improvement in reversal. However, the ineffectiveness of overtraining in amphetamine treated animals is in line with the proposition that amphetamine enhances the associability of the relevant stimuli during training to criterion. Overtraining increases the associability of the discriminative stimuli if associability is low at the start of overtraining but is without an effect when associability is already high [16,35]. Since amphetamine-treated animals enter the stage of overtraining when the associability of the discriminative stimuli is high (it will be recalled that if switched to reversal at this point, these animals reverse extremely rapidly), overtraining does not lead to further increments in associability. However, a question arises as to why in amphetamine treated animals overtraining was not merely ineffective, in which case Overtraining-Amphetamine group would perform like Mastery-Amphetamine group, but actually *decreased* associability, leading to poorer performance of Overtraining-Amphetamine as compared to Mastery-Amphetamine group. We suggest that this decremental effect stems from the fact that overtraining reduces control by S−, since at this stage, animals no longer make contact with S− [15]. The repeated exposure to S+ alone leads to the extinction of increased associability of S−, retarding the subsequent rate of conditioning to S− when conditions of reinforcement are changed.

In summary, the present experiment replicated our previous finding [36] that amphetamine administration leads to facilitated reversal learning as a consequence of a rapid shift to the new S+. This facilitation, however, is obtained only in animals trained to a criterion, whereas additional training attenuates the effect. These results indicate that amphetamine enhances the associability of, or the attention to, the discriminative stimuli. This may have important implications for the animal amphetamine model of schizophrenia [8, 30, 31]. Overly active attentional mechanism has been repeatedly referred to in the human schizophrenia literature as the central characteristic of the disorder (e.g., [12, 18, 20, 23, 25, 32]). Amphetamine-induced enhancement of attention to discriminative stimuli may provide an animal analogue to this feature of the clinical syndrome.

ACKNOWLEDGEMENTS

This study was supported by grants from the Israel Academy of Science—Basic Research Fund and from the Tel-Aviv University Basic Research Fund to I. Weiner.

REFERENCES

1. Ahlenius, S., A. Carlsson and J. Engel. Antagonism by baclophen of the d-amphetamine-induced disruption of successive discrimination in the rat. *J Neural Transm* **36**: 327–333, 1975.
2. Calhoun, W. H. and E. A. Jones. Methamphetamine's effect on repeated acquisition with serial discrimination reversals. *Psychopharmacologia* **39**: 303–308, 1974.
3. Evenden, J. L. and T. W. Robbins. The effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on food reinforced tracking of a visual stimulus by rats. *Psychopharmacology (Berlin)* **85**: 361–366, 1985.
4. 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. *Psychopharmacologia* **18**: 38–49, 1970.
5. Hill, R. T. Facilitation of conditioned reinforcement as a mechanism of psychomotor stimulation. In: *Amphetamine and Related Compounds*, edited by E. Costa and S. Garattini. New York: Raven Press, 1970.
6. Hooper, R. Variables controlling the overlearning reversal effect (ORE). *J Exp Psychol* **73**: 612–619, 1967.

7. Koek, W. and J. L. Slangen. Effects of d-amphetamine and morphine on discrimination: signal detection analysis and assessment of response repetition in the performance deficits. *Psychopharmacology (Berlin)* **80:** 125–128, 1983.
8. Kokkinidis, L. and H. Anisman. Amphetamine models of paranoid schizophrenia: An overview and elaboration of animal experimentation. *Psychol Bull* **3:** 551–579, 1980.
9. Ksir, C. Scopolamine and amphetamine effects on discrimination: Interaction with stimulus control. *Psychopharmacologia* **43:** 37–41, 1975.
10. Ksir, C. and B. Slifer. Drug effects on discrimination performance at two levels of stimulus control. *Psychopharmacology (Berlin)* **76:** 286–290, 1982.
11. Kulig, B. M. and W. H. Calhoun. Enhancement of successive discrimination reversal learning by methamphetamine. *Psychopharmacologia* **27:** 233–240, 1972.
12. Lang, P. J. and A. H. Buss. Psychological deficit in schizophrenia. II. Interference and activation. *J Abnorm Psychol* **70:** 77–106, 1965.
13. Lyon, M. and T. W. Robbins. The action of central nervous system stimulant drugs: a general theory concerning amphetamine effects. In: *Current Developments in Psychopharmacology*, vol 2, edited by W. B. Essman and L. Valzelli. New York: Spectrum, 1975.
14. Mackintosh, N. J. Further analysis of the overtraining reversal effect. *J Comp Physiol Psychol Monogr* **67:** part 2, 1969.
15. Mackintosh, N. J. *The Psychology of Animal Learning*. London: Academic Press, 1974.
16. Mackintosh, N. J. *Conditioning and Associative Learning*. New York: Oxford University Press, 1983.
17. Matthysse, S., B. J. Spring and J. Sugarman (Eds). *Attention and Information Processing in Schizophrenia*. Oxford: Pergamon Press, 1979.
18. McGhie, A. Attention and perception in schizophrenia. In: *Contributions to the Psychopathology of Schizophrenia*, edited by B. A. Maher. New York: Academic Press, 1977.
19. Moerschbaecher, J. M. and D. M. Thompson. Effects of phencyclidine, pentobarbital and d-amphetamine on the acquisition and performance of conditional discriminations in monkeys. *Pharmacol Biochem Behav* **13:** 887–894, 1980.
20. Neale, J. M. and R. L. Cromwell. Attention in schizophrenia. In: *Contributions to the Psychopathology of Schizophrenia*, edited by B. A. Maher. New York: Academic Press, 1977.
21. Nielsen, E. B. Effects of d-amphetamine and LSD on simultaneous discrimination. In: *Quantification of Steady-State Operant Behavior*, edited by C. M. Bradshaw, E. Shabadi and C. F. Lowe. Amsterdam: Elsevier, 1981.
22. Nielsen, E. B. and J. B. Appel. The effects of drugs on the discrimination of color following a variable delay period: a signal detection analysis. *Psychopharmacology (Berlin)* **80:** 24–28, 1983.
23. Nuechterlein, K. H. Reaction time and attention in schizophrenia: a critical evaluation of the data and theories. *Schizophr Bull* **3:** 373–428, 1977.
24. Paul, C. Effects of overlearning upon single habit reversal in rats. *Psychol Bull* **63:** 65–72, 1965.
25. Payne, R. W. The measurement and significance of overinclusive thinking and retardation in schizophrenic patients. In: *Psychopathology of Schizophrenia*, edited by P. Hoch and G. Zubin. New York: Grune and Stratton, 1966.
26. Reid, L. S. The development of noncontinuity behavior through continuity learning. *J Exp Psychol* **46:** 107–112, 1953.
27. Ridley, R. M., H. F. Baker and T. A. J. Haystead. Perseverative behavior after amphetamine: dissociation of response tendency from reward association. *Psychopharmacology (Berlin)* **75:** 283–286, 1981.
28. Ridley, R. M., T. A. J. Haystead and H. F. Baker. An analysis of visual object reversal learning in the marmoset after amphetamine and haloperidol. *Pharmacol Biochem Behav* **14:** 345–351, 1981.
29. Robbins, T. W. and B. J. Sahakian. Behavioral effects of psychomotor stimulant drugs: clinical and neuropsychological implications. In: *Stimulants: Neurochemical, Behavioral and Clinical Perspectives*, edited by I. Creese. New York: Raven Press, 1983.
30. Segal, D. S. and D. W. Janowsky. Psychostimulant-induced behavioral effects: Possible models of schizophrenia. In: *Psychopharmacology: A Generation of Progress*, edited by A. Lipton and A. Killam. New York: Raven Press, 1978.
31. Segal, D. S. and M. A Schuckit. Animal models of stimulant-induced psychosis. In: *Stimulants: Neurochemical, Behavioral and Clinical Perspectives*, edited by I. Creese. New York: Raven Press, 1983.
32. Shakow, D. Segmental set: A theory of the formal psychological deficit in schizophrenia. *Arch Gen Psychiatry* **6**: 17–33, 1962.
33. Siegel, S. Overtraining and transfer processes. *J Comp Phsyiol Psychol* **64:** 471–477, 1967.
34. Stein, L. Self-stimulation of the brain and the central stimulant action of amphetamine. *Fed Proc* **23:** 836–850, 1964.
35. Sutherland, N. S. and N. J. Mackintosh. *Mechanisms of Animal Discrimination Learning*. New York: Academic Press, 1971.
36. Weiner, I. and J. Feldon. Reversal and nonreversal shifts under amphetamine. *Psychopharmacology (Berlin)*, in press.