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Severe Aggression in Rats Induced by Mescaline But Not Other Hallucinogens

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Abstract. Pairs of male Sprague-Dawley rats were administered mescaline, lysergic acid diethylamide (LSD), psilocin, N,N-dimethyltryptamine (DMT), 3,4-dimethoxyphenylethylamine (DMPEA), or 5-hydroxydopamine (5-OHDA) IP prior to being placed in a shock-elicited aggression situation. When foot shock was delivered, controls struck each other with their forepaws, but never engaged in either biting or injurious fighting. Mescaline-treated rats (50 or 250 mg) rarely struck each other, but engaged in nearly lethal biting. While LSD (25–400 μg/kg), psilocin (2.0 mg/kg), and DMT (5 mg/kg) produced some biting, this did not significantly differ from controls and never resulted in injuries. At higher doses, psilocin, DMT, and DMPEA decreased the amount and intensity of fighting. Rats treated with 5-OHDA (8–200 mg/kg) or LSD (25–400 μg/kg) did not differ from controls. These results suggest that mescaline's ability to induce pathological aggression in rats exposed to foot shock is not shared by other hallucinogens or nonhallucinogenic mescaline analogues.

Key words: Mescaline – Hallucinogens – 3,4-Dimethoxyphenylethylamine 5-hydroxydopamine – Shock-elicited aggression – Rats

A common experimental paradigm for studying irritable aggression consists of exposing a pair of animals to electric foot shock. Under these conditions, rats typically assume an upright 'boxing' posture and strike each other with their forepaws when foot shock is delivered. Unlike some other aggression paradigms, biting or other injurious behavior rarely occur, and the fighting rarely outlasts the termination of foot shock (Sbordone and Carder, 1974). Using the shock-elicited aggression paradigm, it has been reported (Sbordone and Carder, 1974; Sbordone and Garcia, 1977; Sbordone et al., 1978) that in rats mescaline not only increases the duration of fighting, but also produces 'pathological' aggression, which consists of a change in the topography of fighting from upright boxing to nearly lethal biting. Furthermore, the fighting episodes become less tied to the delivery of foot shock and may continue for several hours in the absence of shock (Sbordone, 1976).

At the present time, mescaline, lysergic acid diethylamide (LSD), N,-N-dimethyltryptamine (DMT), and delta^9-tetrahydrocannibol (THC) are the only hallucinogenic drugs that have been investigated in a shock-elicited aggression situation. LSD (20–160 μg/kg IP) has been shown to increase the number of fights in this situation in rats (Brunaud and Siou, 1959; Sheard et al., 1977), but higher doses (640 μg/kg) IP) failed to increase fighting (Sheard et al., 1977). DMT also has been found to have a biphasic effect on shock-elicited aggression in rats. Low doses (0.125 and 1.0 mg/kg) have been reported to produce a 'weak and inconsistent' excitatory effect, while higher doses (4 and 8 mg/kg) had a depressant effect (Walters et al., 1978). The literature concerning the effects of acute administration of THC on shock-elicited fighting behavior in rats is rather complex and contradictory (Carlini, 1978). For example, dosages of 0.25–0.5 mg/kg IP have been reported to increase fighting, while dosages of 1.0–2.0 mg/kg IP were reported to decrease it (Carder and Olsen, 1972). However, Manning and Elsmore (1972) have reported that dosages of 0.06–6.4 mg/kg IP had no effect.

In the study of each hallucinogenic drugs (except mescaline), the proportion or number of fights that occur due to shock was used as the sole dependent measure of fighting. Since these investigators did not report whether their animals engaged in either vicious biting or injurious fighting, it is not known whether LSD or DMT produced pathological aggression in any

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of these studies. For example, Sbordone and Carder (1974) found that while all of the mescaline-treated rats' fights consisted of biting attacks (the vast majority of which penetrated the victim's skin and resulted in nearly lethal injuries) no difference was found in the number of fights that occurred due to shock between mescaline-treated rats and controls (which only engaged in relatively innocuous upright boxing episodes). This finding has been replicated in later studies (Sbordone and Garcia, 1977; Sbordone et al., 1978). The inadequary of the above dependent measure of fighting in the shock-elicited aggression situation has been previously pointed out by Ghiselli and Thor (1974) and Krsiak and Steinberg (1969).

Drugs that are nonhallucinogenic structural analogues of mescaline have never been investigated in this situation. For example, 3,4-dimethoxyphenylethylamine (DMPEA) and 3,4,5-trihydroxyphenylethylamine (5-hydroxydopamine) (5-OHDA) are close structural analogues of mescaline (3,4,5-trimethoxyphenylethylamine). DMPEA resembles mescaline in some animal behavior effects (Gorelick and Bridger, 1977), but is not hallucinogenic in humans (e.g., Charalampous, 1971). 5-OHDA is an adrenergic false neurotransmitter (Tranzer and Thoenen, 1967) which can have nonspecific sedating effects when administered intraventricularly (Brus et al., 1977). There have been no reports in the literature regarding the effects of either drug on any type of aggressive behavior.

The purpose of the present study is to determine whether mescaline's ability to induce pathological aggression in rats is shared by other hallucinogenic drugs or by nonhallucinogenic structural analogues of mescaline. This was done by comparing the effects, on shock-elicited aggression in male Sprague-Dawley rats, of three dosage levels of mescaline, LSD, DMT, psilocin, DMPEA, and 5-OHDA.

Materials and Methods

Subjects. Subjects were 200 experimentally naive male Sprague-Dawley rats (Simonsen Breeding Laboratory, Gilroy, CA) 90–100 days old (330–550 g) which housed individually with food and water continuously available.

Apparatus. Aggression testing was performed in a clear Plexiglas cylindrical chamber with inside dimensions of 30 × 30 cm. Electric foot shock was delivered through a grid floor consisting of stainless steel rods 0.634 cm in diameter, spaced 1.27 cm apart (center to center). The shock source was a David (model 276) shock generator operating through a Davis (model 255) grid scrambler, with shock duration and intershock interval controlled by two Davis (model D 501) time-interval generators. Shock intensity was continuously monitored by a Tektronics (model 502) oscilloscope. Behavioral data and parameters of shock delivery were recorded concurrently on Davis digital counters, electric cumulative timers, and an Esterline-Angus 20-channel event recorder. The latter device provided a permanent paper-tape record of each aggressive episode with respect to shock presentation. The aggression test chamber was housed in a sound-deadened room adjacent to the room housing the rest of the apparatus. Both observers sat in this adjacent room and observed the test chamber through a one-way glass window.

Procedure. Rats were weighed at the beginning of the experiment and paired on the basis of similar body weight (within 10 g). Four pairs were randomly assigned to each of six drug treatments at either a control, low, medium, or high dosage level: Mescaline hydrochloride (0, 20, 50, or 250 mg/kg); LSD (0, 25, 100, or 400 µg/kg); DMT fumarate (0, 1, 5, or 25 mg/kg); psilocin (0, 0.4, 2.0, or 10 mg/kg); DMPEA hydrochloride (0, 8, 40, 200 mg/kg); or 5-OHDA (0, 8, 40, or 200 mg/kg). The dosages of DMPEA and 5-OHDA were roughly equimolar to mescaline, while the dosages of LSD, DMT, and psilocin were based on their potency relative to mescaline. All drugs except psilocin were dissolved in distilled water and administered IP to both members of each pair 20 min prior to placement in the test chamber. Psilocin was dissolved in 25 mmol ascorbic acid plus 50 mmol sodium phosphate (pH 5.6) with HCl added equivalent to the amount of psilocin free base. Each control group (0 dosage level) received the corresponding drug vehicle.

Immediately after placement in the test chamber, each pair of rats received 100 foot shock of 4.0 mA and 1.5-s duration, with an intershock interval of 30 s. The entire test session lasted about 52.5 min. During the session, one observer pressed one of six microswitches to indicate which type of aggressive behavior was occurring and released the switch when the behavior ended. A second observer recorded any idiosyncratic behaviors or unusual events. Both observers were blind to drug treatment.

Agressive behavior (fighting) was coded into six mutually exclusive categories according to the criteria of Sbordone and Garcia (1977): Shoving-lunging (pushing, shoving, or striking partner with one or both forepaws); boxing (striking partner with boxing-like movements of forepaws); lunge and bite attempt (lunging forward and attempting to bite partner); mild biting (bite does not penetrate skin); moderate biting (bite penetrates skin, but does not draw blood or cause serious injury); or severe biting (bite draws blood or causes serious injury). Previous work had shown that these categories were easily observable and distinguishable, and could be coded with an interobserver reliability coefficient of 0.98 (Sbordone and Garcia, 1977).

Results

Differences in aggressive behavior were examined using a two-way design with type of drug and dosage level as between-subject factors. The dependent variables were the number of fights (total number of fighting episodes during the experimental session regardless of type), number of bites (the combined total of mild, moderate, and severe biting episodes), duration of fighting (the combined total duration of all fighting categories measured in seconds), and the index of pathological aggression, which assigned scores of 1 to shoving-lunging, 2 to boxing, 3 to biting attempts, 4 to mild biting, 5 to moderate biting, and 6 to severe biting episodes: The frequency of observations for each type of aggressive behavior was multiplied by its respective weight, and the sum of all types of fighting was then divided by the total number of observations (Sbordone and Garcia, 1977). A square-root transformation was applied to the number of fights and to the number of bites to make the cell variances more homogenous for

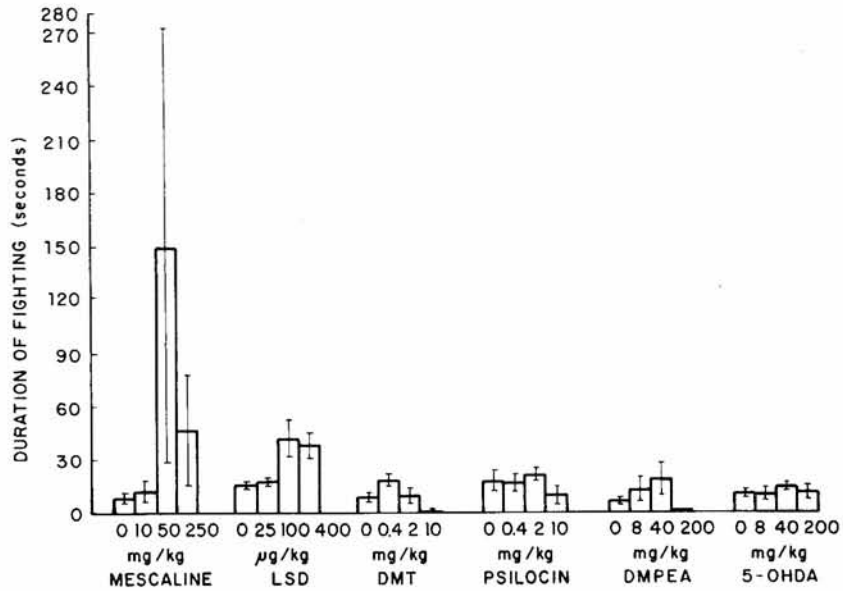

Fig. 1
Mean duration of fighting for six drug treatment conditions at four dosage levels ±S.E.

these variables (Winer, 1971). A logarithmic transformation was applied to the scores for duration of fighting to normalize their distribution (Winer, 1971).

A multivariate analysis of variance (MANOVA) revealed significant main effects attributable to the type of drug [$F(12, 236) = 6.608$, $P < 0.001$] and to the dosage level [$F(12, 188) = 5.080$, $P < 0.001$), and a significant interaction of drug type × dosage level [$F(60, 279) = 2.398$, $P < 0.001$]. Subsequent univariate analyses (Hummel and Sligo, 1971) revealed significant drug type × dosage level differences for the number of fights [$F(15, 74) = 1.978$, $P < 0.028$], the number of bites [$F(15, 74) = 4.403$, $P < 0.001$], the duration of fighting [$F(15, 74) = 2.886$, $P < 0.001$], and the index of pathological aggression [$F(15, 74) = 5.115$, $P < 0.0001$]. For each of these measures of aggressive behavior, the two-way interaction was analyzed further by assessing the simple main effects of dosage level for each of the drugs, and then by performing appropriate a posteriori comparisons using Duncan's multiple range tests.

Analysis of the simple main effects indicated that mescaline significantly increased the duration of fighting [$F(3, 74) = 4.74$, $P < 0.01$] (Fig. 1), the index of pathological aggression [$F(3, 74) = 15.36$, $P < 0.0001$] (Fig. 2), and the number of bites [$F(3, 74) = 26.54$, $P < 0.00001$] which increased from a mean of 0.0 bites with vehicle to (±SEM) 1.8 ± 4.0, 38.5 ± 35.6, and 20.0 ± 19.1 bites at 10, 50, and 250 mg/kg, respectively, of mescaline. However, mescaline had no effect on the number of fights [$F(3.74) = 0.59$, $P > 0.50$], which averaged about 30–50 fights per session at all dosages. A posteriori tests revealed that both the 50 and 250 mg/kg dosages of mescaline produced significantly longer fighting episodes ($P < 0.05$), more biting ($P < 0.001$), and a higher index of pathological aggression ($P < 0.05$) than either 10 mg/kg or control groups. There were no differences between the latter two groups on any variable ($P > 0.40$). The 250 mg/kg group had a shorter duration of fighting than the 50 mg/kg group (Fig. 1) although this difference was not statistically different ($P > 0.25$). This was probably due severe ataxia produced by the higher dosage of mescaline. These two groups did not differ significantly in the index of pathological aggression (Fig. 2) ($P > 0.25$) or any other aggression variables.

Analysis of the simple main effects of LSD indicated that this drug had no effect on the number of fights [$F(3,74) = 1.19$, $P > 0.25$], the duration of fighting $F(3,74) = 1.19$, $P > 0.30$], or the index of pathological aggression [$F(3, 74) = 0.145$, $P > 0.50$] (Figs. 1 and 2). Although LSD-treated rats were observed to engage in some biting (mean of 4 bites per session), this did not differ statistically from controls [$F(3,74) = 1.22$, $P > 0.251$] and never produced injuries.

Analysis of the simple main effects of DMT and psilocin revealed that these drugs significantly decreased the number of fights [$F(3,74) = 6.84$, $P < 0.001$; $F(3,74) = 2.78$, $P < 0.05$, respectively]. The highest dosage (25 mg/kg) of DMT decreased the number of fights to 1.5 ± 3.0 per session as compared to 32.75 ± 9.9 for the vehicle, while the highest dosage of psilocin reduced fighting to 24.75 ± 28.6 bouts per session as compared to 48 ± 22.1 for the vehicle. DMT also significantly decreased the duration of fighting [$F(3,74) = 6.49$, $P < 0.001$; $F(3,74) = 2.66$, $P = 0.05$,

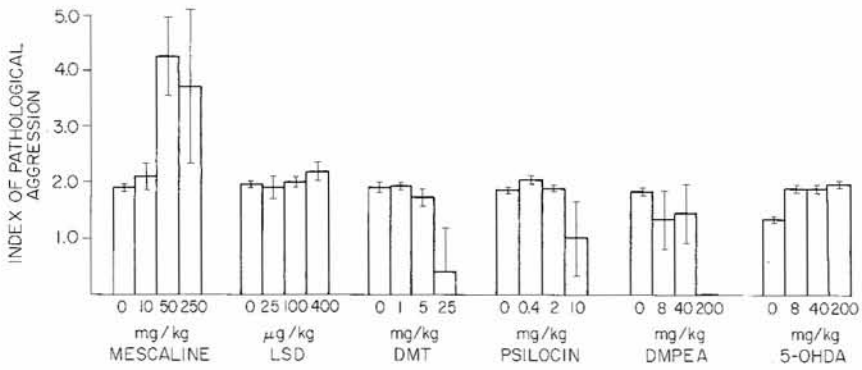

Fig. 2
Mean index of pathological aggression for six drug treatment conditions at four dosage levels ±S.E.

respectively] (Fig. 1), and lowered the index of pathological aggression [$F(3,74) = 6.00$, $P < 0.001$] (Fig. 2). A posteriori tests indicated that in all cases the highest dosage of drug differed from the other dosages and controls ($P < 0.05$), while there were no significant differences between the medium and low dosages and the controls ($P > 0.25$). Neither DMT nor psilocin significantly affected biting [$F(3,74) = 0.013$, $P > 0.50$; $F(3,74) = 0.107$, $P > 0.50$, respectively], although the medium dosages produced 1–2 bites per session in some of the animals.

Both DMPEA and 5-OHDA produced behavioral sedation at the medium and high dosages. However, analysis of the simple main effects revealed that only DMPEA produced a statistically significant decrease in the number of fights [$F(3,74) = 5.45$, $P < 0.002$], the duration of fighting [$F(3,74) = 6.10$, $P < 0.001$], (Fig. 1) and the index of pathological aggression [$F(3,74) = 7.46$, $P < 0.002$] (Fig. 2). 5-OHDA had no effect on the number of fights [$F(3,74) = 0.46$, $P > 0.50$], the duration of fighting [$F(3,74) = 0.34$, $P > 0.50$], the number of bites [$F(3,74) = 0.00$, $P > 0.50$], or the index of pathological aggression [$F(3,74) = 0.02$, $P > 0.50$].

Discussion

In the present experiment, mescaline produced dose-dependent pathological aggression in rats exposed to foot shock, confirming prior reports (Carder and Sbordone, 1975; Sbordone and Carder, 1974; Sbordone and Garcia, 1977). None of the other drugs, regardless of the dosage administered, produced this effect. LSD, DMT, and psilocin produced minimal amounts of biting that did not differ statistically in frequency from controls. Since biting was never seen in any controls, its occurrence suggests that these hallucinogens may share a trace of mescaline's ability to induce pathological aggression. However, the frequency and intensity of LSD-induced biting was the same at all three dosage levels, suggesting that higher doses would not have produced full-fledged pathological aggression. Biting induced by DMT and psilocin was confined to the medium dose, suggesting that a significant effect was not missed because of use of inappropriate dosage levels. Psilocin, DMT, and DMPEA all decreased the number and duration of fights at the highest doses used. This finding is consistent with the general sedating and behaviorally inhibiting effects of these drugs at high doses (e.g., Gorelick and Bridger, 1977; Sheard, 1977). 5-OHDA, while having no effect on aggression variables, was also behaviorally sedating at the two highest dosages. This is consistent with a prior report of sedating effects of intraventricularly administered 5-OHDA (Brus et al., 1977), and suggests that peripherally administered 5-OHDA does not have as potent a sedating action as DMPEA, perhaps because it does not cross the blood-brain barrier as effectively.

Two different hypotheses may account for the present data. The first suggests that mescaline-induced pathological aggression is due to a decrease in the activity of the serotonergic median raphe system. For example, Aghajanian et al. (1970) have shown that mescaline inhibits the firing of serotonergic raphe neurons by indirect negative feedback on serotonergic neurons. Treatments which decrease raphe neuronal activity such as lesions on specific raphe nuclei (Jacobs and Cohen, 1976) or administration of the serotonin synthesis inhibitor *P*-chlorophenylanine (PCPA) (Ellison and Bresler, 1974; Sheard, 1977), have been found to increase shock-elicited fighting in rats. Thus, mescaline's neuropharmacological effect of decreasing raphe neuronal activity may result in increasing the duration and intensity of shock-elicited fighting behavior. This hypothesis, however, does not adequately explain why LSD and DMT failed to increase the duration and intensity of fighting in the present experiment, since these drugs also inhibit the firing of raphe neurons (Aghajanian et al., 1970). Thus, the data in the present study suggest the median raphe system may not

play an important role in mescaline-induced pathological aggression.

The second hypothesis argues that mescaline-induced pathological aggression is due to increased central nervous system (CNS) catecholaminergic activity, which mediates mescaline's excitatory behavioral effects (Gorelick and Bridger, 1977) and ability to induce CNS arousal (Winters, 1974; Winters and Wallach, 1970). Since LSD and DMT do not share mescaline's ability to increase CNS catecholaminergic activity, these drugs might not share mescaline's ability to induce pathological aggression. This hypothesis would explain why LSD and DMT failed to enhance shock-elicited fighting behavior in the present study. The ability of the dopamine receptor agonist apomorphine (AP) to induce spontaneous biting in rats (e.g., McKenzie, 1971; Patni and Dandiya, 1974) is consistent with a CNS catecholaminergic role in pathological aggression. However, this hypothesis does not adequately explain why the stimulant drug amphetamine, which also increases CNS catecholaminergic activity, either inhibits or has no effect on shock-elicited fighting behavior (Eichelman and Thoa, 1973; Geyer and Mandell, 1973; Lal et al., 1968; Powell et al., 1973). Thus mescaline-induced pathological aggression may not be the direct result of excitatory behavioral properties mediated by increased CNS catecholaminergic activity.

The finding, in the present study, that LSD failed to significantly increase shock-elicited fighting behavior, contradicts previous reports that LSD enhances fighting in this situation (Brunaud and Siou, 1959; Sheard et al., 1977). This discrepancy may be due to differences in methodology, including the criteria used to identify aggressive behavior in these studies. In both prior LSD studies, fighting was recorded when the rats made contact in an upright posture, whereas in the present study the nature of this contact was more precisely defined. Since visual observation of the topography of the fighting behavior indicated that LSD-treated rats were highly reactive to shock and engaged in considerable upright threat postures, it is possible that the present results would be consistent with the findings of the above investigators if their broader criteria of aggressive behavior had been used.

In the present study, 4.0 mA shock intensity was used because it does not cause tissue damage and produces consistent behavioral effects. One prior LSD study (Sheard et al., 1977) used a lower shock level (2.0 mA), but it is not clear how differing shock levels might alter fighting. Ulrich and Azrin (1962) reported that the probability of shock-elicited fighting in drug-free rats was an inverted U-shaped function, with the peak at 2.0 mA. Powell et al. (1969), however, reported that maximum fighting occurred at 4.0 mA. More recently, Follick and Knutson (1974) reported no difference between 2.0 and 4.0 mA. None of these investigators, however, administered drugs to their animals. It is possible that hallucinogenic drugs may change the animal's sensitivity to shock, since such changes have been reported from hormonal changes (e.g., Beatty and Fessler, 1977; Gispen et al., 1973) and from adrenergic changes (Lal et al., 1970; Stolk et al., 1974). Thus, it is possible that mescaline's enhancement of pathological aggression could be due to a lowering of the shock threshold in rats. This explanation, however, is inconsistent with visual observations of mescaline-treated rats (50 mg/kg) which indicate that they are considerably less reactive to shock than controls (Sbordone and Carder, 1974), and contradicts the only report in the literature on the effect of hallucinogens on shock thresholds in rats, which found that mescaline slightly increased shock threshold (Leifer and Bridger, 1976). Thus, mescaline-induced pathological aggression in rats does not appear to be due to a lowering of shock thresholds.

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