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LSD and d-Amphetamine Effects on Fixed Interval Responding in the Rat

CHARLES KSIR AND SIDNEY NELSON

Department of Psychology, The University of Wyoming
Laramie, WY 82071

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KSIR, C. AND S. NELSON. *LSD and d-amphetamine effects on fixed interval responding in the rat.* PHARMAC. BIOCHEM. BEHAV. 6(3) 269–272, 1977. – Food-deprived rats were trained to press a key which produced a food pellet for the first press after 3 min had elapsed (FI 3 min). Daily sessions consisted of 10 such intervals. Graded doses of LSD (0.04–1.28 mg/kg) and a d-amphetamine (0.5–2.0 mg/kg) were given 30 min before sessions. LSD produced a decrease in response rate at doses of 0.32 mg/kg and above, but did not disrupt the typical FI pattern of responding except at the highest dose (1.28 mg/kg). Amphetamine did not significantly alter the overall response rate, but caused a dose-related disruption of the FI response pattern, with previously low response rates increased more than higher rates, and occasional decreases in the previously highest rates. The experiment was repeated using the same rats responding on a multiple FIFR schedule. The presence of a 2000 Hz tone signalled FR periods; the tone was absent during FI periods. During the FR components, a pellet was produced after 30 responses had been emitted. The FI components were unchanged. LSD (0.08–0.32 mg/kg) again produced decreases in FI rate without altering the pattern, and amphetamine again altered the FI pattern without significantly changing overall rate.

Fixed interval responding LSD d-Amphetamine

DEWS [2] was the first to suggest that the direction and magnitude of amphetamine-induced changes in behavior depended on the rate of occurrence of the behavior prior to drug administration. If a food-deprived animal is enclosed in a chamber and, after being trained to press the key, is given access to food for the first response on the key after some constant interval of time has elapsed, the rate of responding on the key typically is low at the beginning of the interval, increasing to some higher rate at the end of the interval. When amphetamine is given to animals responding on such a fixed interval schedule the low rates early in the interval are increased while the higher rates at the end of the interval may be decreased. Kelleher and Morse [4] reviewed evidence that the rate-dependent effects of amphetamine may be seen either within fixed interval performances or when comparing the drug effects on behaviors maintained under different reinforcement schedules which generate different predrug response rates. Sanger and Blackman [8] have recently reviewed evidence for the rate-dependent effects of several psychoactive drugs. Ksir [6] has pointed out that drugs which disrupt the typical pattern of responding on fixed interval schedules such that response rates are constant throughout the interval are producing effects which have been called rate dependent. In fact, any treatment which reduces differences in response rates can be thought of as producing rate-dependent effects.

Altman and Appel [1] recently reported that LSD produced rate-dependent effects on fixed interval responding in rats. These effects consisted of increases in the low response rates early in the interval with all doses of LSD tried (0.01 to 0.32 mg/kg) and decreases in the high rates later in the interval with high doses (0.16 and 0.32 mg/kg). At the time that report appeared we had just completed experiments comparing LSD and amphetamine effects on fixed interval and on multiple fixed interval, fixed ratio schedules, also using rats. Those results are presented in the current paper.

EXPERIMENT 1

The first experiment examined the effects of several doses of LSD and of d-amphetamine on a simple fixed interval (FI) reinforcement schedule.

Method

Animals. The six male Long-Evans derived hooded rats were 90–120 days old at the beginning of the experiment. The rats were housed individually with free access to water in the home cages. Each rat was fed 10–12 g of Purina Lab Chow daily.

Apparatus. The operant conditioning chamber (15 × 25 × 20 cm) contained a single Gerbrands model B response key and a pellet magazine mounted on one end wall. The magazine was in the center of the end wall, 2.5 cm from the grid floor. The response key, 5 cm to the left of the magazine and 5 cm above the floor, was transilluminated from behind by a 7.5 W white lamp. This lamp was continuously lit during the experimental sessions and provided the only illumination inside the sound and light attenuating enclosure surrounding the operant chamber.

Events in the chamber were controlled and recorded by electromechanical programming equipment.

Behavioral procedure. Each rat was trained to press the response key by presenting a 45 mg Noyes lab animal food pellet after each operation of the key. The minimum time interval between pellet presentations was gradually increased over several sessions until the FI 3 min schedule was reached. A food pellet followed the first response after 3 min had elapsed without a pellet. Each session consisted of 10 such intervals. Responses in each tenth (18 sec) of the interval were cumulated during each session. Sessions were conducted daily except Saturday and Sunday.

Pharmacological procedure. After 18 sessions on the FI 3 min schedule, drug injections were begun. All injections were given intraperitoneally, 30 min before the session, in a volume of 1 ml/kg body weight. Each rat received two injections of each of the following doses of LSD: 0.04, 0.08, 0.16, 0.32, 0.64 and 1.28 mg/kg. Doses were given in an ascending, then descending order, except that the two injections of 1.28 mg/kg were given after the other doses. LSD was supplied by the National Institute on Drug Abuse (NIDA). Each rat was then given two injections of each of the following doses of d-amphetamine sulfate: 0.5, 1.0, and 2.0 mg/kg (salt weights). These doses were also given in an ascending, descending order. Injections were given twice a week (Tuesdays and Fridays).

Results

Rate of responding (responses/sec) for the entire session was calculated, and a mean computed for each rat for each dose of LSD and for all control days during the LSD portion of the experiment (control days were Thursdays – no injections were given). A mean was also computed for each rat for each dose of d-amphetamine and for the corresponding control days. Figure 1 shows the control mean for all rats and the mean for all rats at each dose. It can be seen that LSD produced a dose-related decrease in responding at doses of 0.32 mg/kg and above. An analysis of variance for repeated measures examined the effect of drug dosage (control data were included as one level of the dose factor). The dose effect was found to be significant, $F(6,30) = 6.44$, $p<0.001$. Similar data are given for d-amphetamine. There was no significant effect of d-amphetamine on overall FI rate, $F(3,15) = 0.23$.

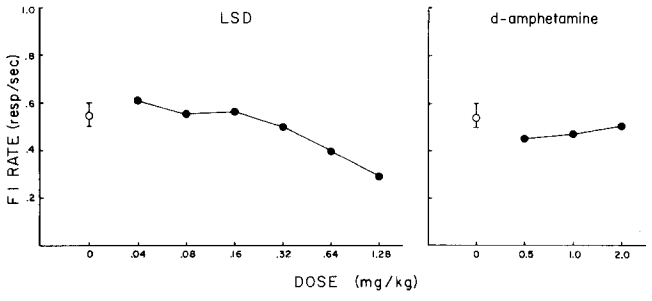

FIG. 1. Effects of LSD and d-amphetamine on mean overall response rate during a FI 3 min schedule for all six rats. Bars above and below the open circle represent the range of mean nondrug rates associated with each dose.

The Index of Curvature [3] was developed as a measure of the degree of rate change during fixed intervals. This statistic, based on a division of each interval into four segments, was employed by Altman and Appel [1] in their study of LSD effects on FI responding. The Curvature index comparing response rates in each tenth of the interval with the average rate was calculated for all control and drug sessions for each rat. Figure 2 shows the mean curvature index for all rats at each dose, and for the control sessions nearest each dose, for LSD and d-amphetamine. It is obvious from Fig. 2 that d-amphetamine produced a consistent, dose-related decrease in the curvature index. This effect was found to be highly significant by an analysis of variance, $F(3,15) = 38.22$, $p<0.001$. LSD also produced a significant effect on the curvature index, $F(6,30) = 7.41$, $p<0.001$. Individual t-tests comparing drug and control values at each dose found that only the highest (1.28 mg/kg) dose produced a significant effect $t = 4.16$, $df = 5$, $p<0.01$.

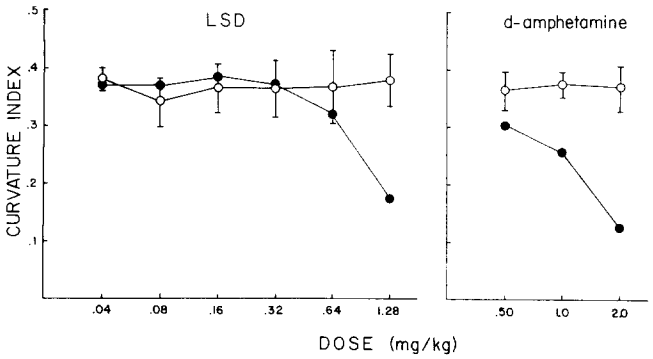

FIG. 2. Effects of LSD and d-amphetamine on the index of curvature, which indicates the amount of change in response rate during the FI. Solid circles represent the mean for all rats of the two sessions on which a particular dose was given. Open circles represent the mean for all rats of the two control sessions nearest in time to the two drug sessions. Bars show the standard error of the mean for the control sessions.

Discussion

Although we had not yet seen the Altman and Appel data, we had expected to see disruptions of the FI pattern at doses of LSD below the clearly debilitating level of 1.28 mg/kg. Since the procedure was sensitive enough to detect highly significant changes in FI pattern with d-amphetamine, it seemed possible that the LSD used, although it was carefully mixed and stored, may have lost some potency. Another possible approach was to try to increase the sensitivity of the behavior to drug influence.

EXPERIMENT 2

A fresh supply of LSD was obtained from NIDA, and an attempt was made to increase the sensitivity of the behavioral procedure. Several previous reports have indicated, under a wide variety of conditions, that behavior under weaker control is more susceptible to drug effects than behavior which is more strongly controlled by the schedule and stimulus conditions [5,7]. It was felt that the addition of a fixed ratio (FR) component to the procedure,

with a tone signalling when the FR was in effect, might weaken the control exerted by the FI component sufficiently to enable even a weak drug effect to be seen.

Method

Animals and apparatus. The same rats were used as in Experiment 1. The operant chamber was modified by the addition of a loudspeaker, through which could be presented a 90 dB, 2000 Hz tone (background noise was measured at approximately 80 dB).

Behavioral procedure. The reinforcement schedule was altered by the addition of another component. With a probability of 0.50, the tone would begin immediately following presentation of a food pellet. In the presence of the tone, a fixed number of responses produced a pellet, regardless of how much time had elapsed. The number of required responses started at 10 and was increased over the next 6 sessions to 30 (fixed ratio of 30, FR 30). The tone terminated upon presentation of a pellet, and the next component was again chosen at random. When the tone was not present, a FI 3 min schedule was in effect, as in Experiment 1. The entire schedule is referred to as a multiple fixed interval 3 min, fixed ratio 30 response schedule of reinforcement (mult FIFR). Each session lasted for one hour.

Pharmacological procedure. After 38 sessions on the mult FIFR schedule, the session was shortened to 30 min and drug injections were resumed. Injections were given as in Experiment 1, except that the d-amphetamine injections were all given before the LSD injections, and only the 0.08, 0.16, and 0.32 mg/kg doses of LSD were given. Doses were again given in an ascending, then descending order; a total of two injections per dose per rat.

Results

Mean response rates during the FI component were calculated as in Experiment 1 and are shown in Fig. 3. LSD produced a dose-related decrease in FI responding, $F(3,15) = 7.91$, $p<0.005$. There was no relationship between amphetamine dose and FI response rate, $F(3,15) = 0.91$.

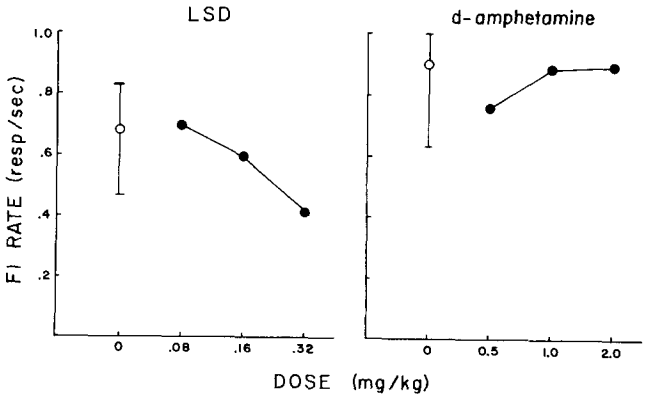

FIG. 3. Effects of LSD and d-amphetamine on mean overall response rate during the FI portion of a mulitple schedule. Bars above and below the open circle represent the range of mean nondrug rates associated with each dose.

Figure 4 presents the mean curvature index for each dose of d-amphetamine and of LSD, compared with the nearest control sessions. Amphetamine again produced a highly significant effect, $F(3,15) = 14.47$, $p<0.001$, whereas LSD did not produce a significant effect, $F(3,15) = 0.33$.

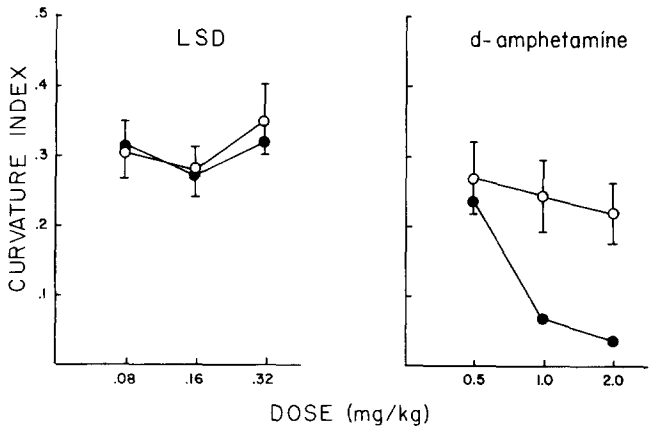

FIG. 4. Effects of LSD and d-amphetamine on the index of curvature for the FI component of the multiple schedule. Solid circles: mean for all rats for the two drug sessions at each dose. Open circles: mean control rates ± standard error of the mean.

Response rates during the FR components were calculated for each session, and mean rates for control sessions and for each dose of LSD and of d-amphetamine are presented in Fig. 5. LSD produced a significant decrease in FR rates, $F(3,15) = 6.43$, $p<0.01$, whereas amphetamine produced a significant increase in FR rates, $F(3,15) = 9.20$, $p<0.005$.

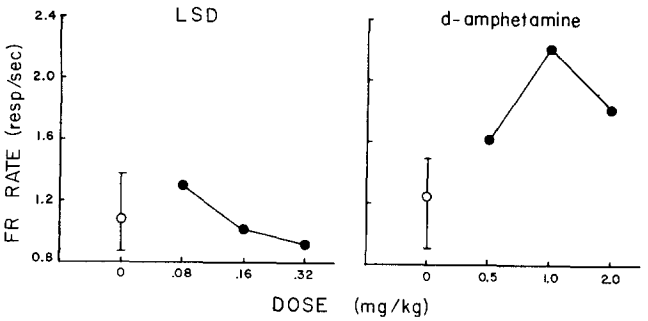

FIG. 5. Effects of LSD and d-amphetamine on mean response rate during the FR30 components of the multiple schedule. Bars above and below the open circle represent the range of mean nondrug rates associated with each dose.

Discussion

LSD again decreased response rates, this time in both components, and amphetamine did not change overall FI rates. The increase in FR rates seen with amphetamine was unexpected and is not consistent with previous findings [4].

The failure of LSD to disrupt the pattern of responding on FI is consistent with the results of Experiment 1, and shows that the increased complexity of the schedule did not render the performances more susceptible to LSD effects, even though the greater overall FI rates and lower curvature indices under the multiple schedule indicate that

FI responding was not as well controlled by the multiple schedule.

CONCLUSIONS

There are a number of procedural differences between the Altman and Appel [1] study and this one, including the strain of rats used, the session length and time of injection, and the FI duration (5 min vs 3 min). In light of their data showing LSD effects on FI curvature after very careful establishment of strong schedule control under FI 5 min, it is apparent that our strategy of decreasing schedule control to increase sensitivity was wrong. Under carefully controlled conditions Altman and Appel found small but significant effects of LSD on FI curvature. The present data place those results into perspective by demonstrating that amphetamine produces much greater effects on FI curvature than LSD, and does so under conditions in which LSD produces no disruption of LSD pattern while decreasing overall FI response rate.

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