Psychopharmacologia (Berl.) 21, 174—186 (1971)

Effects of LSD on Time-Based Schedules of Reinforcement

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Received December 1, 1970
Final Version: March 10, 1971

Abstract. The functional relationship between rate of bar-pressing and a wide range of dosages of LSD was studied under different conditions or schedules of reinforcement, i.e., variable-interval (VI), differential reinforcement of low rate (drl), and drl plus concurrent periods of punishment. In general, low doses (0.01—0.04 mg/kg of LSD) increased or facilitated responding as an inverse function of base line response rate and high doses (0.08—0.32 mg/kg) depressed behavior not already depressed by environmental contingencies.

Key Words: Lysergic Acid Diethylamide (LSD) — Variable Interval (VI) — Timing Behavior — Punishment — Rats.

While there has been considerable interest in the effects of hallucinogenic drugs such as LSD on animal behavior in recent years (Appel, 1968), few attempts have been made to study dose-response relationships in relatively well-controlled behavioral situations. Furthermore, no one has yet evaluated the extent to which schedule and other reinforcement parameters can influence these relationships.

On ratio schedules, when very high response rates normally occur because rate of reinforcement depends on rate of response, the principal effect of LSD is to induce one or more periods of pausing or non-responding which, on fixed-ratio (FR), begin abruptly about 4—8 min following intra-peritoneal (I.P.) injection and which generally end, less abruptly, by the end of 32-min (Freedman *et al.*, 1964) or 1-h (Appel *et al.*, 1968) experimental sessions. The duration of the period of non-responding is directly related to dose (Freedman *et al.*, 1964; Appel and Freedman, 1965; Appel *et al.*, 1968) and to such variables as level of deprivation (Appel *et al.*, 1968) and history of prior drug administration (Appel and Freedman, 1964; Freedman *et al.*, 1964; Appel and Freedman, 1967; Appel, Lovell, and Freedman, 1970). The value of the ratio (n) does not, however, seem to affect the response to LSD, at least when $n = 5$, 15, 30 or 40 (Freedman *et al.*, 1964).

The main concern of this paper is with schedules in which reinforcement is presented on the basis of elapsed time and on rate of responding. Such

schedules are of interest because they do not generate maximal response rates and potential facilitatory, i.e., rate-increasing, effects of drugs like amphetamines can therefore be observed (Sidman, 1955, 1959).

All of the studies that have been reported of the effects of LSD on time-based schedules of positive reinforcement concern variable-interval (VI). On this schedule, reinforcement is contingent on the first response that occurs after some period of time, the average duration of which defines the VI.

It is clear that relatively high doses of LSD depress the average rate of VI responding (Jarrard, 1963; Freedman, *et al.*, 1964; Gardner, 1965). They do not, however, eliminate behavior as was the case on FR (Freedman *et al.*, 1964). The time of onset and the duration of effects appear to be comparable on VI 1.5 and FR 5, 15 and 40 at comparable doses (0.13 to 0.195 mg/kg of LSD) but both the nature of the effect (partial as opposed to complete suppression) and pattern of tolerance differ as a function of schedule of reinforcement (Freedman *et al.*, 1964). It is important to note, in view of the finding of Hamilton and Wilpizeski (1961) that LSD inhibits food intake, that rats continue to obtain and consume reinforcement on VI under the influence of the drug.

Unfortunately, the effects of low doses of LSD on VI, or on any schedule other than FR, are less clear. Jarrard (1963) reports that 0.05 mg/kg of LSD increases the rate of responding for dry food on a VI 2 schedule and, since doses of 0.2, 0.4 and 0.8 mg/kg of LSD decrease rate, that there is a biphasic dose-response relationship; Gardner (1965), who also studied a wide range of somewhat lower doses on VI 1 (0.015—0.500 mg/kg of LSD), found that only the depressing effects were significant.

In the present experiments we: (1) re-examined the effects of LSD on VI 1 (Experiment 1), (2) obtained dose-response relationships on a differential reinforcement of low rate (drl) schedule (Experiment 2), (3) evaluated the possibility that base line rate might be an important determinant of direction as well as extent of LSD effect by varying the drl value (Experiment 2) and (4) further explored this possibility by giving LSD to animals whose rate of drl responding was suppressed by punishment (Experiment 3).

Methods

Experiment 1

The relationship between rate of bar pressing on VI 1 and dose of LSD.

Subjects. Fourteen male albino rats of Sprague-Dawley strain were obtained from the Charles River Breeding Laboratories, Wilmington, Massachusetts. In this, and all other experiments, they were housed in individual cages in a room of constant temperature (75°F) and humidity

(40—50%) and maintained on a 12-h (7:00 A.M.-7:00 P.M.) day-night cycle. Each animal was approximately 90 days old and weighed between 250 and 300 g at the beginning of the experiment.

Apparatus. The first experiment was conducted in two experimental chambers which have been described in detail elsewhere (Freedman *et al.*, 1964). Each box contained a single lever or bar located in the center of one of its sides (about 5 cm above the floor); a force of 10—15 g activated the lever and defined a bar-pressing response. A dim, 28-v D.C. house light was mounted behind a white, translucent panel directly above the lever. White noise of moderate intensity entered the box from a 10.16 cm speaker mounted on the outside of the wall which contained both the lever and the light.

To the right and slightly below the lever, a dipper delivered 0.05 ml of a liquid diet of sweetened evaporated milk and vitamins into a feeding cup. Each box was housed in a wooden outer chest which provided sound and light attenuation. All experimental events were programmed by switching and timing circuits in an adjoining room. Responses were recorded on electromagnetic counters and cumulative recorders.

Behavioral Prodecure. Upon arrival in the laboratory, each rat was weighed, coded, and placed into its home cage. For a period of at least one week it was allowed continual access to both food and water. During the second week, each rat was weighed, handled and given about 20 g of dry Pruina Lab Chow each day; its weight thereby stabilized. All solid food was removed for a period of two days at the beginning of the third week; on the second of these deprivation days, each animal was given a small amount (less than 1 ml) of the liquid diet used as a reinforcer. Bar-pressing training was then begun.

After the rat was placed into the apparatus, the house light and the white noise were turned on. Next, the dipper was presented for 10 sec every 20 sec until the rat was observed to eat. This normally required less than 10 min. Once eating occurred as soon as the dipper was presented, the duration of the 10-sec reinforcement cycle was gradually shortened to 3 sec. The automatic recycling circuit was disconnected and a shaping procedure (Ferster and Skinner, 1957) was instituted to condition the bar-pressing response. Normally, conditioning required less than 20-min. The rat was then allowed to work for milk on a continuous reinforcement (CRF) schedule for the remainder of the first 1-h experimental session. After the session, each animal was weighed and given about 10 g of additional solid food in order to maintain its post-deprivation weight. If, however, an animal did not learn to press the bar on the first day, no additional food was given and shaping was continued for a second day.

On subsequent sessions, responses were reinforced intermittently, first on a VI 15 sec schedule then on a VI $^1/_2$ min and finally on VI 1 min. Each

animal was exposed to the VI schedule every day, seven days a week for a period of 3 weeks to 1 month before the experiment began so that the average rate of responding of animal varied less than 5% before drugs were given.

Pharmacological Procedure. The 14 animals were divided into two groups equated on the basis of average bar-pressing rate during the last three days of pre-drug training. Seven animals (four in Box 1 and three in Box 2) were given LSD[1] intraperitoneally (I.P.) immediately before being placed into the apparatus in an ascending order of doses (0.005, 0.010, 0.020, 0.040, 0.080, 0.160, 0.320 mg/kg[2]) after being accustomed to daily 0.8 ml injections of isotonic saline. At least 5 and usually 7 days of saline injections separated each drug session. The remaining seven animals (three in Box 1 and four in Box 2) were given the same doses of LSD, but in descending order of administration.

Experiment 2

The effects of LSD on behavior which is maintained by the differential reinforcement of a low rate of its occurrence (drl).

Subjects. Eighteen new rats of the same strain as those of Experiment 1 were used.

Apparatus. The apparatus consisted of two commercially available chambers (Lehigh Valley Electronics, Model 1316) housed in sound- and light-attenuated metal shells (LVE-Model 1316C). Each box was equipped with a single lever, a dim overhead house light, white noise, a feedback light directly above the lever, and a liquid feeder (dipper). A force of 7.5 g activated the lever and each reinforcement consisted of 0.01 ml of sweetened milk.

Behavioral Procedure. The deprivation procedure, preliminary training and shaping of bar pressing were similar to Experiment 1.

Once the animals were responding at a steady rate on CRF, the drl was introduced. On this schedule, the beginning of the session or the presentation of reinforcement starts a timer which is set at some value, t. As in other time-based schedules, the first response after t seconds is reinforced, but any response that occurs before t seconds elapse resets the timer such that the animal must wait another t seconds before another opportunity for reinforcement occurs. Thus, the animal must wait at least

1 Ampules containing 0.1 mg/ml of LSD or powder were prepared by Sandoz Pharmaceuticals, Hanover, N.J., and obtained from the National Institute of Mental Health, Center for Studies of Narcotics and Drug Abuse.

2 Volumes were made approximately equivalent by diluting with NaCl solution.

t seconds before responding to maximize probability of reinforcement. This procedure results in a low rate of bar pressing which is directly related to the value of t, and what has been described as "spacing" or "timing" behavior (Wilson and Keller, 1953).

Initially t was 2 sec. This interval was gradually raised during subsequent 90-min sessions until all animals in both boxes were responding at stable rates on drl 10" ($t = 10$ sec). The animals were then divided into two groups one of which was exposed to further gradual increases in t until a drl 25" schedule was in effect. Thus at the end of the period all of the animals were responding at stable low rates on drl 10" or on stable, much lower rates, on drl 25".

Pharmacological Procedure. Daily i.p. injections of 0.8 ml isotonic saline solution were begun 30 min after the beginning of daily 90-min sessions of drl in order to enable us to see within-session drug effects more clearly. Initially, this procedure caused a slight disruption in behavior but, after a few days, no differences in bar-pressing rate could be detected before and after saline injections. Half of the animals in each drl group were then given 0.01, 0.02, 0.04, 0.08 and 0.16 mg/kg of LSD in an ascending order of administration and the remaining animals received the same doses in a descending order. As in the first experiment, at least five days of saline administration separated each dose of LSD.

Experiment 3

Effects of LSD on drl responding which is further suppressed by periods of punishment.

Subjects. Five new male albino Charles River Sprague-Dawley rats were used.

Apparatus. The apparatus was the same as that of Experiment 2.

Behavioral Procedure. The animals were trained to respond on drl 20" in the same manner as in Experiment 2. A 1000 Hz tone was then randomly presented for 3 min three times during each 90-min session.

After it was established that this mild stimulus had no effect on drl behavior, a 0.5 ma shock was introduced for 0.5 sec each time the animal pressed the bar in the presence of the tone. This discriminated punishment procedure resulted in the suppression of bar-pressing during the tone and, initially, in the absence of the tone as well. Response rates soon returned to normal when the tone was off; drugs were then introduced.

Pharmacological Procedures. Daily i.p. injections of saline or LSD were given at the beginning of each session once stable bar-pressing rates were obtained both in the presence and in the absence of the tone. Each animal received 0.02, 0.08, and 0.16 mg/kg of LSD in either ascending

($n = 3$) or descending ($n = 2$) order of administration. Effects of the drugs on responding both in the presence and in the absence of the tone were compared.

Results

Experiment 1

The relationship between rate of bar-pressing on a VI 1 schedule and dose of LSD is shown in Fig. 1. The per cent control for each dose for a given animal is its average rate of responding during the 1-h drug session divided by its average rate during the three preceding saline (control) sessions ($\times$ 100). The means and standard errors of these scores for all 14 animals along with the data of Gardner (1965) are plotted on semi-logarithmic coordinates.

There is, first of all, an orderly, sigmoidal, dose-response relationship. While low doses (0.005—0.02 mg/kg of LSD) appear to increase and high doses (0.04—0.32 mg/kg of LSD) to decrease response rate, statistical comparison of each dose and the mean of three control sessions reveal that LSD has a significant effect only at 0.08, 0.16 and 0.32 mg/kg, perhaps because there is a large variance associated with all but the highest drug doses (Table 1).

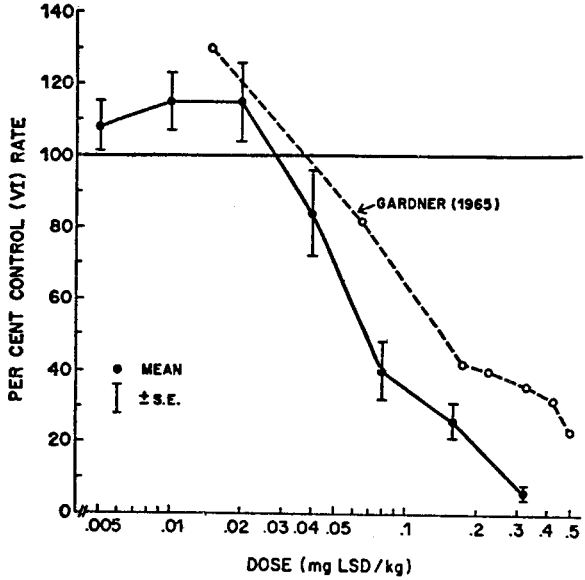

Fig. 1. Per cent of control rates of bar pressing on a VI 1 schedule of milk reinforcement as a function of dose of LSD given i.p. immediately before each 60-min experimental session. The data of Gardner (1965) are re-plotted on the same coordinates to facilitate comparison (see text)

Table 1. *Statistical analysis of the effects of LSD on bar-pressing maintained by a VI schedule of reinforcement*

Dose	$\bar{x}$	Per cent of control responding			
		S.D.	S.E.M.	t_d[a]	p[b]
0.005	108.14	25.44	7.06	1.15	NS
0.010	115.21	27.39	7.60	2.00	NS
0.020	115.28	39.27	10.85	1.41	NS
0.040	83.7	43.89	12.19	1.33	NS
0.080	39.93	29.30	8.13	7.39	< 0.01
0.160	39.21	18.05	5.01	14.72	< 0.01
0.320	6.14	6.52	0.81	52.64	< 0.01

[a] Student's t test for correlated or repeated measures obtained from the same subjects.

[b] Confidence limits for a two-tailed distribution.

Experiment 2

Because the effects of LSD on behavior maintained by drl schedules have never previously been reported, the results of Experiment 2 will be analyzed in somewhat greater detail than those of Experiment 1.

Dose-response relationships on drl are shown in Fig. 2. The per cent control scores were obtained in the same manner as in the first experiment except that only the last 60 min, viz., the part of each session that occurred after drug or saline injection, entered into the calculations. Average rates of responding during the last 60 min of each session, the standard deviations of these scores, the standard deviations of the per cent control data, and the results of statistical analyses are presented in Table 2.

On drl 10″, an animal must respond at a rate of 6 responses per min to maximize the probability of reinforcement. The control rates we obtained average about 7.4 rpm with a range of 6.40 to 8.39 (Table 2). Doses of 0.01—0.08 mg/kg of LSD had no reliable effect on this behavior (Fig. 2, solid line); 0.16 mg/kg of LSD significantly decreased rate and the total number of reinforcements the animals obtained. As was the case in the VI experiment, the animals generally ate following LSD whenever reinforcement was available.

A rate of 2.4 rpm is required to maximize reinforcement on drl 25″. Table 2 shows that the obtained rates under control conditions range between 2.89 and 3.73 rpm with a mean of 3.22. Doses of 0.01—0.04 mg/kg of LSD significantly increased this rate and, while 0.08 also increased the average rate from 2.89 to 3.63 rpm, this increase was not reliable. As on drl 10″ and VI, 0.16 mg/kg of LSD reliably depressed behavior.

The effects of the lowest and highest doses of LSD on rate of drl 10″ and drl 25″ responding over the course of experimental sessions are shown

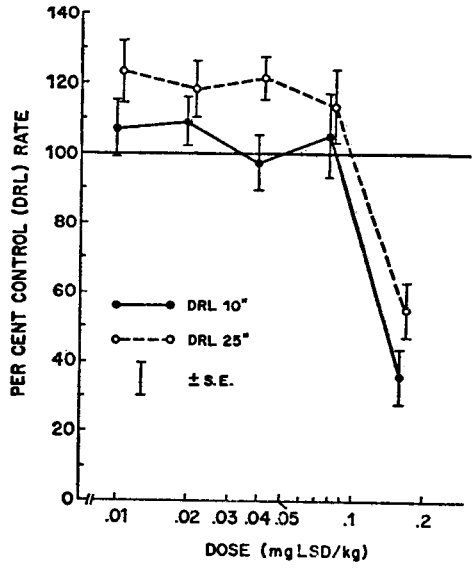

Fig. 2. Per cent of control rate of bar pressing maintained by two drl schedules as functions of dose of LSD (see text)

Table 2. *Analysis of the effects of LSD on bar-pressing maintained by drl 10" and drl 25" schedules of reinforcement*

Dose (mg/kg)	Control rate		Drug-rate		Per cent		t_d[a]	p[b]
	$\bar{x}$	S.D.	$\bar{x}$	S.D.	$\bar{x}$	S.D.		
DRL 10"								
0.01	6.40	1.22	6.80	1.78	107	23	0.81	NS
0.02	7.28	2.70	7.90	2.95	109	22	1.67	NS
0.04	7.48	2.29	7.22	2.45	97	24	−0.41[c]	NS
0.08	7.38	1.35	7.74	2.53	105	35	0.45	NS
0.16	8.39	2.81	2.88	1.98	36	24	−2.93[c]	<0.05
DRL 25"								
0.01	3.11	0.53	3.83	0.93	123	28	2.86	<0.05
0.02	3.21	0.73	3.71	0.62	118	24	2.94	<0.05
0.04	3.16	0.78	3.77	0.86	121	18	3.05	<0.05
0.08	2.89	1.14	3.63	1.25	113	30	1.14	NS
0.16	3.73	1.37	2.08	1.05	55	24	−4.71[c]	<0.05

[a] Student's t test for correlated or repeated measures.
[b] Two-tailed confidence limits.
[c] A negative value denotes a drug-induced decrease in response rate.

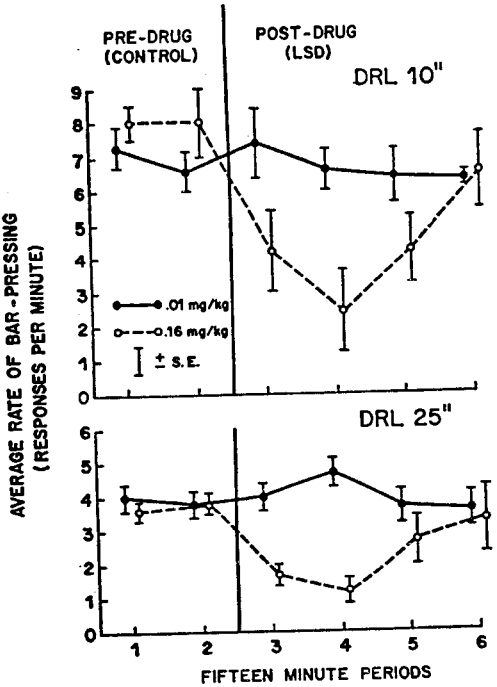

Fig. 3. Average rates of bar-pressing throughout 90-min sessions of drl 10″ or drl 25″ schedules of reinforcement. The effects of the lowest and highest doses of LSD studied are shown

in Fig. 3. On drl 10″, 0.01 mg/kg of LSD (solid line) has no effect on rate. On drl 25″ the same dose has a facilitatory effect which reaches a maximum during the fourth 15-min period (from 15—30 min after i.p. injection) and returns to normal shortly thereafter. Doses of 0.02 and 0.04 mg/kg of LSD (not shown) had similar effects. The depressing effects of 0.16 mg/kg of LSD on both drl schedules begin somewhat earlier (during the first 15 min after i.p. injection) and reach a maximum from 15—30 min after injection. Recovery then occurs and is almost complete by the end of the session (60 min post injection). Thus, the time-course of the depressing effects of LSD on bar pressing maintained by drl schedules is similar to that of the same behavior maintained by either FR or VI (Freedman *et al.*, 1964).

The question naturally arises as to whether drug-induced facilitation in response rate is due to a low base line rate or to some other property of schedules such as drl 25″ (e.g., the relatively greater difficulty of spacing or timing 25 as opposed to 10 sec). While experiments of the kind we are discussing cannot entirely answer this question because the obtain-

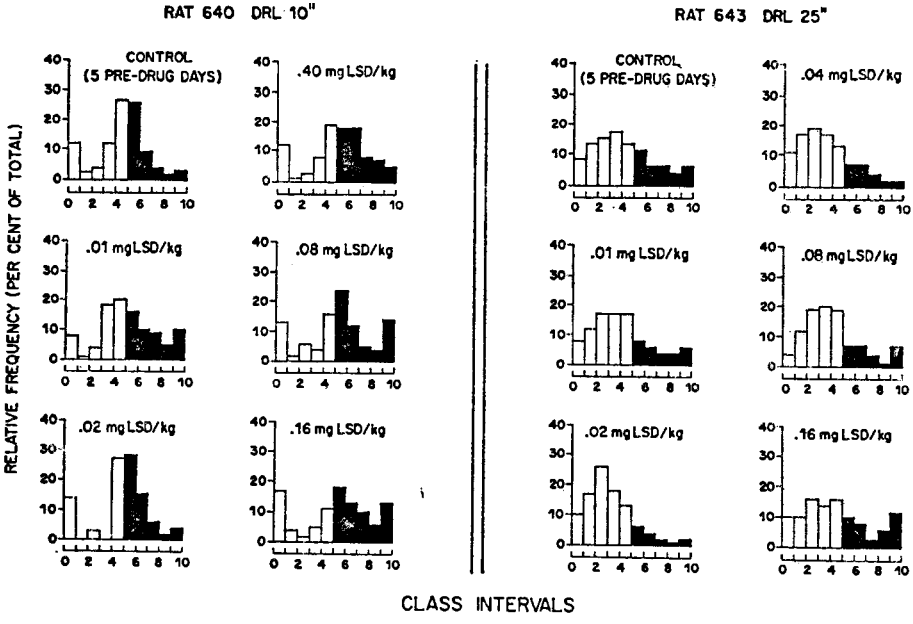

Fig. 4. Inter-response time (IRT) distributions of the bar pressing behavior of two rats on drl 10" and drl 25". Open bars represent unreinforced and dark bars represent reinforced IRT's. The control graph (upper left panel) is the mean of the five days immediately preceding each drug day. The effects of LSD can be seen in succeeding panels (see text)

ed rate depends on the frequency of reinforcement, one analysis suggests that rate is critical. A Spearman rank order correlation (r_s) between the average control rates prior to the most significant facilatatory dose of LSD (0.04 mg/kg) and the per cent change in rate induced by this dose for all animals *independent of the drl value*. The value of r_s was —0.459 which was significant beyond the 0.05 level of confidence. Thus, degree of facilitation appears to be inversely related to base line rate: the lower the rate, the greater will be the drug-induced facilitation.

Timing behavior is examined more closely in Fig. 4 in which frequency of responding throughout the last 60 min of drug and control sessions is separated into different classes defined by the time which elapses between successive responses (inter-response time or IRT). In the case of drl 10" (Fig. 4a) the class or IRT interval is 2 sec and in the case of drl 25" (Fig. 4b) the class interval is 5 sec. The performances of two representative animals (Rats 640 and 643) are shown.

In general, low doses of LSD (0.01—0.04 mg/kg) had little effect on the shape of the frequency distributions (Figs. 4a and b). On drl 10",

these doses did not significantly alter rate but tended to increase the relative frequency of reinforced responding (dark bars). On drl 25" (Fig. 4b) they increased rate significantly and increased the frequency of unreinforced IRT's (open bars). A dose of 0.8 mg/kg of LSD increased the relative frequency of long IRT's (greater than 18 sec on drl 10" and greater than 35 sec on drl 25") without fundamentally altering the shape of the remainder of the distribution. Only the highest doses studied (0.16 mg/kg of LSD) flattened the distribution. In addition, this dose increased long IRT's on both drl 10" and drl 25" and depressed overall rate to about 60%.

Experiment 3

Cumulative records of the performance of one animal under drug (0.02 mg/kg of LSD) and control (saline) conditions are shown in Fig. 5. Less than one response occurred during each tone presentation. (In all animals the mean number of bar-presses in the presence of the tone for three day periods preceding the first drug day was 0.33). Thus, the punishment procedure, like the "high shock conflict" of Geller and Seifter (1960) resulted in essentially complete suppression. No responding occurred during the tone following *any* doses of LSD.

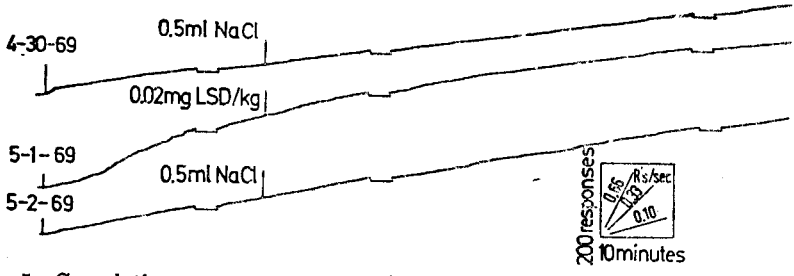

Fig. 5. Cumulative response curves of one animal on drl 20" given saline, 0.02 mg/kg of LSD and saline on successive days. The occurence of tones (and continuous concurrent punishment for any bar presses that might occur in their presence) is indicated by downward displacements of the recording pen

Discussion

The results of the first experiment are in agreement with those of Gardner (1965); low doses *seem* to lead to the facilitation observed by Jarrard (1963), but this increase in response rate is not statistically reliable. Higher doses produce a negatively accelerated, monotonic curve which, on semi-logarithmic coordinates, approaches a straight line (Fig. 1).

Since our dose-response curve consistantly falls to the left of Gardner's, it is apparent that comparable doses of LSD had a somewhat greater depressing and lesser facilitating effect on our animals. This might mean

that our animals were less highly motivated (i.e., were less deprived of food) or had less incentive to respond (i.e., were less reinforced by milk than Gardner's animals were with pellets). Another more likely possibility is that lesser facilitation and greater depression in per cent control scores are the result of a higher base line (control) rate — a condition that could easily be caused by using milk, which is rapidly consumed during the 3-sec reinforcement cycle (not included in rate calculations) rather than pellets, which might take somewhat longer to eat and thereby interfere with other motor responses such as bar-pressing.

The drl data of Experiment 2 clearly indicate that LSD-induced facilitation can occur but that this effect is likely only when the base line response rate is low. Similar results have been reported for amphetamine (Dews, 1956, 1958; Kelleher and Cook, 1969). These effects are particularly interesting in view of the fact that increased response rates on drl result in a loss of reinforcement.

The drl results suggest, but do not prove, that at least high doses of LSD can alter "time sense" or timing behavior in rats as it has been said to do in humans (Hollister, 1968). This effect is, however, confounded by many other possible actions of the drug on the response we used to measure timing, i.e., bar-pressing. The doses of LSD we studied do not, however, noticeably affect motor functioning (Appel *et al.*, 1967), disposition to eat when milk is available (Appel *et. al.*, 1968), or general level of activity (Appel, 1968).

The results of the third experiment show that, like amphetamine, but unlike depressant compounds such as meprobamate, phenobarbital or pentobarbital, LSD does not alter behavior suppressed by strong punishment or "conflict" (Geller and Seifter, 1960) either because it does not modify external stimulus control, does not relieve anxiety or does not attenuate the painful effect of shock. They further suggest one limit to the dependency of the effects of LSD on base line response rate, i.e., when rate is normally suppressed to zero, LSD does not facilitate responding.

In general, these experiments, along with those concerned with FR indicate that the effects of LSD on one well-defined, relatively simple kind of behavior are determined directly by dose and indirectly by those variables which determine base line rate of responding. They do not reveal whether the contingency, schedule, or frequency of reinforcement or some other parameter which controls the rate is the important factor.

Acknowledgements. This research was supported by USPHS Research Grant 7-ROI-MH-13186 and Research Scientist Development Award 1-K2-MH-9355 from the National Institute of Mental Health and by NSF Grant GB-7442 from the National Science Foundation. We thank D. X. Freedman, M.D. for his support and Paul Taylor for expert technical assistance.

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