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SIMILARITIES AND DIFFERENCES BETWEEN MESCALINE, LYSERGIC ACID DIETHYLAMIDE-25 (LSD) AND *d*-AMPHETAMINE ON VARIOUS COMPONENTS OF FIXED INTERVAL RESPONDING IN THE RAT[1]

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ABSTRACT

TILSON, H. A. AND S. B. SPARBER: Similarities and differences between mescaline, lysergic acid diethylamide-25 (LSD) and *d*-amphetamine on various components of fixed interval responding in the rat. J. Pharmacol. Exp. Ther. **184**: 376–384, 1973.

Three male albino rats were trained to lever press for food on a fixed-interval 75-second schedule of reinforcement. Responding in the first and last 15 seconds of the interval, as well as overall response rates, were analyzed. After stabilization of fixed-interval responding, the effects of lysergic acid diethylamide-25 (LSD) (0.005–0.150 mg/kg), *d*-amphetamine sulfate (0.10–0.96 mg/kg) and mescaline hydrochloride (1–12 mg/kg) on fixed-interval responding were investigated. LSD (0.015 mg/kg) increased responding in all portions of the interval, whereas higher doses tended to decrease responding. *d*-Amphetamine (0.15 and 0.48 mg/kg) increased rates of responding except at the highest dose (0.96 mg/kg) which decreased responding in the last 15 seconds of the interval. Mescaline (3–12 mg/kg) produced dose-related increases in responding in the initial 15-second segment while decreasing responding in the last portion of the interval. In rats tolerant to the effects of mescaline (3 mg/kg), there were indications of cross-tolerance to the effects of 0.15 mg of *d*-amphetamine per kg, but no cross-tolerance was observed when the order of drug presentation was reversed. A two-way, partial cross-tolerance was observed between the effects of 0.045 mg of LSD per kg and 3 mg of mescaline per kg and rats tolerant to the effects of 0.015 mg of LSD per kg did not show cross-tolerance to the effects of 0.15 mg of *d*-amphetamine per kg regardless of the order of drug presentation. These data suggest mescaline shares common mechanisms or components of behavioral action with both LSD and *d*-amphetamine in the rat.

Studies of cross-tolerance between the effects of mescaline and lysergic acid diethylamide-25 (LSD) have led some investigators to suggest that they may act on the same central receptor or mechanism (Wolbach *et al.*, 1962; Appel and Freedman, 1968; Silva *et al.*, 1968; Synder and Richelson, 1968; Kang and Green, 1970). Recent

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experiments, however, have indicated that these two psychotomimetics may differ in their neurochemical (Freedman *et al.*, 1970; Tilson and Sparber, 1972) electrophysiological (Winters, 1968; Aghajanian *et al.*, 1970) peripheral (Hollister and Moore, 1967, 1968) and subjective effects (Synder *et al.*, 1970). Furthermore, a critical analysis of data supporting cross-tolerance between LSD and mescaline also points to an equivocal relationship. For example Baldestrieri and Fontanari (1959) reported a marked cross-tolerance in subjects tolerant to LSD and given mescaline. When mescaline-tolerant individuals received LSD, only a partial cross-tolerance was demonstrated (*i.e.*, one-way cross-tolerance). Similar indications of partial cross-tolerance have been reported to occur in man (Wolbach *et al.*, 1962) and animals (Freedman and Aghajanian, 1959; Appel and Freedman, 1968).

Operant behavioral technics have gained general acceptance as tools to measure drug-induced behavioral effects. The fixed-ratio schedule of reinforcement has been used with rats to study cross-tolerance between LSD and mescaline (Appel and Freedman, 1968; Winter, 1971). In addition, Freedman *et al.* (1964) and Silva *et al.* (1968) have reported tolerance to the disruptive effects of LSD or mescaline on variable interval schedules of reinforcement, but investigations of cross-tolerance between the effects of these two drugs on variable interval performance have not been reported. To our knowledge, the effects of mescaline and LSD on fixed-interval (FI) schedules of reinforcement have not been studied, in spite of extensive use of the schedule with Δ^8- or Δ^9-tetrahydrocannabinol (Frankenheim *et al.*, 1971) and central nervous system stimulants such as *d*-amphetamine (Smith, 1964; McKearney, 1968; McMillan, 1968).

The present studies sought to investigate the dose-related effects of LSD and mescaline on responding during various segments of a FI schedule of food reinforcement. We have also included studies with *d*-amphetamine since it produces sympathomimetic effects similar to the hallucinogens but reportedly does not produce cross-tolerance to LSD (Rosenberg *et al.*, 1963; Appel and Freedman, 1968) or mescaline (Sparber and Tilson, 1972a). In addition, we have tested for the development of tolerance and the possibility of cross-tolerance to the behavioral effects of LSD, mescaline and *d*-amphetamine with the FI schedule of reinforcement.

Methods

Subjects and apparatus. Three male albino Sprague-Dawley (Simonsen Laboratories, White Bear Lake, Minn.) rats served as subjects in these experiments. They were housed in separate cages in a room with a 12 hours day/12 hours night rhythm (6:45 A.M. to 6:45 P.M.) and maintained at 25°C and 50% humidity. The animals weighed approximately 350 to 435 g each at the beginning of the experiment and were food-deprived to 70 to 80% of their free-feeding body weight. Water was available in the home cage *ad libitum*. Behavioral sessions were performed in a standard operant chamber (Foringer, Rockville, Md.) which has been described previously (Sparber and Tilson, 1971).

Training and response measurement. Initially, the animals were required to press a lever once for food reinforcement. In subsequent daily sessions, responses were reinforced intermittently at increasing 15-second intervals until FI 75-second responding was maintained. The training procedure required approximately one week. Each animal then received 35 consecutive daily sessions, each of which was terminated after 50 reinforcements. Experiments to determine dose-response effects of i.p. injections of mescaline (1, 3, 6 or 12 mg/kg), LSD (0.005, 0.015, 0.045, 0.090 or 0.150 mg/kg) and *d*-amphetamine (0.10, 0.15, 0.48 or 0.96 mg/kg) then were initiated. Each dose-response experiment began with four consecutive days of injections of 0.5 ml of isotonic saline (NaCl). Drug sessions followed which were separated by at least 72 hours and additional NaCl control sessions were given during this interim.

Responses were automatically recorded by a digital print-out counter, which was activated every 15 seconds in order to divide responding in each 75-second interval into five equal segments. The response measures analyzed were mean overall response rate (segments 1 through 5, responses/75 sec) and mean responding in the first and last 15-second segments (1 and 5, responses/15 sec) of the 75-second interval. Each of the three dose-response experiments required approximately one month to complete and at least two weeks separated the end of one experiment and the beginning of the next one. NaCl was injected in at least 10 sessions during each study and at least two observations (ascending-descending drug order) were made for each drug. From the NaCl control data of each experiment, a mean control rate (100%) was established for each subject. Drug-induced alterations of responding were calculated as a percentage of the animal's own control and individual upper and lower limits of control responding based on ±2 S.D. were established.

All individual values were then averaged to obtain a group mean. For purposes of this discussion, a significant drug response will be defined as that point at which the average behavioral measure is equal to or greater than ±2 S.D. from group control means.

Approximately three weeks after completion of the dose-response experiments, tolerance and cross-tolerance studies began. In most cases, the drugs did not produce identical behavioral effects on all measures and the rationale for each choice of dose is described in the tolerance and cross-tolerance studies section of "Results." Response measures were the same as those used in the dose-response experiments. The procedure was the same for each of the three studies, which were separated by at least two weeks. Briefly, each experiment began with three consecutive NaCl control sessions, followed the next day by a drug control session. Another NaCl control session followed 48 hours later and, on the next day, the second drug was given as a control. Consecutive daily drug sessions followed in which the second drug was given until all responding was within upper and lower limits (2 S.D.) of control rates. The day after tolerance, the rats were given a challenge dose of the first drug and injections were continued until tolerance developed. A test for cross-tolerance in the other direction was followed by two additional NaCl control sessions. Only one determination was made per rat during each manipulation and results are described for individual subjects. Control rates (100%) are based on six NaCl control sessions given each subject.

Drugs. The drug forms injected were mescaline hydrochloride (Aldrich Chemical Company, Inc., Milwaukee, Wis.), *d*-amphetamine sulfate (K & K Laboratories, Plainview, N.Y.) and *d*-lysergic acid diethylamide-25 (LSD) in saline and tartaric acid (FDA-USPHS psychotomimetics agents advisory committee). All drugs were injected i.p. immediately before each session. Dilutions of drugs from stock solutions were made daily and the same stock solution was not used for more than one week. Volumes administered were 1 ml/kg of food-deprived body weight.

Results

FI responding after i.p. injections of NaCl. Responding under control conditions resembled the "scalloped" performance in which higher response rates are generated near the end of the interval and minimal responding is seen in earlier portions of the interval (Ferster and Skinner, 1957). As expected, intermediate rates of responding were emitted in segments 2 to 4 (30–60 seconds). Although the base-line rates tended to shift during the nine-month period from training to completion of the tolerance studies, responding during each block of experiments was more stable. For all three subjects, control rates in the last stages of each experiment were within ±1 S.D. of mean NaCl control responding preceding each study

Dose-related effects of the drugs on FI responding. The lowest dose of mescaline (1 mg/kg) did not produce significant alterations (beyond 2 S.D.) in FI responding (fig. 1). Three and six mg of mescaline per kg produced dose-related increases and decreases in responding in the first and last 15-second segments, respectively, while not significantly affecting overall response rates. The highest dose of mescaline (12 mg/kg) also increased responding in the first 15-second segment, but the change was less than that observed with the two lower doses. The increases in responding in the initial segment were sufficiently offset by response decreases in the last 15-second segment and the mean overall response rate was within the 2 S.D. range.

The lowest dose of LSD (0.005 mg/kg) produced marginal effects on FI responding, whereas 0.015 mg of LSD per kg produced significant increases in FI responding. The two intermediate doses of LSD (0.045 and 0.090 mg/kg) produced dose-related decreases in responding in the first and last 15-second segments which were beyond the 2 S.D. limit. However, the overall rate was not significantly altered by these two doses. The highest dose of LSD (0.150 mg/kg) significantly decreased all FI responding.

The lowest dose of *d*-amphetamine (0.10 mg/kg) produced a slight, but nonsignificant, increase in FI responding (fig. 1), whereas 0.15 and 0.48 mg of *d*-amphetamine per kg elicited rate increases beyond the upper 2 S.D. limit for all measures. The highest dose of *d*-amphetamine (0.96 mg/kg) increased and decreased responding in the first and last 15-second segments, respectively. Response increases early in the interval were negated by decreases later in the interval and the overall response rate was not significantly affected.

Tolerance and cross-tolerance—Mescaline and LSD. In the dose-response experiments, it was shown that the effects of LSD on FI responding were generally different than those of mescaline. However, 3 mg of mescaline per kg

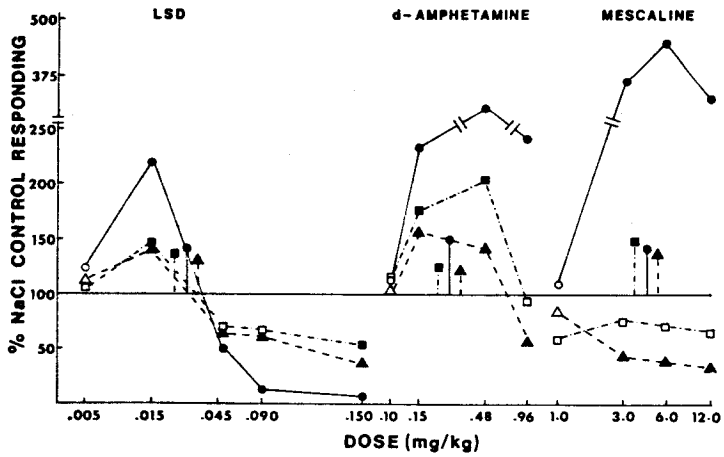

FIG. 1. Dose-related effects of LSD, *d*-amphetamine and mescaline on responding during a FI 75-second schedule of food reinforcement. Each point is the mean of six observations per experiment (two for each of three rats). The data are presented as percentage of NaCl control responding in the first (○ ●) and last (△, ▲) 15-second segments, as well as overall rates (□, ■). The vertical lines indicate average upper limits (2 S.D.) of controls, based on at least 10 NaCl control sessions per rat in each study. Filled characters indicate drug-induced alterations in responding which are beyond upper or lower limits. Average NaCl control rates (100%) of responding in the first 15-second segment were: 0.79, 0.84 and 0.95 response/15 sec for LSD, *d*-amphetamine and mescaline experiments, respectively. Control response rates in the last 15-second segments were 5.01, 4.35 and 4.75 responses/15 sec, and mean overall rates were 8.82, 8.51 and 9.07 responses/75 sec for the LSD, *d*-amphetamine and mescaline experiments, respectively.

and 0.045 mg of LSD per kg produced approximately the same decrease in responding in the last 15-second segment (fig. 1). In this experiment, which was conducted approximately three to four months after the dose-response determination for mescaline, 3 mg of mescaline per kg produced significant increases and decreases in responding in the first and last 15-second segments, respectively (table 1). Overall response rates were not affected. Seventy-two hours later, 0.045 mg of LSD per kg decreased responding in the first and last 15-second segments, whereas the overall response rate was within the 2 S.D. limit of all three subjects. The repeated injection of LSD for three to four days resulted in a gradual return of all responding to within the lower limits. Significant increases in response rates were not observed during the development of tolerance to this dose of LSD. Mescaline (3 mg/kg) the next day significantly increased and decreased responding in the first and last 15-second segments, respectively. However, there was a substantial reduction in the response increase in the first 15-second segment as compared to the drug control of each rat. Decreases in response rates were also less than that observed in the drug control. Continued administration of mescaline further decreased the effectiveness of the drug to alter FI responding and, by four to seven days, all response measures were within upper or lower limits. LSD (0.045 mg/kg) the next day significantly increased responding in the first 15-second segment, as well as increasing the overall response rate. Responding in the last 15-second segment was affected in all animals and the increase was significant for rat A15. This behavioral effect is almost identical to that obtained with the dose of 0.015 mg of LSD per kg (rate increase, fig. 1). Tolerance may be defined as an effect of a specified drug dosage resembling that of a smaller dose and the data of this experiment indicate a partial cross-tolerance between mescaline and LSD.

Mescaline and *d*-amphetamine. During the two weeks intervening between the end of the preceding experiment and the beginning of this study, the base-line responding of each rat tended to decrease (tables 1 and 2). However, the NaCl controls obtained at the end of this study were within 1 S.D. of the mean control responding of each rat.

As in the dose-response experiments, 3 mg of mescaline per kg and 0.15 mg of *d*-amphetamine per kg produced approximately the same increases in responding in the first 15-second segment (table 2). Mescaline generally decreased, whereas *d*-am-

TABLE 1

Tolerance and cross-tolerance with 3 mg of mescaline per kg and 0.045 mg of LSD per kg

Treatment	Subject	Mean Response Rate								
		First 15 sec			Last 15 sec			Total (75 sec)		
		A11	A12	A15	A11	A12	A15	A11	A12	A15
		responses/interval			*responses/interval*			*responses/interval*		
NaCl[a]										
Upper		0.80	0.83	0.38	4.34	7.20	3.97	8.20	15.25	7.75
Mean		0.53	0.65	0.26	3.38	6.80	3.53	6.60	11.20	5.40
Lower		0.26	0.47	0.14	2.42	6.40	3.09	5.00	7.15	3.05
Mescaline, drug control[b]		1.07 (102)[c]	2.12 (224)	1.75 (573)	2.24 (−34)	4.64 (−32)	1.07 (−70)	5.60 (−15)	7.40 (−34)	5.25 (−3)
LSD, drug control		0.16 (−70)	0.44 (−33)	0.05 (−81)	2.40 (−29)	5.10 (−25)	2.96 (−16)	5.05 (−23)	8.50 (−24)	3.80 (−30)
LSD, tolerance		0.38 (−28)	0.70 (8)	0.25 (−4)	4.07 (20)	6.78 (−.3)	3.30 (−7)	7.45 (13)	12.75 (14)	6.75 (25)
Mescaline, cross-tolerance		0.91 (72)	1.20 (86)	0.76 (192)	2.40 (−29)	4.71 (−31)	1.98 (−44)	6.70 (2)	8.85 (−21)	5.70 (6)
Mescaline, tolerance		0.49 (−8)	0.72 (9)	0.24 (−8)	3.47 (3)	6.78 (−.3)	3.21 (−9)	6.90 (5)	12.30 (10)	5.20 (−4)
LSD, cross-tolerance		0.88 (66)	1.00 (54)	0.86 (231)	4.02 (19)	6.86 (1)	4.76 (35)	9.55 (45)	15.95 (42)	10.30 (91)

[a] Data given are the means of six observations for each animal. The upper and lower limits are 2 S.D. above and below the mean rate.

[b] Drug controls were separated by at least 72 hours. All other drug sessions were performed on successive days.

[c] Percent change from control rate.

phetamine increased responding in the other two measures. The effectiveness of *d*-amphetamine to increase responding gradually decreased with repeated injections and, by four days, the responding of rat A11 indicated the development of tolerance. Eight days of injections were required to produce tolerance in rats A12 and A15. Mescaline (3 mg/kg) the next day produced significant increases in responding during the first 15-second segment. Likewise, the overall response rate and responding in the last 15-second segment were decreased. The changes in rates were approximately the same as those observed during the drug controls for mescaline, suggesting the lack of cross-tolerance in this direction. Three consecutive days of mescaline injections resulted in responding that was within 2 S.D. of the upper and lower limits of each rat's own NaCl control values. *d*-Amphetamine (0.15 mg/kg) on the following day significantly affected all measures of responding except for the responding in the first 15-second segment of rat A11. In all cases, the increases in responding by *d*-amphetamine in rats tolerant to mescaline were lower than that obtained under drug control conditions.

LSD and *d*-amphetamine. Doses of *d*-amphetamine (0.15 mg/kg) and LSD (0.015 mg/kg) that produced general increases in responding in the dose-response study were used for comparison in this experiment. The repeated administration of 0.015 mg of LSD per kg resulted in a gradual decline in the effectiveness of this dose to increase responding and, after four to six days, all responding was with 2 S.D. limits of control responding (table 3). The administration of *d*-amphetamine (0.15 mg/kg) the next day produced response increases which were approximately the same as those in the drug controls. The ability of this dose of *d*-amphetamine to increase responding gradually declined with repeated injections of the drug and tolerance was observed in six to nine days. The administration of LSD (0.015 mg/kg) the next day increased FI responding and the effect was similar to that obtained during the initial exposure to LSD in this ex-

TABLE 2

Tolerance and attempted cross-tolerance with 0.15 mg of d-amphetamine per kg and 3 mg of mescaline per kg

Treatment Subject	Mean Response Rate								
	First 15 sec			Last 15 sec			Total (75 sec)		
	A11	A12	A15	A11	A12	A15	A11	A12	A15
	responses/interval			*responses/interval*			*responses/interval*		
NaCl[a]									
Upper	0.51	0.39	1.45	2.25	5.18	1.64	6.75	7.42	4.51
Mean	0.29	0.24	0.95	1.81	4.29	1.24	5.25	6.65	3.55
Lower	0.07	0.09	0.45	1.37	3.40	0.84	3.75	5.88	2.59
Mescaline-drug control[b]	0.82 (183)[c]	0.73 (204)	2.18 (129)	0.98 (−46)	1.80 (−58)	0.09 (−93)	3.10 (−41)	4.65 (−30)	3.25 (−8)
d-Amphetamine, drug control	1.10 (279)	0.94 (292)	1.79 (88)	3.80 (110)	6.78 (58)	1.88 (52)	8.80 (68)	12.10 (82)	5.89 (66)
d-Amphetamine, tolerance	0.24 (−17)	0.18 (−25)	0.94 (−1)	1.85 (2)	4.97 (16)	1.38 (11)	6.25 (19)	6.40 (−4)	4.00 (13)
Mescaline, cross-tolerance	0.97 (234)	0.67 (179)	2.50 (163)	1.09 (−40)	2.09 (−51)	0.08 (−94)	3.75 (−29)	4.80 (−28)	3.30 (−7)
Mescaline, tolerance	0.10 (−66)	0.29 (21)	1.21 (27)	1.68 (−7)	4.76 (11)	1.45 (17)	6.45 (23)	7.35 (11)	3.65 (3)
d-Amphetamine, cross-tolerance	0.30 (3)	0.91 (279)	1.60 (68)	2.64 (46)	6.30 (47)	1.79 (44)	7.05 (34)	10.50 (58)	4.80 (36)

[a] Data given are the means of six observations for each animal ±2 S.D. (upper and lower limits).

[b] Drug control sessions were separated by at least 72 hours. All other drug sessions were performed on consecutive days.

[c] Percent change from control rate.

periment. These data indicate the lack of cross-tolerance between LSD and *d*-amphetamine in either direction.

Discussion

These investigations point to several similarities and differences in the effects of LSD, mescaline and *d*-amphetamine after single or repeated injections. The lowest behaviorally effective dose of LSD (0.015 mg/kg) and low to intermediate doses of *d*-amphetamine (0.15 to 0.48 mg/kg) produced almost identical increases in responding on all measures. Other investigators have indicated that low doses of LSD increase responding under the control of timed contingencies (Jarrard, 1963; Altman and Appel, 1971; Appel, 1971) and that *d*-amphetamine and LSD produce similar subjective and sympathomimetic effects (Rosenberg *et al.*, 1963). In spite of these common effects, the lack of cross-tolerance in either direction suggests different mechanisms of action at these doses. This conclusion is supported by the work of other investigators showing no cross-tolerance between the effects of *d*-amphetamine and LSD under different conditions (Rosenberg *et al.*, 1963; Appel and Freedman, 1968).

Mescaline produced dose-related increases in responding in earlier portions of the interval as did *d*-amphetamine, while decreasing responding in the later portion of the interval. Further indications that these two drugs produce common effects were seen in the tolerance and cross-tolerance experiments. For example when the rats were tolerant to *d*-amphetamine, mescaline produced an effect similar to that observed in the drug control. However, the prior exposure to *d*-amphetamine seemingly affected the time course of tolerance development to mescaline. Only three successive days of mescaline injections were required to produce tolerance as compared to the four to seven days needed when the rats were tolerant to LSD. Furthermore, there was an attenuated response to *d*-amphetamine when the rats were tolerant to the effects of mescaline. This effect is similar to a previous report that rats tolerant to the behaviorally disruptive effects of mescaline on fixed-ratio responding showed some degree of cross-tolerance to equieffective

TABLE 3

Tolerance and attempted cross-tolerance with 0.15 mg of d-amphetamine per kg and 0.015 mg of LSD per kg

Treatment Subject	Mean Response Rate								
	First 15 sec			Last 15 sec			Total (75 sec)		
	A11	A12	A15	A11	A12	A15	A11	A12	A15
	responses/interval			*responses/interval*			*responses/interval*		
NaCl[a]									
Upper	0.41	0.38	0.59	2.66	4.82	2.58	6.90	8.75	6.30
Mean	0.26	0.23	0.38	1.83	3.79	2.23	5.40	7.15	4.30
Lower	0.11	0.08	0.17	1.00	2.76	1.88	3.90	5.55	2.30
d-Amphetamine, drug control[b]	1.01 (288)[c]	0.97 (322)	1.24 (226)	3.77 (106)	7.01 (85)	2.86 (28)	9.40 (74)	13.00 (82)	7.60 (77)
LSD, drug control	0.80 (208)	0.76 (230)	0.92 (142)	3.12 (70)	6.74 (78)	2.75 (23)	8.50 (57)	11.30 (58)	7.35 (71)
LSD, tolerance	0.34 (31)	0.37 (61)	0.34 (−11)	2.58 (41)	3.41 (−10)	2.19 (−2)	6.70 (24)	7.45 (4)	5.10 (19)
d-Amphetamine, cross-tolerance	1.19 (358)	0.79 (243)	1.43 (276)	3.42 (87)	6.63 (75)	3.11 (39)	9.00 (67)	12.10 (69)	9.25 (115)
d-Amphetamine, tolerance	0.37 (42)	0.34 (48)	0.35 (−8)	1.97 (8)	4.57 (21)	2.25 (.8)	5.25 (−3)	7.60 (6)	6.00 (40)
LSD, cross-tolerance	1.93 (642)	1.11 (383)	1.01 (166)	3.33 (82)	7.19 (90)	2.94 (32)	10.45 (94)	12.90 (80)	8.35 (94)

[a] Data given are the means of six observations for each animal. The upper and lower limits are 2 S.D. from the mean.

[b] Drug control sessions were separated by at least 72 hours. All other drug sessions were performed on successive days.

[c] Percent change from control rate.

doses of *d*-amphetamine applied *via* the lateral cerebral ventricles but not when injected i.p. (Sparber and Tilson, 1972a). The indication of a partial cross-tolerance after i.p. injection in this, but not in the previous, study (Sparber and Tilson, 1972a) may be due to the greater sensitivity of the FI schedule to detect the behavioral effects of these drugs.

That *d*-amphetamine and mescaline produced similar behavioral effects might be predicted since both drugs possess similar chemical structures and produce common sympathomimetic effects (Rosenberg *et al.*, 1963). Recent reports have indicated additional similarities in the effects of these two drugs. For example, *d*-amphetamine reportedly increases the firing or produces no effect on neurons lying in the midbrain raphe, an area normally inhibited by LSD (Foote *et al.*, 1969), whereas mescaline appears to have a mixed action by increasing the firing of some of these neurons and decreasing the firing of others (Aghajanian *et al.*, 1970). Although *d*-amphetamine and mescaline have been reported to produce differential effects on the release of norepinephrine into lateral ventricular perfusate (Sparber and Tilson, 1972b; Tilson and Sparber, 1971), other investigators have proposed the involvement of norepinephrine in mescaline's mechanism of action (Menon *et al.*, 1967; Leonard and Tonge, 1969). Further investigations to delineate the role that catecholaminergic systems may play in the behavioral effects of mescaline are now in progress.

The data reported here indicate that LSD and mescaline merely share similar components of action rather than act in an identical fashion, or on the same receptor, as has been suggested by some investigators (Wolbach *et al.*, 1962; Snyder and Richelson, 1968; Kang and Green, 1970; Winter, 1971). If LSD and mescaline act on the same central receptor, they should produce essentially the same behavioral effects and show complete cross-tolerance, criteria not supported by our data. Mescaline (1 to 12 mg/kg) did not produce an overall increase in responding similar to the effect of 0.015 mg of LSD per kg nor did

LSD (0.005 to 0.150 mg/kg) produce an increase in responding in the first 15-second segment with a corresponding decrease in responding in the last 15-second segment. The lack of cross-tolerance between the effects of LSD and *d*-amphetamine and the possibility of a unidirectional, partial cross-tolerance between mescaline and *d*-amphetamine also suggest different components of action for LSD and mescaline. Recent investigations have also indicated differences between LSD and mescaline in their effects on the electroencephalogram (Winters, 1968), on serotonin turnover (Freedman *et al.*, 1970) and release (Tilson and Sparber, 1972), on firing of serotonin-containing neurons in the midbrain raphe (Aghajanian *et al.*, 1970) and on the output of urinary catecholamines (Hollister and Moore, 1967, 1968). It is apparent that there are important differences in the effects of LSD and mescaline and, like the psychotomimetic drug class as a whole, there seems to be a low probability of explaining their mechanism(s) of action in simple and unifying terms (Brawley and Duffield, 1972).

In these experiments, tolerance development to the behavioral effects of LSD and mescaline are probably not associated with metabolic changes related to altered microsomal enzyme function. Winter (1971) has reported that brain and liver levels of LSD in partially tolerant rats did not differ from naive subjects. Similar findings have been reported in a study with cats chronically administered with *d*-amphetamine (Ellison *et al.*, 1971). Furthermore, the "false transmitter" hypothesis to account for amphetamine tolerance (Brodie *et al.*, 1970) is reportedly applicable to the peripheral, but not to the central, effects of *d*-amphetamine (Lewander, 1971). There are some indications that serotonin may be involved in the development of tolerance to psychoactive drugs. For example, increases in the synthesis and turnover of serotonin have been reported in animals chronically administered low doses of LSD or *d*-amphetamine (Diaz and Huttunen, 1971, 1972) and increased amounts of ^{14}C-radioactivity from ^{14}C-serotonin were found in the lateral ventricular perfusate of rats tolerant to the behaviorally disruptive effects of *d*-amphetamine (Sparber and Tilson, 1972c).

Tolerance to the behavioral effects of these drugs also may be interpreted within a behavioral context. In this hypothesis, it is suggested that the performance of the subject is initially affected by drug-related stimuli and, after repeated administration of the drug, the subject learns to compensate for these stimulus changes (Thompson and Schuster, 1968). One of the problems with this interpretation is related to drug effects which enhance, rather than disrupt, responding. Schuster *et al.* (1966) have suggested that tolerance would not develop under such circumstances and reported the lack of tolerance development to the rate-increasing effects of 1.0 mg of *d*-amphetamine per kg on FI responding in a single subject experiment. In these studies, we found tolerance to the rate-increasing effects of 0.15 mg of *d*-amphetamine per kg and 0.015 mg of LSD per kg and to the effects of mescaline on responding in the initial segment of the interval. It is apparent that the concept of behavioral tolerance needs clarification and, if the mechanism of tolerance development is to be elucidated, further research is necessary.

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