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Effects of D-Lysergic Acid Diethylamide on Operant Behavior in the Rat*

By

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With 3 Figures in the Text

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The present experiment was designed, primarily, to determine the dose- and time-response relations for d-lysergic acid diethylamide (LSD-25). According to Russell (1960), there have been relatively few studies of dose- and time-response relations and yet there is an obvious and important need for such information. This is especially true for LSD-25 since there is currently so much research being done with the drug.

A second purpose was to compare the effects of different doses of the drug on behavior maintained by positive reinforcement with the effects on behavior maintained by negative reinforcement. Thus, subjects in one operant conditioning situation pressed a bar for food reward and in the other situation subjects pressed to avoid shock.

Method

Subjects and Apparatus

The subjects were 12 male albino rats of the Wistar strain, purchased from Research Animals, Inc., Pittsburgh, Pennsylvania. They were 90 to 100 days of age at the start of the experiment and averaged 172.6 gm. (SD = 12.7) in body weight.

The apparatus consisted of two Skinner-type boxes, each placed inside separate, relatively soundproof, ice chests. One box was wired so that electric shock could be delivered through a grid scrambler to the floor of the experimental chamber. Shocks of 1.6 ma. with a duration of 0.5 sec. were used. The second box was equipped for food reinforcement and delivered 45-mg. Noyes Co. pellets.

Programming of the testing sessions was controlled by timers and relay circuitry which automatically delivered the shock and food pellets.

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The D-lysergic acid diethylamide used in this study was supplied by Sandoz Pharmaceuticals, Hanover, N.J., through the courtesy of Sidney Gimpel.

The number of bar presses made in each box as well as the number of pellets and shocks received was recorded by both magnetic counters and cumulative recorders. This equipment was located in a room adjacent to the experimental room.

Procedure and Experimental Design

Seven days before preliminary training all subjects were placed in individual living cages and fed 10 gm. of food per day. This feeding regimen was continued for the duration of the experiment. Water was continuously available in the home cages.

The 12 subjects were evenly divided into two groups that were equated for body weight. One group was trained with a shock avoidance procedure that has been described elsewhere (SIDMAN 1953). Shocks were presented at 10 sec. intervals as long as no bar-pressing response was emitted. Each bar press reset the timer that controlled the shock and thus served to delay the shock for 10 sec. from the time of that response. The second group of 6 subjects was trained to press the bar for food pellets on an aperiodic reinforcement schedule (VI 2 min.). After preliminary training, each subject was tested at the same time every day for 2 hrs. Immediately after the session, subjects were fed the daily food ration in the home cages with amount for the food reinforcement subjects being adjusted according to the number of pellets received during the session. Training was continued for 21 days by which time relatively stable rates of responding were obtained. The level of stability was computed by employing a procedure similar to the one described by SHOENFELD et al. (1956). It was found that the difference between the 3-day submeans for each rat was less than 8 per cent of the six day's mean.

D-lysergic acid diethylamide was dissolved in distilled water and injected intraperitoneally. Two concentrations of the drug were used so that the volume of injection was always between 0.1 and 0.5 cc. regardless of the dose. It was found in an unpublished study carried out in this laboratory that volume differences within this range did not result in significant differences in bar pressing.

Each subject served as his own control and was injected with a control physiological saline solution, 0.05, 0.10, 0.20, 0.40, and 0.80 mg/kg of LSD-25. The principle of the latin square was used in assigning different treatments to the subjects so that each treatment appeared in each ordinal position. A similar experimental design was used for each of the conditioning situations. Immediately after injection, the subject was placed in a Skinner box for the 2-hr. session. Three control sessions with no injections were interspersed between each drug session.

Results

The basic data consisted of number of bar presses for each of the two experimental situations, number of pellets, and number of shocks. Data for the 2-hr. sessions were divided into 30-min. periods for purposes of analysis.

The effects of different amounts of LSD-25 on bar pressing for food are shown graphically in Fig. 1. On the ordinate is mean number of bar-pressing responses and on the abcissa is time in 30-min. periods. Analysis of variance of these data revealed that there were significant differences

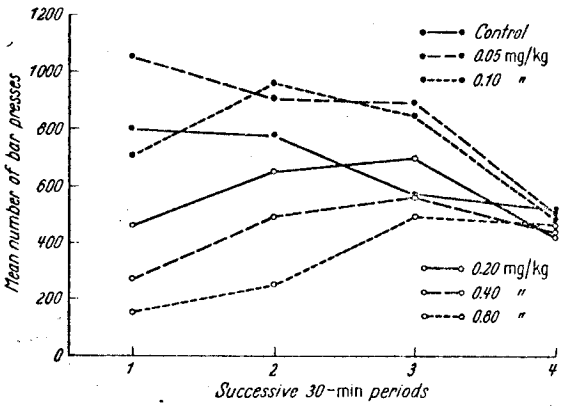

Fig. 1. Mean number of bar presses for food during successive 30-min. periods following injection

for the effects of the different drug dosages ($F = 7.48$; 5/40 df; $P < .01$), there were significant changes over time ($F = 4.11$; 3/30 df; $P < .05$), and subjects differed significantly ($F = 13.76$; 5/40 df; $P < .01$). Differences in means for the individual pairs of dosage scores were tested for significance at the .05 level by applying the t test. It was found that injections of 0.40 and 0.80 mg/kg resulted in significantly fewer responses over the 2 hrs. than any of the other treatments. Observation of the animals indicated that with 0.80 mg/kg, performance was severly impaired 3 to 5 min. after injection and the subjects would often not press the bar for as long as 20 to 30 min. Doses of 0.20 mg/kg were found to cause significantly fewer responses than 0.05 and 0.10 mg/kg.

The significant drugs by time interaction ($F = 10.75$; 15/75 df; $P < .01$) indicates differential effects for the various drug dosages over time. It is apparent from inspection of Fig. 1 that the greatest effect for the large doses (0.20, 0.40, and 0.80 mg/kg) was obtained during the first 30 min. of the session. There is a suggestion that, when compared to the results for the control injection, the greatest effect for 0.05 and 0.10 mg/kg was obtained during the third 30-min. period. Comparison of pairs of means

with the t test indicated that injections of 0.05 mg/kg resulted in a significantly greater number of responses during the first 30 min. than the control injection of normal saline. With increasing amounts of the drug the result during the first time period was fewer bar presses for food. By the last 30 min. of the session there were no significant differences between any of the treatment conditions.

Analysis of the data for number of food pellets received revealed results similar to those for number of bar presses, therefore, the analysis is not presented here.

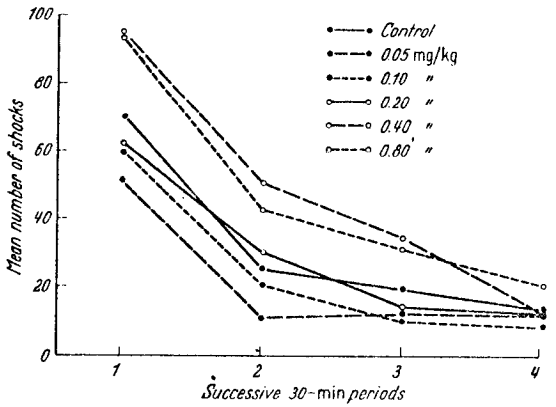

Fig. 2. Mean number of shocks received during successive 30-min. periods following injection

In Fig. 2 is presented the mean number of shocks received for the different treatment conditions during each 30-min. period of the avoidance session. An analysis of variance of these data was carried out after Bartlett's test indicated that the variances were homogeneous. The main effect of drug dose was significant ($F = 2.77$; 5/40 df; $P < .05$), there were significant changes over time ($F = 35.14$; 3/30 df; $P < .01$), and subjects differed significantly ($F = 8.55$; 5/40 df; $P < .01$). The difference between means required for significance for the over-all effects of the drugs revealed that with injections of 0.40 and 0.80 mg/kg, the subjects received significantly more shocks than when the injections were 0.05 and 0.10 mg/kg.

The trends within the 2-hr. session for the different drug dosages are interesting. For the data on number of shocks received, there was a significant interaction between dosage and time ($F = 1.82$; 15/75 df; $P < .05$). As can be seen in Fig. 2, amount of drug was especially important in affecting the number of shocks received during the first hour of the session. Comparison of the differences between pairs of means with the t test indicated that animals treated with 0.05 mg/kg received fewer

shocks during the first 30 min. than they did in the control condition. Injections of 0.40 and 0.80 mg/kg resulted in significantly more shocks being received during the first 30 min. following injection. The significant decrease in number of shocks received from the first to the second 30-min. period after the control injection is not usually found in animals that have been trained for extended periods of time. There were no significant differences between any of the conditions during the last 30 min. of the session.

An analysis of number of bar presses emitted by those subjects in the shock avoidance situation indicated only significant increases in number of bar presses over time. No significant effects due to the different drug dosages were found.

In order to determine whether a tolerance to the drug had developed over the period of testing, the means and standard deviations were computed for the six drug days. If a tolerance had developed, one would expect a systematic change over days in the direction of less variability. Inspection of the data and analysis of variance did not indicate that there were any significant changes over time. Thus, it appears from the behavioral data obtained in the present study with the rat that a tolerance did not develop when 96 hrs. elapsed between injections. These results agree with those found in a study by FREEDMAN et al. (1958) in which no apparent tolerance in the rat was encountered when injections of LSD-25 were given every 72 hrs.

Discussion

The results of this experiment indicate that LSD-25 affects both food- and avoidance-maintained behavior over a considerable range of doses. Small doses were found to increase the number of bar presses for food and decrease the number of shocks received in the avoidance situation; larger doses of the drug had just the opposite effects.

A facilitation of performance in food reinforcement situations has not been found by most investigators of LSD-25 (BLOUGH 1957; GLOW 1957; WINTER and FLATAKER 1956). In several cases this difference can probably be attributed to a failure to use doses as small as those employed in the present study. For example, BLOUGH found a decrease in rate of responding in an operant-type situation with 0.20 and 0.50 mg/kg. However, he did report an increase in accuracy of discrimination. According to BLOUGH, there was a suggestion that greater accuracy and less response depression was obtained with the smaller dose. It is possible that the experimental procedures employed by several other investigators limited the direction in which changes in performance could take place. Using performance in a straightway and doses comparable to those employed in the present study, GLOW found significant increases in both

latency and running time with injections of large doses; the average latency for a group receiving 0.06 mg/kg was shorter than that of the control group but the difference was not statistically significant. Since all subjects were well trained and the latencies were small before testing for drug effects, it is possible that a facilitating effect of the magnitude necessary for a statistically significant difference could not be obtained in this situation.

In the shock avoidance situation in the present study there were no differences in number of bar presses for the various drug doses but there

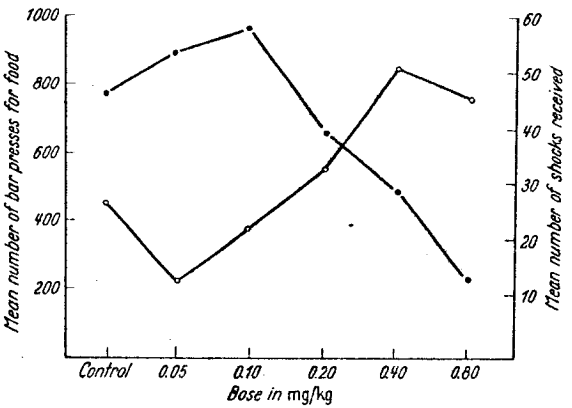

Fig. 3. Dose-response relations for LSD-25 and number of bar presses for food and number of shocks received during the second 30-min. period following injection; •—• food-maintained behavior; o—o avoidance-maintained behavior

were differences in number of shocks received. With injection of 0.05 mg/kg the subjects emitted the same number of bar presses during the first 30 min. as in the control condition but they did receive fewer shocks. A similar improvement in avoidance performance with very low doses of LSD-25 was found by TAESCHLER et al. (1960) in latency of jumping on a rod, and HAMILTON (1960) for running speed in a straightway. When the shock avoidance subjects in the present study received 0.40 and 0.80 mg/kg, there was no significant change in the number of bar presses emitted but more shocks were received over the first hour. These results agree very well with the impaired performance of a pole-climbing response found with large doses by COOK and WEIDLEY (1957). The present finding with the Sidman-type avoidance procedure that total number of bar presses was not affected while small doses resulted in fewer shocks being received and larger doses resulted in an increase in shocks should be confirmed with a study in which measurements of the time intervals between successive bar presses are obtained. This is especially true since human observers in a clinical study of LSD-25

reported that one effect of the drug was to distort the sense of time (ARONSON, SILVERSTEIN, and KLEE 1959).

The dose-response relations between LSD-25 and both food- and avoidance-maintained behavior can best be seen in Fig. 3. In this figure is presented the mean number of bar presses for food and the mean number of shocks received for the different drug doses during the second 30-min. period following injection. It is apparent from inspection of this figure that with the interval schedule the number of responses increase at low dose levels and decrease at high dose levels. With the shock-avoidance schedule the number of shocks received decrease at the low dose levels and increase at high dose levels. Such biphasic effects with different doses on both food- and avoidance-maintained behavior support an interpretation of central-stimulating and central-depressing effects of LSD-25 depending on the dose level.

In general, the data on time-response relations agrees with other investigators who have determined the duration of action of the drug (BLOUGH 1957; HAMILTON 1960). The effects of the drug were found to persist for approximately 1 hr. and 30 min. By the last 30 min. of the session there were no significant differences between any of the treatment conditions. No attempt was made to analyze the data to determine the time between administration of the drug and onset of the effects but inspection of the cumulative curves and observation of the subjects suggested that behavior was affected 5 to 7 min. after injection.

Summary

Twelve albino rats were used to determine the effects of LSD-25 on operant behavior. Half of the subjects were trained to press a bar for food on an aperiodic schedule and half were trained with a Sidman-type avoidance procedure to press a bar to avoid shock. A latin square design was employed in which each subject served as his own control and was injected intraperitoneally with a control saline solution, 0.05, 0.10, 0.20, 0.40, and 0.80 mg/kg. The following results were obtained:

1. In the food-reward situation injection with 0.05 mg/kg increased the number of bar presses emitted; doses of 0.20, 0.40, and 0.80 mg/kg decreased the number of responses.

2. In the shock-avoidance situation there was a decrease in the number of shocks received during the first 30 min. when the subjects were treated with 0.05 mg/kg but injections of 0.40 and 0.80 mg/kg resulted in more shocks during this time period. No significant differences in number of bar presses were found for any of the dosages.

3. The effects of the drug were found to persist for approximately 1 hr. and 30 min. following injection.

The present results support an interpretation of central-stimulating and central-depressing effects of LSD-25 depending on the dose level.

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