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Facilitation and Disruption by Mescaline and 3,4-Dimethoxyphenylethylamine of Shock Avoidance in Rats

DAVID A. GORELICK and WAGNER H. BRIDGER*

Departments of Pharmacology and Psychiatry, Albert Einstein College of Medicine
Bronx, New York 10461, U.S.A.

Abstract. The effects of mescaline hydrochloride (4.95–79.2 mg/kg i.p.) and its non-hallucinogenic analogue 3,4-dimethoxyphenylethylamine hydrochloride (DMPEA) (12.5–100 mg/kg i.p.) on shock avoidance in a shuttlebox were studied in male Long-Evans rats trained to high (above 88%, good performers) or low (below 6%, poor performers) stable base-line avoidance rates. In good performers, mescaline and DMPEA caused a dose-dependent decrease in avoidance rate (ED50's 44.6 and 39.2 mg/kg, respectively) without affecting presession (5-min adaptation period) or intertrial shuttlebox crossings. In poor performers, mescaline caused a dose-dependent increase in avoidance rate (ED50 = 24.8 mg/kg) and intertrial crossings, without affecting presession crossings. The results suggest that mescaline, but not DMPEA, has dual facilitative and disruptive effects on avoidance behavior at similar dose ranges. The facilitative, but not the disruptive, effect may be related to changes in motor activity.

Key words: Mescaline – 3,4-Dimethoxyphenylethylamine-DMPEA – Shuttlebox – Avoidance.

The hallucinogenic drug mescaline can both facilitate and disrupt conditioned behavior at the same dose. For example, mescaline (50 or 100 mg/kg) improves the performance of naive rats during acquisition of a shock-avoidance task, while disrupting the performance of experienced, well-performing rats on the same task (Bridger and Mandel, 1971; Bridger et al., 1973). Even at the same stage of training, mescaline (12.5 or 25 mg/kg) disrupts the performance of experienced well-performing rats in a positively reinforced or shock-avoidance task during the initial part of the experimental session, while improving performance during the later part of the session (Bailey and Pradhan, 1972; Smythies and Sykes, 1964). Other hallucinogenic drugs such as LSD or DMT can also have opposite behavioral effects depending on the stage of training or time of drug action (Banerjee, 1971; Smythies et al., 1967; Wray, 1972).

The ability to produce opposite behavioral effects at the same dose raises the question of whether a single mechanism of action can account for both effects, or whether mescaline has two distinct actions. One approach to this question is to determine whether mescaline's opposite effects can occur while keeping constant the experimental variables of stage of training and time of drug action. Another approach would be to study dependent measures of behavior, which might suggest the nature of the behavioral changes produced by mescaline and whether the same behavoral changes could account for both the facilitative and disruptive effects. For example, mescaline might increase motor activity. This action could be facilitative during acquisition of shock-avoidance behavior (e.g., by attenuating freezing), but disruptive in experienced, well-performing animals (e.g., by increasing maladaptive competitive or intertrial responses).

Drug dose is another experimental variable that influences the behavioral effect of hallucinogens. For example, mescaline improves the performance of experienced, well-performing rats in a positively reinforced or shuttlebox shock-avoidance task at low doses (6.3 or 12.5 mg/kg), while disrupting performance at higher doses (12.5 or 25 mg/kg) (Bailey and Pradhan, 1972; Smythies and Sykes, 1964; Tonge and Leonard, 1972). LSD has a similar dual effect on experienced, well-performing rats, with low doses improving performance and high doses disrupting it

* To whom offprint requests should be addressed

(Appel, 1971; Jarrard, 1963; Marquis et al., 1973; Ray and Bivens, 1966; Torre and Fagiani, 1968). It is possible that stage of training or time of drug action could influence the effective drug dose, making the opposite behavioral effects of mescaline a function of dose, as in the examples cited above. Thus, it would be important to study the occurrence of mescaline's effects over a broad dose range.

3,4-Dimethoxyphenylethylamine (DMPEA), a close structural analogue of mescaline (3,4,5-trimethoxyphenylethylamine), has aroused interest because of its reported presence in the urine of schizophrenics (Friedhoff and Van Winkle, 1962; Siegel and Tefft, 1971), although its relation to schizophrenia has remained controversial (Smith and Hartley, 1973; Wyatt et al., 1971). It resembles mescaline in producing catatonia in animals (Brown et al., 1965; Ernst, 1965) and disrupting the performance of experienced well-performing animals (e.g., Bueno et al., 1969; Vogel and Horwitt, 1967), but, unlike mescaline, it is not hallucinogenic in humans (Brown et al., 1968; Charalampous, 1971; Hollister and Friedhoff, 1966) and does not have a facilitative effect that is dependent on stage of training or time of drug action (Smythies and Sykes, 1966; Stoff et al., 1974). There are only two reports in the literature showing a facilitative effect of DMPEA on conditioned behavior: improved performance during acquisition of a classically conditioned response (Bridger and Mandel, 1967) and some improved performance in some rats during acquisition of a shock-avoidance task (Levis and Caldwell, 1971). Stoff et al. (1974), however, have previously reported the failure of one dose of DMPEA (50 mg/kg) to facilitate the shuttlebox shock-avoidance performance of experienced, poorly-performing rats, with response latency as the dependent variable.

The present report has three purposes:

1. To determine the role played by stage of training, time of drug action, and drug dose in producing the facilitative and disruptive behavioral effects of mescaline. This was done with a dose-response study of the effects of mescaline on shuttlebox shock avoidance in Long-Evans rats. Since this strain has both poorly and well-performing individuals, stage of training (in the sense of exposure to the behavioral task) could be kept constant, while varying the actual performance level (and number of reinforcements received) of the subjects.

2. To determine what behavioral changes might accompany the facilitative and disruptive effects of mescaline. Dependent variables of response rate and response latency were measured which could reflect such factors as responsivity to the discriminative stimulus, responsivity to the negative reinforcer, and motor activity.

3. To determine whether the property of having both facilitative and disruptive effects on conditioned behavior is shared by mescaline with the structurally related but nonhallucinogenic drug DMPEA in an experimental paradigm where mescaline does have both effects.

METHODS

Subjects. *S*s were 30 male Long-Evans rats (300–630 g) with a stable base-line avoidance rate of greater than 88% (14 good performers) or less than 6% (16 poor performers).

Apparatus. Shock-avoidance training and testing were conducted in a Lehigh Valley Electronics model no. 146-04 rat toggle floor shuttlebox divided into two equal-sized compartments by a floor-to-ceiling metal partition with a 6×6.5 cm rectangular opening centered along the bottom edge. The discriminative stimulus was 17 W white light pulsing at 10 Hz (50 ms duty cycle), but only the lamp mounted in the compartment in which the *S* was located was activated at the beginning of each trial. The negative reinforcer was 1.0 ma scrambled electric shock delivered to the grid floor of the shuttlebox by a Grason-Stadler model no. E6060B or 700 shock generator. The discriminative stimulus came on 5 s before the shock; a shuttlebox crossing during this interval terminated the stimulus and prevented shock onset (avoidance response). A crossing more than 5 s after stimulus onset terminated both stimulus and shock (escape response). The intertrial interval was 20 s. Response latencies (to the nearest 0.1 s) and shuttlebox crossings were measured and recorded on paper tape by a Lafayette Instrument Co. model no. 5710 event timer. The shuttlebox and shock generator were housed in a darkened, sound-attenuated room adjacent to the room housing the event timer and electromechanical digital equipment that automatically controlled the presentation of stimuli.

Procedure. Ss were trained until they achieved a stable, base-line avoidance rate. The criterion for stability was an avoidance rate within (plus or minus) ten percentage points of the rate achieved during the previous session. Test days followed 6-day rest periods during which Ss remained undisturbed in their home cages. These rest periods allowed the effects of previous drug treatments to dissipate and prevented the possible development of tolerance from closely spaced drug injections. After each test day, *S*s were given successive retraining days until they returned to base-line avoidance rates (defined as a rate within ten percentage points of the previous base-line rate). Thus, at least one retraining day occurred after each drug test day and six days in the home cage were interposed between a test day and the last previous retraining (base-line) day.

Ss received saline on all training and retraining days. A saline test day was run 6 days before each drug experiment to ensure the stability of avoidance behavior over the 6-day rest intervals which preceded each test day. Mescaline hydrochloride or DMPEA hydrochloride was given on test days, according to a repeated-measures design. Twelve poor performers and nine good performers received each of six mescaline doses (4.95, 9.9, 19.8, 39.6, 59.4, or 79.2 mg/kg) in random order on separate test days, while 10 poor performers and nine good performers received each of five DMPEA doses (12.5, 25, 50, 75, or 100 mg/kg). There was some overlap between drug experiments, with six poor performers and four good performers receiving both drugs.

The same procedure was used on all training, retraining, and test days. Ss were given an i.p. injection (1 ml), returned to their home cages for 15 min, then placed in the shuttlebox for a 5-min presession adaptation period during which no stimuli were presented. The 100-trial shock-avoidance session began immediately after the adaptation period.

RESULTS

Data were collected on five dependent variables: (1) avoidance rate, (2) number of shuttlebox crossings during the 5-min presession adaptation period (presession crossings), (3) total number of shuttlebox crossings during the session's intertrial intervals (intertrial crossings), (4) trials (avoidance mean response latency on avoidance latency), and (5) mean response latency on escape trials (escape latency). Each variable was analyzed separately for each drug and performance group using a one-way (drug dose) repeated-measures analysis of variance (Winer, 1971). Post hoc comparisons between group means were made with Duncan's multiple range test (Winer, 1971). The method of Litchfield and Wilcoxon (1949) was used for quantal analysis of the avoidance rate data.

There were no significant differences on any of the dependent variables among the seven base-line days for the mescaline groups or the six base-line days for the DMPEA groups (with two exceptions), indicating that the base-line day performance of the *S*s remained stable throughout the experiment. Therefore, the mean of the base-line day scores for each *S* on the stable variables was used as the base-line (control) score for later analysis of treatment effects. The two cases where significant differences occurred among base-line day scores were the avoidance latency variable in good performers given mescaline and the escape latency variable in poor performers given DMPEA. Since base-line day performance in these experimental groups for these variables was not stable throughout the experiment, these variables were not used as measures of drug effects in these groups. Post hoc analyses for the remaining variables showed no significant differences between base-line means and saline test day means (with one exception), indicating that performance remained stable over the 6-day rest periods that separated each test day from the previous base-line day. The one case where the saline test day score differed significantly from the base-line score was the presession crossings variable in poor performers given DMPEA. Since performance on this variable was not stable over the 6-day rest period, it was not used as a measure of drug effect in this group.

In poor performers, mescaline caused a significant increase in avoidance rate (Fig. 1; $F = 6.67$, $df = 7/77$, $P < 0.001$), with an ED50 of 24.8 mg/kg (100 μmoles/kg) and 95% confidence limits of 11.6–52.2 mg/kg (47–212 μmoles/kg). Post hoc analyses showed a clear dose-dependent trend: the groups receiving the four highest doses differed significantly from the base-line and saline groups, while the groups receiving the three highest doses also differed significantly from the 4.95 mg/kg group. Furthermore, the 59.4 mg/kg group differed significantly from the 9.9 and 19.8 mg/kg groups, while the 39.6 mg/kg group differed significantly from the 9.9 mg/kg group. These differences suggest that, while 4.95 mg/kg and 9.9 mg/kg were ineffective doses, 19.8 mg/kg and higher doses were effective in facilitating avoidance behavior. The highest dose used (79.2 mg/kg) produced a motor disability in 3 of the 12 *S*s tested: hind limb hyperextension with inability to keep the plantar surface of the paws in contact with the grid floor of the shuttlebox. Mescaline's facilitative effect was present throughout the shock-avoidance session at all the doses at which it occurred. However, the effect increased as the session progressed, significantly so at the 59.4 mg/kg dose ($F = 5.48$, $df = 4/44$, $P < 0.005$; one-way ANOVA by 20-trial blocks). There was also a slight, but significant increase in avoidance rate during the session on the base-line days ($F = 7.20$, $df = 4/44$, $P < 0.001$).

Mescaline's facilitative effect on avoidance rate was not reflected in the avoidance or escape latencies. Although there was a significant effect on escape latency ($F = 3.26$, $df = 7/77$, $P = 0.004$), post hoc analyses showed that this was due to the increased latencies in the 79.2 mg/kg group, attributable to the 3 *S*s in this group that suffered a motor disability. Mescaline had no significant effect on avoidance latency ($F = 0.52$, $df = 7/67$, $P = 0.82$).

Mescaline produced increases in presession and intertrial crossings of borderline significance ($F = 2.05$, $df = 7/77$, $P = 0.06$ for presession crossings; $F = 2.10$, $df = 7/77$, $P = 0.053$ for intertrial crossings). Post hoc analyses for presession crossings showed no significant differences among groups, but for intertrial crossings showed significant differences between the base-line and saline groups and the 39.6 and 59.4 mg/kg groups. There was no significant correlation between avoidance rate and intertrial crossings at those two doses ($r = 0.54$, $t = 2.03$, $P = 0.07$ for 39.6 mg/kg; $r = 0.43$, $t = 1.52$, $P = 0.16$ for 59.4 mg/kg), but there was a significant correlation at 79.2 mg/kg ($r = 0.81$, $t = 4/44$, $P = 0.001$) and for all treatments combined ($r = 0.51$, $t = 5.79$, $P < 0.001$).

In good performers, mescaline caused a significant decrease in avoidance rate (Fig. 1; $F = 10.06$, $df = 7/56$, $P < 0.001$), with an ED50 of 44.6 mg/kg (180 μmoles/kg) and 95% confidence limits of 22.0–89.9 mg/kg (89–363 μmoles/kg). This ED50 was not significantly different from the ED50 for mescaline's facilitative effect in poor performers. Post hoc analyses showed a clear dose-dependent trend: the groups receiving the three highest doses differed significantly from the base-line, saline, 4.95, and 9.9 mg/kg groups, while the group receiving the highest dose also differed significantly from the 19.8, 39.6, and 59.4 mg/kg

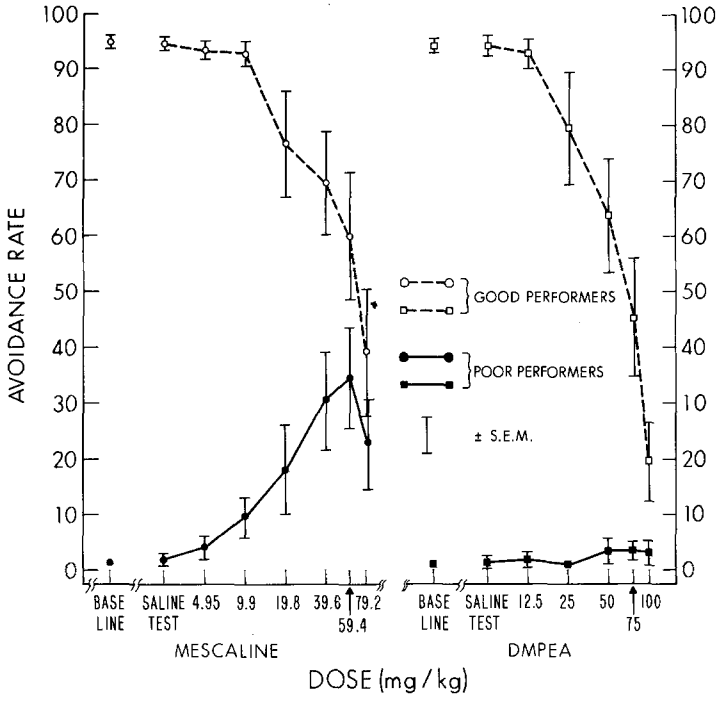

Fig. 1. Effect of mescaline hydrochloride and DMPEA hydrochloride on avoidance rate of well and poorly performing Long-Evans rats

groups. These differences suggest that the three lowest doses were ineffective in disrupting avoidance behavior, while the three highest doses were effective. The highest dose used (79.2 mg/kg) produced a motor disability in 3 of the 9 *S*s tested which was identical to that produced by the same dose in 3 of the 12 poor performers tested. However, a disruptive effect still occurred in the 6 *S*s without motor disability. Mescaline's disruptive effect was present throughout the shock-avoidance session at all the doses at which it occurred. However, at two doses the effect decreased as the session progressed, significantly so at 39.6 mg/kg ($F = 3.0$, $df = 4/32$, $P < 0.05$; one-way ANOVA by 20-trial blocks). There was also a slight but significant warm-up effect present on the base-line days ($F = 11.0$, $df = 4/32$, $P < 0.001$), with the first trial block having a significantly lower avoidance rate than the later trial blocks.

Mescaline's disruptive effect on avoidance rate was not fully reflected in the escape latencies. Although there was a significant effect on escape latency ($F = 3.77$, $df = 7/56$, $P = 0.002$), post hoc analyses showed that this was due to the increased latencies in the 79.2 mg/kg group attributable to the 3 *S*s in this group that suffered a motor disability.

Mescaline had no significant effect on presession or intertrial crossings in good performers ($F = 0.99$, $df = 7/56$, $P = 0.45$ for presession crossings; $F = 1.38$, $df = 7/56$, $P = 0.23$ for intertrial crossings).

In poor performers, DMPEA, unlike mescaline, had no significant effect on avoidance rate (Fig. 1; $F = 0.93$, $df = 6/54$, $P = 0.48$), intertrial crossings ($F = 0.33$, $df = 6/54$, $P = 0.92$), or avoidance latencies ($F = 0.74$, $df = 6/25$, $P = 0.63$).

In good performers, DMPEA, like mescaline, caused a significant decrease in avoidance rate (Fig. 1; $F = 17.33$, $df = 6/43$, $P < 0.001$), with an ED50 of 39.2 mg/kg (180 μmoles/kg) and 95% confidence limits of 24.4 – 63.1 mg/kg (112 – 290 μmoles/kg). This ED50 is identical, on a molar basis, with the ED50 for mescaline's disruptive effect, indicating that DMPEA is about as potent as mescaline in disrupting avoidance behavior. Post hoc analyses showed a clear dose-dependent trend: the groups receiving the three highest doses differed significantly from the base-line, saline, and 12.5 mg/kg groups, while the group receiving the highest dose differed significantly from all the other groups. Furthermore, the 75 mg/kg group also differed significantly from the 25 mg/kg group. These differences suggest that the two lower doses were ineffective in disrupting avoidance behavior, while the three higher doses were effective. The highest dose used (100 mg/kg) produced a motor disability in 3 of the 9 *S*s tested which was similar to that produced by the highest dose of mescaline. A disruptive effect still occurred in the *S*s without motor disability. DMPEA's disruptive effect was present throughout the shock-avoidance session at all the doses at which it occurred. However, the effect decreased significantly as the session progressed ($F = 14.27$, $df = 4/28$, $P < 0.001$ for 50 mg/kg; $F = 7.29$, $df = 4/28$, $P < 0.001$ for 75 mg/kg; $F = 3.38$, $df = 4/28$, $P < 0.025$ for 100 mg/kg; one-way ANOVA by 20-trial blocks). There was also a slight but significant warm-up effect

present on the base-line days ($F = 9.04$, $df = 4/32$, $P < 0.001$), with the first trial block having a significantly lower avoidance rate than the later trial blocks.

DMPEA's disruptive effect on avoidance rate was not fully reflected in the avoidance or escape latencies. Although there were significant increases in escape latency ($F = 2.34$, $df = 6/51$, $P = 0.045$) and avoidance latency ($F = 6.49$, $df = 6/46$, $P < 0.001$), post hoc analyses showed that these were due to the increased latencies in the 100 mg/kg group, attributable to the 3 *S*s in this group that suffered a motor disability.

DMPEA had no significant effect on presession or intertrial crossings in good performers ($F = 2.17$, $df = 6/43$, $P = 0.065$ for presession crossings; $F = 0.87$, $df = 6/43$, $P = 0.53$ for intertrial crossings).

All the drug effects reported above were temporary ones disappearing within 24 or 48 h of the drug test day. Mesacline's disruptive effect in good performers was still present 24 h later on the (first) post-drug (saline) day ($F = 5.48$, $df = 6/45$, $P < 0.001$ for avoidance rate). Post hoc analyses showed that this was due to the decreased avoidance rate in the two groups that had received the highest doses: 81.6 (5.8) 59.4 mg/kg and 72.4 (10.0) at 79.2 mg/kg (mean (S.E.M.)). At neither dose was there a significant difference from base-line avoidance rate remaining by the second post-drug day [mean (S.E.M.)]: 93.9 (1.6) at 59.4 mg/kg ($t = 0.83$, $P > 0.5$) and 80.5 (7.0) at 79.2 mg/kg ($t = 2.31$, $P > 0.05$). For the other experimental groups, there were no significant drug effects remaining by the first post-drug day (mescaline in poor performers: $F = 1.91$, $df = 6.65$, $P = 0.09$ for avoidance rate; DMPEA in good performers: $F = 1.07$, $df = 5/29$, $P = 0.40$ for avoidance rate).

DISCUSSION

The present study demonstrated the ability of mescaline to produce dose-dependent facilitative and disruptive effects on conditioned behavior while keeping constant the strain of experimental subject (Long-Evans rats), the stage of training (in terms of exposure to the task), the time of drug action (20–60 min after drug injection), and the drug dose. Both effects occurred over similar dose ranges (19.8–79.2 mg/kg and 39.6–79.2 mg/kg) and with similar potencies (ED50's of 24.8 and 44.6 mg/kg not significantly different). By excluding the influence of these experimental variables, these results are consistent with, although they do not prove, the existence of two separate behavioral actions of mescaline.

Analysis of the dependent variables other than avoidance rate provides some evidence as to what behavioral changes accompany mescaline's facilitative and disruptive effects. The absence of any significant change in avoidance latency in poor performers and the continued presence of orienting responses to the discriminative stimulus during experimental sessions suggest that mescaline caused no simple change in reactivity to the discriminative stimulus. The absence of any significant changes in escape latency (except for increases at the highest dose attributable to motor disability in some *S*s) suggests that mescaline caused no analgesia or change in reactivity to the negative reinforcer. In good performers, the absence of any significant decrease in presession or intertrial crossings or of competitive stereotyped responses or gross motor disability (except in some *S*s at the highest dose) suggests that mescaline's disruptive effect was not related to changes in motor processes. In poor performers, mescaline significantly increased intertrial crossings at two (39.6 and 59.4 mg/kg) of the four doses causing a facilitative effect. This suggests that increased motor activity could account for at least part of mescaline's facilitative effect. However, the absence of any significant correlation between avoidance rate and intertrial crossings, except at the highest dose and for all treatments combined, provides some evidence against this interpretation. The significant correlation for all treatments combined may have been an artifact of the dose-dependent effect of mescaline on each variable. For none of the dependent variables did a similar change accompany both facilitative and disruptive effects, suggesting that a single behavioral action may not account for mescaline's opposite behavioral effects.

Base-line response rate is another experimental variable that can influence the behavioral effects of drugs. For example, LSD's facilitative effect at low doses in a positively reinforced conditioned task is inversely correlated with the base-line response rate (Appel, 1971). It is not clear which response rate in the present discriminative, discrete trial task is the appropriate one for consideration of the influence of response rate on mescaline's behavioral effects. All responses (shuttlebox crossings) had the same typology, but some were evoked by the discriminative stimulus (avoidance responses) or negative reinforcer (escape responses), while some were apparently spontaneous and not reinforced (intertrial crossings). Both good and poor performers had the same base-line rate of successful escape responses (although differing in number of escape opportunities), but good performers had a significantly higher base-line mean avoidance rate and a greater mean number of base-line intertrial crossings (7.1 vs. 2.6, $t = 2.12$, $P = 0.05$). These base-line differences suggest that base-line response rate may influence the occurrence of mescaline's opposite behavioral effects, with facilitation occurring at low rates and disruption at high rates.

This role of response rate or performance level is consistent with past reports showing facilitative effects of hallucinogens in naive animals during acquisition (poor performance levels) and disruptive effects at the same doses in more experienced animals (good performance levels) (Banerjee, 1971; Bridger and Mandel, 1971; Bridger et al., 1973; Stoff et al., 1974). Two exceptions have been reported to the pattern of facilitation in naive animals and disruption in experienced animals, but these are actually consistent with the postulated role of performance level. Gorelick and Bozewicz (1975) reported a disruptive effect of mescaline on shuttlebox shock-avoidance acquisition in naive F 344/f mai rats, but this is an inbred strain which performs so well on avoidance tasks that the control group achieved an overall avoidance rate of 71.5% on the first acquisition session. Bignami et al. (1965) reported a facilitative effect of LSD on shuttlebox shock-avoidance behavior in experienced rats, but this effect occurred only during the first half of the experimental session, when avoidance rates were low because of a large warm-up effect. Even the reported biphasic effect in experienced animals during a single experimental session (Bailey and Pradhan, 1972; Smythies and Sykes, 1964; Smythies et al., 1967; Wray, 1972) can be fit within the performance level pattern by postulating that the initial disruptive effect lowers the performance level of the experienced animals enough to allow the facilitative effect to occur. Incidental observations during the present study on four rats that switched stable performance levels are also consistent with the performance level pattern of mescaline effects. In two good performers that became stable poor performers, mescaline's effect changed from disruption (when good performers) to facilitation (when poor performers). In two poor performers who became stable good performers, mescaline's facilitative effect disappeared, and a disruptive effect (when a good performer) appeared in one animal.

Neither the present experiment nor past reports provide evidence as to what specific factor differentiating good and poor performers (e.g., rate of reinforcement) determines the occurrence of facilitation or disruption. One hypothesis that has been advanced is that increased stress (such as might be produced by the increased number of electric shocks received by animals with poor performance in avoidance tasks) is an important factor in determining when hallucinogens will have a facilitative effect. However, in a direct test of the stress hypothesis, it was found that increased exposure to a nonspecific stressor (electric foot-shock) did not cause mescaline to have a facilitative effect on shuttlebox shock-avoidance performance, but rather potentiated its disruptive effect in good performers (Gorelick and Bridger, 1975).

Mescaline's ability to produce both facilitative and disruptive effects in the present experiment was not shared by DMPEA, a nonhallucinogenic mescaline analogue. DMPEA had no facilitative effect in poor performers, but caused a dose-dependent disruptive effect in good performers with a potency similar to mescaline. These results are consistent with numerous past reports of the disruptive effect of DMPEA in experienced, well-performing animals (e.g., Bueno et al., 1969; Smythies and Sykes, 1966) and the absence of reports of a facilitative effect in situations where mescaline facilitates behavior (Smythies and Sykes, 1966; Stoff et al., 1974). The similarity between DMPEA and mescaline in potency of disruptive effect is contrary to several previous reports which had suggested that DMPEA was about one-half as potent as mescaline in many situations (Bueno et al., 1969).

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