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Acute and Chronic Effects of LSD and 3,4-Dimethoxyphenylethylamine on Shuttlebox Escape/Avoidance in Rats

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Abstract. Three experiments were conducted in rats to study the effects of acute and chronic LSD and 3,4-dimethoxyphenylethylamine (DMPEA) on acquisition of shuttlebox escape/avoidance and of acute DMPEA on performance in the shuttlebox of pretrained poor performers. In Experiments 1 and 2, separate groups of male hooded rats were injected (i.p.) either once with LSD (0.1 or 0.5 mg/kg),DMPEA (25, 50, or 100 mg/kg) or saline or daily for 5 days with LSD (0.5 mg/kg), DMPEA (25 or 100 mg/kg) or saline before an initial acquisition test. The acute drug groups were retested 24 h later under saline. In Experiment 3, pretrained rats which had achieved a low, stable baseline rate of shuttlebox performance were injected once with DMPEA (50 mg/kg) before a performance test and retested 24 h later under saline. It was found that all LSD treatments decreases escape/avoidance latencies (excitatory effect) on the acquisition test and saline retest, while all DMPEA treatments were without effect.

Key words: LSD — 3,4-Dimethoxyphenylethylamine — DMPEA — Tolerance — Shuttlebox Escape/Avoidance — Acquisition.

Introduction

Bridger and coworkers have previously demonstrated that mescaline administration has an excitatory effect on escape/avoidance behavior in

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rats in three different shuttlebox situations: 1. acutely on acquisition of shuttlebox escape/avoidance (Bridger and Mandel, 1971), 2. chronically on acquisition of shuttlebox escape/avoidance, indicating lack of tolerance to this excitatory effect (Bridger, Mandel, and Stoff, 1973), and 3. acutely on shuttlebox performance of pretrained poor performers (Bridger, Stoff, and Gorelick, 1972). It is important to determine whether mescaline's excitatory effect and lack of tolerance is also true for other hallucinogens, such as LSD, using the same paradigm and strain of animals as in our previous work. Others have already reported that LSD has an excitatory effect on performance of pretrained poor performers of shuttlebox escape/avoidance (Bignami, Robustelli, Janku, and Bovet, 1965).

The reports in the literature dealing with the acute effects of LSD on an initial acquisition test of shuttlebox avoidance have shown an inhibitory effect for 0.25 mg/kg (Sugrue, 1969) or no effect for doses ranging from 0.05 to 0.30 mg/kg (Bignami, 1972; Buxton, 1972). However, the paradigm and strain of animals were different from that used in our laboratory. There are several reports that low doses of LSD (0.05 to 0.40 mg/kg) have an excitatory effect in pretrained animals performing various avoidance tasks (Jarrard, 1963; Key, 1964; Taeschler, Weidmann, and Cerletti, 1960; Torre and Fagiani, 1968) and there is one report that chronic drug treatment in doses ranging from 0.13 to 1.0 mg/kg does not produce tolerance to LSD's excitatory effect on previously learned non-signalled escape behavior (Hamilton, 1960).

It would be of interest to study an endogenously produced compound, 3,4-dimethoxyphenylethylamine (DMPEA) and determine whether this agent has excitatory effects in the 3 different shuttlebox escape/avoidance situations as has been reported for hallucinogens. DMPEA is structurally similar to mescaline, lacking only a methoxy group in position 5 of the benzene ring, shares a catatonia-inducing effect with mescaline in animals (Brown, Lang, and Gershon, 1965; Ernst, 1965), and has been found in the urine of schizophrenics (Friedhoff and Van Winkle, 1962) although its causal role in schizophrenia is controversial (Wyatt, Termini, and Davis, 1971). Bridger and Mandel (1967) reported that acute DMPEA, like mescaline, has an exitatory effect on the potentiated startle response during classical conditioning and there is some suggestion that acute DMPEA, like mescaline, may have an excitatory effect on acquisition of pole-jumping avoidance at low shock intensity (Levis and Caldwell, 1971). In a series of structure-activity relationship studies of mescaline analogues, Smythies and Sykes (1966) have shown that during well-established shuttlebox avoidance acute DMPEA, like mescaline, has an inhibitory effect, but, unlike mescaline (Symthies and Sykes, 1964) does not have a subsequent excitatory effect. There is tolerance to this inhibitory effect, but it develops considerably more slowly for DMPEA

than mescaline (Smythies, Sykes, and Lord, 1966). There are no studies reported in the literature dealing with either acute or chronic effects of DMPEA on acquisition of shuttlebox avoidance, or on performance of pretrained poor performers.

The present report was designed to answer three questions:

1. Will acute administration of LSD and DMPEA produce an excitatory effect on acquisition of shuttlebox avoidance?

2. Will chronic administration of LSD and DMPEA produce tolerance to the effect on acquisition of shuttlebox avoidance?

3. Will acute administration of DMPEA produce an excitatory effect on performance of pretrained poor performers?

This report consists of three experiments: the first dealing with acute effects of LSD and DMPEA on acquisition of shuttlebox escape/avoidance; the second dealing with chronic effects of LSD and DMPEA on acquisition of shuttlebox escape/avoidance; and the third dealing with acute effects of DMPEA on shuttlebox escape/avoidance performance of pretrained poor performers. In Experiment 1, 0.1, 0.5 mg/kg LSD and 25, 50, 100 mg/kg DMPEA were acutely administered to rats prior to an initial acquisition test and a saline retest 24 h later. In Experiment 2, 0.5 mg/kg LSD and 25, 50 mg/kg DMPEA were chronically administered to rats for 5 days prior to an initial acquisition test in order to determine whether there was tolerance to the effect on acquisition. In Experiment 3, 50 mg/kg DMPEA was acutely administered to pretrained poorly performing rats prior to a performance test in the shuttlebox.

Apparatus

The basic apparatus was a Lehigh Valley two-compartment, center-hinged, grid-floored shuttlebox with stainless steel rods of 3/32 in diameter, spaced 11/32 in apart, and a 3-1/4 in center hurdle. Both a Mallory Sonalert auditory signal (2800 Hz tone) and a 12 V light bulb were mounted on the rear wall of each compartment. These two devices, driven by 10 Hz pulses, comprised the compound Conditional Stimulus (CS). Only one pair of these devices were activated at a time depending upon the compartment in which the *S* was at the beginning of a trial. The Unconditional Stimulus (US) was a 1.3 mA electric shock delivered to the grid floor by a Grason-Stadler Model No. 6070B scrambled shock generator. The CS-US interval was 5 sec; a hurdle jump during this interval terminated the CS and prevented the US. A jump occurring more than 5 sec after the onset of the CS terminated both CS and US.

The time between CS onset and jump was automatically timed to the nearest 0.1 sec by a Lafayette Instrument Co. Model 5710 Event Timer and recorded on a Sodeco printout counter. Each trial began 20 sec after the previous hurdle jump. The shuttlebox and shock generator were

placed in a darkened, sound-deadened chamber; the fully automated digital control and recording equipment was placed in an adjoining instrument room.

Experiment 1

LSD

Method

Subjects. The *Ss* were 45 experimentally naive, male, hooded rats (Marland Farms), 90—100 days old, maintained on *ad-lib* food and water in individual living cages.

Procedure. The *Ss* were randomly assigned to one of three groups prior to two successive days of testing. Each *S* received 200 trials per day and was injected i.p. 10 min prior to testing. On Day 1, Group I was injected with 0.1 mg/kg LSD dissolved in 1.0 ml saline; Group II with 0.5 mg/kg LSD; and Group III with 1.0 ml saline. On Day 2 all *Ss* received 1.0 ml saline.

Results

The 200 trials per day were divided into two 100 trial blocks with each *S* assigned as a score his mean latency for each block. This procedure yielded two (i.e., Day 1 and Day 2) 3×2 analyses of variance with repeated measures on one factor (halves). Table 1 presents the group mean latencies of acute LSD and Saline on Days 1 and 2 in each trial block.

Day 1: The analysis of variance demonstrated that there were significant differences among the overall group means ($F = 13.94$, $df = 2/42$, $P < 0.001$). Although there was a significant halves main effect ($F = 139.50$, $df = 1/42$, $P < 0.001$) demonstrating that the overall mean latency on the second half was lower than the first half, there was no statistically significant Groups $\times$ Halves interaction ($F = 2.56$, $df = 2/42$, $P > 0.05$).

Table 1. Group mean latencies ($\pm$S. D.) for effects of acute LSD and DMPEA on acquisition (Experiment 1)

Groups	Dose (mg/kg)	Day 1: Drug test		Day 2: Saline test	
		First half	Second half	First half	Second half
I LSD	0.1	2.13 ± 0.67	1.40 ± 0.60	1.93 ± 0.91	1.75 ± 0.78
II LSD	0.5	2.56 ± 0.62	1.39 ± 0.51	2.49 ± 1.06	2.04 ± 0.76
III Saline[a]	—	3.71 ± 1.21	2.61 ± 1.09	3.18 ± 1.30	2.88 ± 1.17
IV DMPEA	25	3.67 ± 1.10	2.22 ± 1.03	3.01 ± 1.43	2.60 ± 1.20
V DMPEA	50	4.38 ± 1.23	2.75 ± 1.42	3.42 ± 1.72	3.13 ± 1.40
VI DMPEA	100	4.55 ± 0.91	2.97 ± 1.37	3.00 ± 1.20	2.72 ± 1.17
VII Saline[b]	—	3.92 ± 1.18	3.03 ± 1.59	3.25 ± 1.31	2.68 ± 0.84

[a] Saline control for LSD.
[b] Saline control for DMPEA.

Further analysis of the differences among group means using the Newman-Keuls *post-hoc* technique described by Winer (1971, pp. 191 ff.) demonstrated that although both LSD groups had a lower mean latency than the Saline group ($P < 0.01$) the mean latencies for the two dosages did not differ ($P > 0.05$).

Day 2: The analysis of variance yielded results analogous to those obtained on Day 1, i.e., a significant difference among group means ($F = 5.74$, $df = 2/42$, $P < 0.025$), a significant halves main effect ($F = 12.27$, $df = 1/42$, $P < 0.001$), and no indication of an interaction ($F < 1.0$).

The *post-hoc* analysis of the overall group means yielded results identical to those obtained on Day 1, i.e., both LSD groups had a significantly lower mean latency than saline ($P < 0.01$), but did not themselves differ ($P > 0.10$).

DMPEA

Method

Subjects. The *Ss* were 60 experimentally naive, male, hooded rats (Marland Farms), 90—100 days old, maintained on *ad-lib* food and water in individual living cages.

Procedure. The *Ss* were randomly assigned to one of four groups prior to two successive days of testing. Each *S* was injected i.p. 10 min prior to a 200 trial avoidance test on each day. On Day 1, Group IV was injected with 25 mg/kg DMPEA dissolved in 1 ml saline; Group V with 50 mg/kg DMPEA, Group VI with 100 mg/kg DMPEA; and Group VII with 1.0 ml saline. On Day 2 all *Ss* received 1.0 ml saline.

Results

The method of analysis was identical to that used with the LSD groups. Table 1 presents the group mean latencies of acute DMPEA and Saline on Days 1 and 2 in each trial block.

Day 1: The data analysis yielded only a significant halves main effect ($F = 160.60$, $df = 1/56$, $P < 0.001$). There were no significant differences among the overall drug means ($F = 1.32$, $df = 3/56$, $P > 0.10$) nor was there any interaction ($F = 2.48$, $df = 3/56$, $P > 0.05$).

Day 2: The data analysis yielded results identical to those obtained on Day 1, i.e., a significant halves main effect ($F = 21.61$, $df = 1/56$, $P < 0.001$), no significant differences among drug means ($F < 1.0$), and no interaction ($F < 1.0$).

Experiment 2

LSD

Method

Subjects. The *Ss* were 30 experimentally naive, male, hooded rats (Marland Farms), 90—100 days old, maintained on *ad-lib* food and water in individual living cages.

Table 2. Group mean latencies (±S. D.) for effects of chronic LSD and DMPEA on acquisition (Experiment 2)

Groups	Dose (mg/kg)	Halves	
		First half	Second half
I LSD	0.5	2.62 ± 0.87	1.78 ± 0.70
LSD (acute)[a]	0.5	2.56 ± 0.62	1.39 ± 0.51
II Saline[b]	—	4.39 ± 1.22	2.98 ± 1.05
III DMPEA	25	3.42 ± 1.21	2.24 ± 0.97
DMPEA (acute)[a]	25	3.67 ± 1.10	2.22 ± 1.03
IV DMPEA	100	4.35 ± 1.31	2.58 ± 0.84
DMPEA (acute)[a]	100	4.55 ± 0.91	2.97 ± 1.37
V Saline[c]	—	3.54 ± 0.72	2.52 ± 0.80

[a] Data taken from Experiment 1.
[b] Saline control for LSD.
[c] Saline control for DMPEA.

Procedure. The *Ss* were randomly assigned to one of two groups. Group I *Ss* were given an i.p. injection of 0.5 mg/kg LSD dissolved in 1.0 ml saline on each of four consecutive days and returned to their living cages. On the fifth day each *S* was again given 0.5 mg/kg LSD and after 10 min had elapsed was placed in the testing apparatus for a 200 trial acquisition test. The procedure for Group II was identical to that of Group I except that all injections were of 1.0 ml saline.

Results

The 200 trials were divided into two 100 trial blocks with each *S* assigned as a score his mean latency for each block. This procedure yielded a 2×2 analysis of variance with repeated measures on one factor (halves). Table 2 presents the group mean latencies of chronic LSD and Saline in each trial block. The analysis of variance yielded both a significant group main effect ($F = 19.14$, $df = 1/28$, $P < 0.001$), demonstrating that the LSD group had a faster mean latency than Saline, and a significant halves main effects ($F = 90.33$, $df = 1/28$, $P < 0.001$), demonstrating that the overall mean latency for the second half was significantly faster than for the first half. There was, in addition, a significant Groups × Halves intercation ($F = 5.66$, $df = 1/28$, $P < 0.025$). Further analysis, using the techniques described by Winer (1971, pp. 529 ff.) for the four possible comparisons demonstrated that the LSD group had a significantly lower mean latency than Saline during both the first and second half ($P < 0.001$) and that both groups had significantly lower mean latencies during the second half than during the first ($P < 0.001$).

DMPEA

Method

Subjects. The *Ss* were 45 experimentally naive, male, hooded rats (Marland Farms), 90—100 days, maintained on *ad-lib* food and water in individual living cages.

Procedure. The *S*s were randomly assigned to one of three groups. Group III *S*s were given an i.p. injection of 25 mg/kg DMPEA dissolved in 1.0 ml saline on each of four consecutive days and returned to their living cages. On the fifth day each *S* was again given 25 mg/kg DMPEA and after 10 min had elapsed was placed in the testing apparatus for a 200 trial acquisition test. The procedure for Group IV and Group V was identical to that of Group III except that injections for Group IV were of 100 mg/kg DMPEA while those for Group V were 1.0 ml saline only.

Results

The 200 trials were divided into two 100 blocks with each *S* assigned as a score his mean latency for each block. This procedure yielded a 3×2 analysis of variance with repeated measures on one factor (halves). Table 2 presents the group mean latencies of chronic DMPEA and Saline in each trial block. The results of the analysis of variance failed to demonstrate any significant differences among the overall means for the three groups ($F = 1.81$, $df = 2/42$, $P > 0.10$). There was, however, a significant halves main effect ($F = 142.91$, $df = 1/42$, $P < 0.001$) again demonstrating an overall lower mean latency in the second half, than the first, and a significant ($F = 4.32$, $df = 2/42$, $P < 0.025$) Groups $\times$Halves interaction. Further analysis of the interaction term demonstrated that each group had a lower mean latency during the second half than the first ($P < 0.001$). However there were significant differences among the group means only during the first half ($F = 3.88$, $df = 2/42$, $P < 0.05$), but not during the second half ($F < 1.0$). As can be seen in Table 2 this result was due to the *longer* mean latency of the DMPEA 100 mg/kg group as compared to either the DMPEA 25 mg/kg or Saline group.

Experiment 3

Method

Apparatus. The apparatus used was identical to that used in a previous experiment which showed mescaline's excitatory effect on pretrained poor performers (Bridger *et al.*, 1972). This apparatus differs from that used in Experiments 1 and 2 in three respects: 1. the CS was simply a 12V bulb, rather than being compound; 2. the US was 1.0 mA electric shock; 3. the shuttlebox was divided into two compartments by a floor to ceiling partition with a 2 and $^1/_2$ inch square opening cut in the center of the bottom edge.

Subjects. The *S*s were 11 male, hooded rats (Blue Spruce), 130—155 days old, maintained on *ad-lib* food and water in individual living cages. All *S*s had achieved a stable, low baseline rate of avoidance behavior because of their use in previous experiments. This baseline rate was not permanently affected by prior drug treatments, nor was it affected by 6 day rest periods interposed to allow drug effects to wear off.

Procedure. Following a previous experiment, all *S*s were tested with saline to establish that their performance had returned to baseline rates. Then, on the first day following a 6 day rest period, each *S* was given DMPEA (50 mg/kg i.p. in 1 ml saline) 20 min prior to receiving 100 trials in the shuttlebox. On the following day, each *S* received 1.0 ml saline 20 min before another 100 trials in the shuttlebox.

Table 3. Group mean latencies (±S. D.) for effects of acute DMPEA on poor performers (Experiment 3)

Predrug saline	DMPEA 50 mg/kg	Postdrug saline
7.26 ± 1.42	8.89 ± 2.49	7.29 ± 1.76

Results

Each *S* was assigned as a score his mean latency for the 100 trials. Matched pair *t*-tests were done to compare the predrug saline day (prior to the 6 day rest period) with the drug day and the postdrug saline day. Table 3 presents the group mean latencies. There was no significant change in mean latency on the drug day ($t = -1.95$, $df = 10$, $P > 0.05$), although there was a suggestion of an inhibitory effect. Nine of the 11 *S*s showed an increase in latency, with a predrug saline-drug latency difference of -2.61 ± 1.70 sec (mean ± S.D.). Two *S*s showed a decrease in latency, with a mean predrug saline-drug latency difference of $+1.78$ sec. There was no significant difference in mean latency between the pre- and postdrug saline days ($t = -0.032$, $df = 10$, $P > 0.9$). Six of 11 *S*s showed an increase in latency, while 5 showed a decrease.

Discussion

The present report demonstrated that acute administration of 0.1 or 0.5 mg/kg LSD produced an excitatory effect, in terms of faster avoidance response latencies, on an initial test of shuttlebox avoidance (Experiment 1). Furthermore, the excitatory effect is not subject to tolerance after 5 daily injections of LSD (Experiment 2). The acute excitatory effect for 0.1 or 0.5 mg/kg LSD was still present on the following saline test day (Day 2) suggesting that it may be due to learning rather than performance variables. These results indicate that mescaline's previously reported excitatory effects on acquisition of shuttlebox avoidance after acute and chronic administration (Bridger and Mandel, 1971; Bridger, *et al.*, 1973) are also true for LSD. These similarities, plus the reports of cross tolerance between mescaline and LSD on inhibition of well-learned appetitively reinforced behavior in rats (Appel and Freedman, 1968; Winter, 1971) and on some autonomic and psychological effects in man (Wolbach, Isbell, and Miner, 1962), suggest that these two hallucinogenic agents share a common mode of action. All doses of DMPEA were without an effect on acquisition of shuttlebox avoidance after acute (Experiment 1) and chronic administration (Experiment 2) as well as on performance of pretrained poor performers after acute administration (Experiment 3).

The finding of an excitatory effect in Experiment 1 for LSD is contradictory with reports in the literature which show that acute administration of LSD either inhibits or has no effect on an initial acquisition test of shuttlebox avoidance (Bignami, 1972; Buxton, 1972; Sugrue, 1969). The major differences between the studies reported in the literature which did not show an excitatory effect for LSD on acquisition of shuttlebox avoidance and our experiments which did show an excitatory effect for LSD is that the former studies used a non-directional CS and albino strain of rats while the experiment reported here used a directional CS and Long-Evans hooded rats.

The results from Experiment 1 that a single administration of LSD has an excitatory effect on the saline test 24 h after injection (Day 2) as well as its previously mentioned excitatory effect on an initial drug acquisition test (Day 1), may be interpreted as facilitation of learning rather than performance. If LSD and/or its metabolites are no longer active when additional avoidance trials are given 24 h after drug injection, the improvement in avoidance observed on the saline test day (Day 2) then could not be attributed to performance variables such as sensory, motivation, and response processes. However, if LSD's effects do not dissipate completely over a 24 h period then there may be continued improvement in avoidance due to associational or learning factors. In order to examine this possibility in a preliminary experiment, a group of male, hooded rats (250—300 g) was injected with LSD 0.5 mg/kg (i.p.) and given an initial shuttlebox avoidance acquisition test 24 h later. After the 24 h postinjection period elapsed, the LSD group did not differ from a comparable saline control in mean response latency on the initial shuttlebox avoidance test. This suggests that LSD's excitatory effect on the saline test day (Day 2) is not due to residual effects of the drug 24 h later and must be explained in terms of a previous shuttlebox avoidance experience under the influence of the drug. Furthermore, there is indirect evidence from Experiment 1 supporting this conclusion from the fact that the lower dose (0.1 mg/kg) is still more excitatory than the higher dose (0.5 mg/kg) on the saline test day (Day 2) which would not be expected if the excitatory effect present 24 h later is due to residual drug effects.

The failure of chronic drug treatment to evoke tolerance to LSD's excitatory effect in Experiment 2 is consistent with 3 other reports in the literature where chronic LSD was excitatory on aversively motivated behavior: 1. during well-learned nonsignalled escape after 7 daily injections of 0.13, 0.26, and 0.50 mg/kg LSD (Hamilton, 1960), 2. during pole-climbing avoidance, in terms of the incidental behavioral observations of excitement, increased alertness, hyperkinesia, quicker response times, jumps, and myoclonic jerks, after 6—7 daily injections of

0.05 mg/kg LSD (Banerjee, 1971), and 3. once asymptotic shuttlebox avoidance responding was achieved after 4 daily injections of 0.05, 0.10, and 0.20 mg/kg LSD (Bignami, 1972).

The demonstrated lack of tolerance to LSD's excitatory effect after five daily drug injections is inconsistent with the reports of tolerance to LSD's inhibition of well-learned appetitively reinforced behavior in rats (Appel and Freedmann, 1968; Freedman *et al.*, 1958; Winter, 1971) and to some of its autonomic and psychological effects in humans (Abramson, Jarvik, Gorin, and Hirsch, 1956; Wolbach *et al.*, 1962). The lack of tolerance to the excitatory effects of an exogenous hallucinogen, reported previously for mescaline and presently for LSD, makes an endogenous hallucinogen model of psychosis more viable, since psychosis is often a chronic state lasting longer than the time required for tolerance to develop. Bridger (1973) has suggested that the inhibitory effects of hallucinogens in animals may be analogous to the pleasant "psychedelic" effects in humans, both of which occur in relatively nonstressful situations and are subject to tolerance. However, the excitatory effects in animals may be analogous to the more pathological "psychotomimetic" effects in humans, both of which occur in relatively stressful environments and are not subject to tolerance (Bowers, 1972; Glass and Bowers, 1970; Kleber, 1970; Tucker, Quinlan, and Harrow, 1972).

The failure to find an excitatory effect of DMPEA on acquisition of shuttlebox avoidance after acute (Experiment 1) or chronic (Experiment 2) administration or on shuttlebox performance of pretrained poor performers after acute administration (Experiment 3) is at variance with previous work in these avoidance situations for both mescaline (Bridger and Mandel, 1971; Bridger *et al.*, 1973; Bridger *et al.*, 1972) and LSD (Bignami *et al.*, 1965) and the present report for LSD. These animal findings suggest that DMPEA is behaviorally different from other hallucinogenic agents such as mescaline and LSD. Furthermore, these animal studies are consistent with the clinical and metabolic studies in humans that oral administration of acute or chronic DMPEA, with and without monoamine oxidase inhibitors, is psychologically inactive (Brown, McGeer, and Moser, 1968; Charalampous, 1971; Hollister and Friedhoff, 1966).

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