Psychopharmacologia 6, 475—479 (1964)

Short Communications · Kurze Originalmitteilungen Communications brèves

Responsibility for the contents of "Short Communications" devolves exclusively on the authors themselves. — Für den Inhalt von „Kurze Originalmitteilungen" sind die Autoren stets selbst verantwortlich. — Seuls les auteurs sont responsables des informations et opinions contenues dans la rubrique: «Communications brèves».

From the Veterans Administration Hospital, Coatesville, Pennsylvania

Drug-induced Decrement in Spatial Reversal Learning in the White Rat

By

CHESTER R. WILPIZESKI* and CHARLES L. HAMILTON

With 2 Figures in the Text

(Received March 30, 1964)

Much evidence indicates psychotomimetic drugs administered in comparatively small amounts have a deleterious effect upon performance (KETY 1957). Typically, an animal is trained under drug-free conditions and later tested on the same task while medicated. Little, however, is known concerning the action of these drugs on the learning process itself. Quite likely the paucity of data in this area is a consequence of motivational and temporal considerations. While food has proved to be a powerful reinforcer for establishing learned behavior, its use in drug studies is not always desirable because with certain drugs (amphetamine and LSD-25, for example) eating is markedly suppressed during the medicated state (HARRIS et al. 1947; WINTER and FLATAKER 1956; HAMILTON and WILPIZESKI 1961). Furthermore, the learning tasks frequently require days to master and quite often drug tolerance complicates the interpretation of acquisition rates. We discovered that a simple spatial reversal learning problem using a water-filled T-maze minimized these difficulties and afforded good experimental circumstances for studying the effects of LSD-25, amphetamine sulfate and chlorpromazine on learning.

Method

Animals. Sprague-Dawley male albino rats, approximately 100 days old at the time of training, were maintained on full food and water rations throughout the study. They were extensively handled by daily weighing for two weeks prior to the experiment.

Apparatus. A single-unit T-maze was constructed of galvanized metal with a stem 173 cm long, a cross arm of 76 cm and an alley width

* VA trainee in physiological psychology.

of 9 cm. The entire unit was filled to a depth of 23 cm with tap water maintained at a temperature of 20° to 25° C. A movable wire-mesh escape ladder, extending into the water, could be placed at either end of the cross arm. Illumination barely sufficient for observing the animals was provided by a 7.5 watt red lamp suspended over the base of the stem. The room was otherwise completely darkened. An electric fan located under the supporting table created a constant background noise.

Experiment I. Preliminary training was carried out by using the stem of the maze as a straightway with the escape ladder in the alley just short of the choice point. Each rat was given 10 practice swims in the straightway. The animal was oriented toward the choice point, then gently placed into the water at the base of the stem. Escape from water could be gained only by swimming down the alley and climbing up the wire mesh. Between swims each animal was placed in a sound-insulated box for 15 sec.

On the first experimental day 40 rats were required to learn which side of the cross arm led to immediate escape. In order to avoid reinforcing an inherent turn bias, the animal was deliberately forced to make an incorrect choice on his first trial. The ladder, which was placed on the side opposite his first turning response, was not lowered until after the choice had been made. Thereafter, the ladder remained on that side until the animal reached the criterion of 10 consecutive correct turns. A choice point response was considered a turn if the rat entered either side of the cross arm for a distance equal to one body length exclusive of tail. Earlier work in this laboratory (unpublished) verified that albino rats could not visually detect the ladder under the low illumination conditions of the experiment. An error correction procedure was used throughout the investigation with the restriction that the rat was prevented from retracing the stem by means of a transparent plastic door lowered at the choice point. Between acquisition trials the animal was detained in the sound-insulated box for 15 sec.

On the second experimental day 4 groups of 10 rats each were formed. All groups had approximately equal mean learning scores (number of errors to criterion) on the original learning task. The following drugs and doses were administered subcutaneously in the region of *m. semitendinosus*: LSD-25, 0.5 mg/kg body weight, injected 15 min before the first reversal trial; amphetamine sulfate, 2 mg/kg, 30 min before; chlorpromazine, 1 mg/kg, 60 min before. Each drug was added to Ringer's solution so that all animals received equal volumes of fluid in proportion to body weight. A control group was injected with Ringer's solution only, 15 min before the first reversal trial. While medicated, the rats were required to reverse their previously-acquired turning response and learn to escape from the opposite side of the cross arm.

On the third experimental day (under drug-free conditions), the animals learned to reverse the response previously acquired during the drugged state.

Experiment II. Pretraining and acquisition procedures were identical to those in Experiment I. On the second experimental day 3 groups of 6 rats each were subcutaneously injected with LSD-25 in doses of 0.13 mg/kg or 0.52 mg/kg or with Ringer's solution 15 min before reversal learning.

Results

Learning to escape from the nonpreferred side of a water-filled T-maze is an easy task for nondrugged rats. Considering the data from both experiments, 26 out of 58 rats (45%) learned the response after committing a single forced error. The mean number of errors in mastering

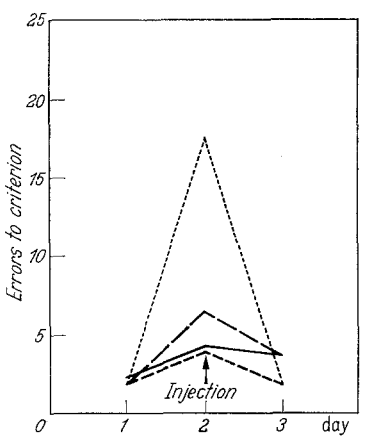

Fig. 1

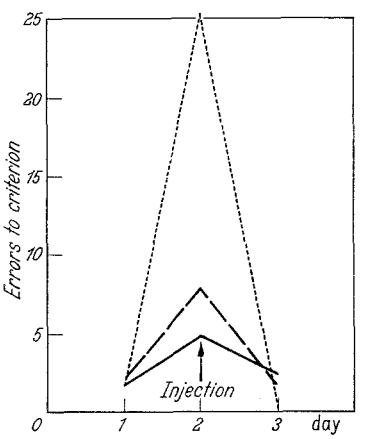

Fig. 2

Fig. 1. Mean number of errors to criterion for learning to escape from a water-filled T-maze. During the drugged state, albino rats were required to learn a turning response opposite the one acquired on preceding and succeeding days. All groups contain 10 rats each. ---- 0.50 mg/kg LSD-25; —— 2 mg/kg Amphetamine; —— Ringer's; – – – 1 mg/kg Chlorpromazine

Fig. 2. Mean number of errors to criterion for learning to escape from a water-filled T-maze. During the drugged state, albino rats were required to learn a turning response opposite the one acquired on preceding and succeeding days. All groups contain 6 rats each. ---- 0.52 mg/kg LSD-25; —— 0.13 mg/kg LSD-25; —— Ringer's

this task was 2.2. Learning to reverse the original turning response, however, was more difficult and depended somewhat upon the degree of medication.

Experiment I. Fig. 1 gives the results of the first experiment. It can be seen that injection of 0.5 mg/kg of LSD-25 seriously retards learning a spatially-reversed turning response. The differences in number of errors to criterion between LSD-amphetamine, LSD-chlorpromazine and LSD-Ringer's groups are statistically reliable at the 5% level of

confidence. All other pairwise comparisons, including those on pre- and post-injection days, fell short of significance. (Statistical reliability was evaluated by means of the Link-Wallace one-way analysis of variance, MOSTELLER and BUSH 1954.) On the day after treatment, all groups learned to reverse their turns with about equal facility.

Experiment II. The results of the second experiment are graphed in Fig. 2. On the day of injection, learning to reverse the initially-correct turn was impaired as a function of increased dose of LSD-25. While the 0.13 mg/kg group does not differ statistically from Ringer's in number of errors, the 0.52 mg/kg group is significantly retarded (5% level) in comparison to both the low dose and the control animals. On the post-injection day, however, the rats previously given 0.52 mg/kg LSD-25 committed significantly fewer errors than did those receiving Ringer's.

The data were analyzed also in terms of number of trials to criterion. Because the findings remain essentially the same, the subsidiary analysis is not included.

Discussion

It is clear that LSD-25 in doses greater than 0.13 mg/kg depresses the acquisition of a simple spatial reversal habit in a T-maze. The other drugs tested, amphetamine and chlorpromazine, did not produce any significant impairments in this response, although modifications in other types of behavior have been demonstrated at the dose levels used in this investigation (unpublished data from this laboratory). Inasmuch as the LSD-treated rats persisted in turning to the initially-correct side of the maze, they apparently had good retention of the original habit. The difficulty in learning the reverse turn seemed to be in inhibiting the previously-correct response. Furthermore, there is some suggestion that what was learned during the heavily-drugged state was not retained on the post-injection day. Pooling the data from both experiments, 9 out of 22 animals (41%) treated with LSD made no errors on the third day. In other words, there seemed to be little interference generated by the competing response acquired under drugged conditions.

Summary

This study investigated the effects of LSD-25, amphetamine sulfate and chlorpromazine on a simple spatial reversal learning problem in a water-filled maze. Following subcutaneous injections of 0.50 and 0.52 mg/kg of LSD-25, albino rats were significantly handicapped in acquiring a reversed turning response. The performance of groups given 0.13 mg/kg LSD-25, 1 mg/kg chlorpromazine and 2 mg/kg amphetamine sulfate was not reliably different from a Ringer's-injected control group.

The LSD-treated rats seemed to be hindered in learning the reversed response because of a failure to relinquish the previously-correct response. Competing responses learned while drugged did not interfere seriously with reversal learning on the day after drug administration.

References

HAMILTON, C. L., and C. WILPIZESKI: Effects of LSD-25 on food intake in the rat. Proc. Soc. exp. Biol. (N.Y.) **108**, 319—321 (1961).

HARRIS, S. C., A. C. IVY, and L. M. SEARLE: The mechanism of amphetamine induced loss of weight. J. Amer. med. Ass. **134**, 1468—1476 (1947).

KETY, S. S.: The pharmacology of psychotomimetic and psychotherapeutic drugs. Ann. N. Y. Acad. Sci. **66**, 417—480 (1957).

MOSTELLER, F., and R. R. BUSH: Selected quantitative techniques. In G. LINDZEY (Ed.): Handbook of social psychology. Cambridge, Mass.: Addison-Wesley 1954.

WINTER, C. A., and L. FLATAKER: Effects of lysergic acid diethylamide upon performance of trained rats. Proc. Soc. exp. Biol. (N. Y.) **92**, 285—289 (1956).

CHESTER R. WILPIZESKI, Research Associate,
Dept. of Otolaryngology, Jefferson Medical College Hospital,
Philadelphia, Pennsylvania, 19107, U.S.A.