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Effects of N,N-Dimethyltryptamine (DMT) and 5-Methoxy-N,N-dimethyltryptamine (5-MeODMT) on Shock Elicited Fighting in Rats[1]

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WALTERS, J. K., M. H. SHEARD AND M. DAVIS. *Effects of N,N-dimethyltryptamine (DMT) and 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) on shock elicited fighting in rats.* PHARMAC. BIOCHEM. BEHAV. 9(1) 87–90, 1978.—Rats were tested for shock elicited fighting under various doses of N,N-dimethyltryptamine (0.12, 0.25, 0.50, 1.0, 4.0, 8.0 mg/kg) and 5-methoxy-N,N-dimethyltryptamine (0.06, 0.12, 0.5, 2.0 mg/kg). Both drugs produced an inhibition of fighting at higher doses but no significant effects at lower doses. The effects of these drugs on shock elicited fighting, as well as on other behaviors, thus differ from those of another indole hallucinogen, d-lysergic acid diethylamide, and are discussed in relation to their effects on single unit activity of the raphe-serotonin system and their interaction with other neurotransmitter systems.

N-N-Dimethyltryptamine 5-Methoxy-N,N-dimethyltryptamine Shock elicited fighting Hallucinogens Serotonin

RECENTLY Sheard, Astrachan and Davis [16] reported that the indole hallucinogen d-lysergic acid diethylamide (LSD) had differential effects on shock elicited fighting (SEF) behavior in rats depending on the dose employed. Low doses of LSD (20 to 160 μg/kg) facilitated fighting whereas a higher dose (640 μg/kg) had no significant effect. An attempt was made to interpret these findings with data from single cell studies in which LSD's effects were determined on midbrain raphe neurons as well as on neurons postsynaptic to raphe cells [2, 3, 4, 11]. Such studies have shown low doses of LSD to specifically inhibit raphe neurons and have little effect postsynaptically. Higher doses, however, are capable of inhibiting both raphe cells and those postsynaptic to the raphe.

Thus fighting might be facilitated at low dose of LSD when inhibitory raphe neurons cease firing. Fighting might be unaffected or inhibited at higher doses when postsynaptic cells which are excitatory to SEF also decreases their firing. Such a mechanism was proposed by Davis and Sheard [7] to explain LSD's similar biphasic dose-response effect on acoustic startle.

Other indole hallucinogens also influence the acoustic startle response. Both N,N-dimethyltryptamine (DMT) and psilocybin have been shown to biphasically affect startle as did LSD, although their facilitation was less pronounced [6,9]. Surprisingly, 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) influenced startle responding in a quite different manner (Davis *et al.*, submitted). It produced monotonic increases in startle amplitude over a wide range of doses from 0.12 to 8.0 mg/kg. No hint of a biphasic dose-response function was obtained.

It was the purpose of the present study to determine the generality of the relationship between drug effects on single cells of the raphe serotonin system and SEF behavior using DMT and 5-MeODMT.

METHOD

A total of 316 male albino Sprague-Dawley rats (Charles River Co.) were used. They weighed between 275–350 g at the time of experimentation and were paired on the basis of weight with animals living apart. Rats were housed four to a cage in a colony room maintained on a 12:12 light-dark cycle. Food and water were freely available.

Shock elicited fighting was tested in a 30×28×24 cm Plexiglas and metal cage which had a grid floor of 0.5 mm parallel bars. This cage was housed in a dimly lighted Lehigh Valley sound attenuated chamber. Fighting was observed through a window from a darkened room. The chamber fan produced a background noise level of about 55 db through-

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out. A Lehigh Valley shocker and scrambler delivered shocks to the grid floor. Shock intensities, shock duration and intershock interval (ISI) were controlled by solid state circuitry.

Prior to drug treatment, 12 pairs of rats were pretested to determine baseline levels of SEF. During pretesting rats were allowed 5 min to adapt to the chamber before receiving 15 shocks of 1 sec duration, five each at 1.0, 1.5, 2.0 mA with a 15 sec ISI. Fights were defined as a directed movement toward the opponent resulting in contact plus one of the following: biting, sparring, upright attack posturing or supine submissive posturing adopted by the attacked rat. Based on the total number of fights for each of the 12 pairs during pretesting, rats were divided into either two matched groups of six pairs or three matched groups of four pairs (depending on the experiment), each having similar mean levels of SEF.

Two or three days after pretesting, each matched group was designated for injection with a different dose of a given drug. Doses and number of pairs at each dose were as follows 0.12 (18 pairs), 0.25 (30), 0.50 (12), 1.0 (9), 4.0 (17) and 8.0 mg/kg (11) for DMT; 0.06 (16), 0.12 (18), 0.50 (16) and 2.0 mg/kg (12) for 5–MeODMT. DMT was prepared by dissolving it in 10 drops of 1 N hydrochloric acid, adding the 0.9% NaCl vehicle and then adjusting the pH to 6.5 with 1 N sodium hydroxide. 5–MeODMT was prepared by dissolving it in 10 drops of glacial acetic acid, adding the distilled water vehicle and then adjusting the pH to 6.5 with 1 N sodium hydroxide. All animals were tested twice, once after drug injection and once after an injection of the vehicle alone, thus serving as their own controls. Half were given the drug first and two days later the vehicle, while the other half were given the vehicle first and then the drug. Drugs and vehicles were given IP in a 1 ml injection volume. Immediately after injection the rats were placed in the test chamber for 5 min of adaption. Thirty, 1-sec shocks were then delivered, five each in the following order: 1.0, 1.5, 2.0, 2.0, 1.5 and 1.0 mA. A 15-sec ISI was used with 1 min between every five shocks. Fewer pairs of rats were tested at drug doses where the results were clear-cut; additional pairs were tested at drug doses where the results required further verification.

RESULTS

Figure 1 shows the mean percent of total trials on which fighting occurred for those rats receiving DMT. There was no marked facilitation of SEF at any of the doses used. Rather, DMT appeared to have little effect at low doses but a pronounced inhibitory effect at high doses. A three-way analysis of variance revealed significant effects of Drug, $F(1,90)=9.30$, $p<0.003$, Shock Intensity, $F(2,180)=59.70$, $p<0.001$, and Drug×Dose Interaction, $F(5,90)=5.54$, $p<0.001$. Individual comparisons using paired t tests confirmed the lack of facilitation by DMT. There were no significant differences between the saline and DMT tests at any dose until the 4.0 mg/kg dose was reached. Here the animals fought significantly less under DMT at the 1.5 mA, $t(16)=2.62$, $p<0.02$, and the 2.0 mA, $t(16)=2.44$, $p<0.05$ shock intensities. The suppression of fighting was even greater at the 8.0 mg/kg dose with significantly less fighting under DMT at all three intensities: 1.0 mA, $t(10)=4.82$, $p<0.001$, 1.5 mA, $t(10)=5.04$, $p<0.001$, and 2.0 mA, $t(10)=3.29$, $p<0.01$.

Figure 2 gives the percent fighting scores for groups which received 5–MeODMT. The trend across doses is similar to that for DMT seen in Fig. 1. The apparent facilitation of SEF at the 0.06 dose of 5–MeODMT was not confirmed statistically. A three-way analysis of variance revealed significant effects of Dose, $F(3,58)=3.93$, $p<0.01$, Shock Intensity, $F(2,116)=35.05$, $p<0.001$, Drug×Dose Interaction, $F(3,58)=3.87$, $p<0.01$ and Dose×Shock Intensity Interaction, $F(6,116)=3.06$, $p<0.01$. The only significant comparisons were at 2.0 mg/kg where 5–MeODMT treatment suppressed fighting at both 1.5 mA, $t(11)=3.66$, $p<0.001$, and 2.0 mA, $t(11)=2.57$, $p<0.01$.

DISCUSSION

The results show that both DMT and 5–MeODMT affected SEF in a similar manner. If there was any facilitation of SEF at all by these drugs at low doses it was extremely slight, difficult to detect and probably shock intensity dependent. Several additional pairs of rats were tested at lower doses of each drug (0.06 and 0.03 mg/kg DMT; 0.03 mg/kg 5–MeODMT) but no facilitation of fighting was observed. On the other hand, both DMT and 5–MeODMT produced a pronounced depression of SEF at higher doses.

The doses of DMT and 5–MeODMT chosen for this study were in the range of doses which have been shown to affect the acoustic startle response ([6], Davis *et al.*, submitted). The reason for this choice was that other drugs affecting the serotonin system such as p-chloramphetamine [8,17] and LSD [7,16] have produced similar effects on both startle and SEF at comparable doses. This experiment provides the first major exception to that generalization. DMT gave a biphasic dose-response function with acoustic startle but produced no facilitation with SEF. DMT has been reported to produce a dose dependent disruption of conditioned avoidance responding with rats in a shuttle box [18]. Here too there was no evidence for any facilitation at low doses like that found with LSD in avoidance situations. 5–MeODMT produced monotonic increases in startle as the dose increased but only served to depress SEF at higher doses. A recent study with 5–MeODMT in two Stumptail macaque monkeys reported that some behaviors show a dose dependent biphasic effect (e.g., wet shakes) with facilitation followed by depression, while others (e.g., initiated social activity) showed only a dose dependent decrease [15]. Davis, *et al.* (submitted) have suggested that 5–MeODMT may be an especially effective 5–HT agonist at spinal cord receptors. This hypothesis is supported by the finding that the behavioral syndrome which results from either increased synaptic serotonin or increased stimulation of postsynaptic serotonin receptors can be produced by 5–MeODMT [20]. The neural mechanisms mediating this serotonin syndrome appear to be localized within the lower brainstem and spinal cord [12]. The difference in 5–MeODMT's effects on SEF and startle may thus indicate that spinal 5–HT receptors play a much greater role in modulating startle than SEF.

Sheard, Astrachan and Davis [16] found LSD to substantially increase SEF at several doses between 20–160 μg/kg and across a range of shock intensities. One might expect DMT and 5–MeODMT to similarly facilitate SEF at low doses, for all three drugs specifically inhibit raphe neurons in the low dose range without affecting cells postsynaptic to the raphe [4, 10, 11]. The release of inhibitory raphe activity might then be expected to increase SEF.

This explanation for a low dose behavioral facilitation depends on the fact that there is a differential dose effect of these drugs on the electrophysiology of the serotonin sys-

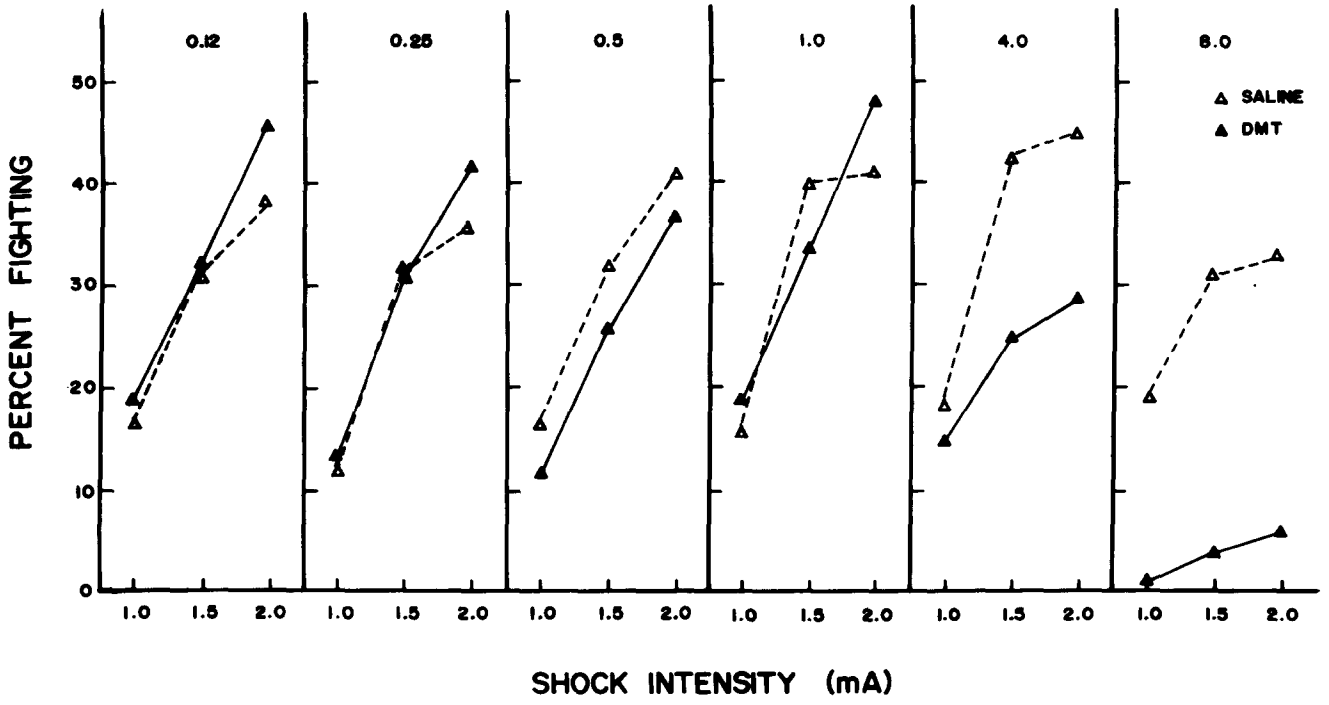

FIG. 1. Mean percent of total trials on which animals fought when receiving either DMT or saline plotted as a function of shock intensity (mA) for 0.12, 0.25, 1.0, 4.0 and 8.0 mg/kg doses of DMT.

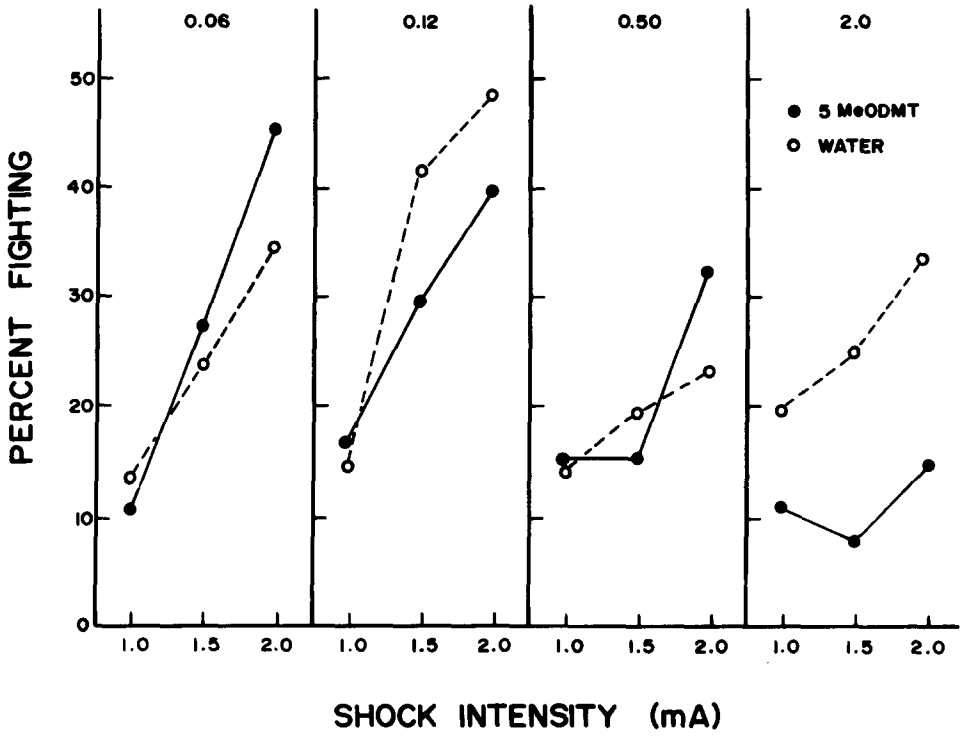

FIG. 2. Mean percent of total trials in which animals fought when receiving either 5-MeODMT or water plotted as a function of shock intensity (mA) for 0.06, 0.12, 0.50 and 2.0 mg/kg doses of 5-MeODMT.

tem, with low doses inhibiting only raphe neurons and higher doses inhibiting both raphe cells and cells postsynaptic to the raphe. One reason DMT may not have produced a facilitation of SEF is that the differential between doses inhibiting just raphe neurons and doses inhibiting both raphe and postsynaptic cells is rather small [4]. Therefore, the facilitation might be small and transient. Such is not the case for 5-MeODMT, however. There is relatively large dose differential for this drug which is nearly as great as the differential for LSD [10]. Why 5-MeODMT did not produce a biphasic response with SEF similar to that for LSD remains unclear. One possibility is that its presumed potency at spinal cord receptors may have interfered with a more rostrally mediated facilitation.

Another possible explanation for the differential behavioral effects of these three drugs may relate to LSD's substantial affinity for brain dopamine binding sites [5]. This affinity is not shared by DMT or the other indole hallucinogens derived from tryptamine which have been tested to date. LSD may thus stand apart from other indole hallucinogens in this respect. Behavioral stereotypes associated with dopamine receptor activation can be induced by low doses of LSD (100 μg/kg), but not by DMT [14]. Regarding SEF, however, the dopamine receptor agonist apomorphine seems only to enhance spontaneous and not shock elicited fighting [13,19]. The interaction of indole hallucinogens with dopamine and other neurotransmitter systems requires further study before this alternative can be fully evaluated.

Changes in sensitivity to electric shock may also be used to explain changes in SEF if the drugs employed produce either an analgesia or hyperalgesia. Preliminary experiments revealed that electroshock sensitivity was not markedly affected by either DMT or 5-MeODMT at the doses employed in the present study.

The results of this experiment point up very important differences between the effects of 5-MeODMT and LSD on SEF despite their close similarity of action on single cells of the raphe-serotonin system. LSD is predominantly excitatory to SEF over a wide range of doses while 5-MeODMT is predominantly inhibitory. With respect to acoustic startle, on the other hand, both LSD and 5-MeODMT produced a facilitation with 5-MeODMT causing a more potent excitation. These findings reveal that the action of the indole hallucinogens upon behavior is relatively specific and cannot be precisely predicted from only a knowledge of their effects upon single units in the serotonergic system.

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