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THE INDOLE HALLUCINOGENS, *N,N*-DIMETHYLTRYPTAMINE (DMT) AND 5-METHOXY-*N,N*-DIMETHYLTRYPTAMINE (5-MeO-DMT), HAVE DIFFERENT EFFECTS FROM MESCALINE ON RAT SHUTTLEBOX AVOIDANCE

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Summary—The indole hallucinogenic drugs, *N,N*-dimethyltryptamine (DMT) and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), had a different psychopharmacological profile from mescaline on rat shuttlebox avoidance; the differences were strain and/or baseline-dependent. *N,N*-dimethyltryptamine and 5-MeO-DMT shared dose response disruptive effects with mescaline on avoidance behaviour in two rat strains who were performing the conditioned avoidance response at a high baseline (i.e. during acqusition in Fischer 344s—Experiment 1; on pretrained good performing hooded rats Experiment 2). *N,N*-dimethyltryptamine and 5-MeO-DMT were without an effect when the baseline conditioned avoidance response was low (i.e. during acquisition in Zivic–Millers, Hoods or Roman Low Avoiders—Experiment 1; on pretrained poorly performing hooded rats—Experiment 2) but mescaline was facilitatory in these situations. There were strain-related differences in sensitivity to the drugs with Roman High Avoiders insensitive to DMT, 5-MeO-DMT and mescaline, while Fischer 344s were the most sensitive to these three drugs. The relative potency of these three hallucinogens in disrupting avoidance behavior (5-MeO-DMT > DMT > mescaline), in terms of mg/kg paralleled reports of their relative potency on central serotonergic activity. The facilitatory effect produced by mescaline, but not produced by DMT nor 5-MeO-DMT, may be related to the findings that mescaline has a stronger action on the catecholaminergic system than the indoles.

Mescaline and *N,N*-Dimethyltryptamine (DMT) are prototype hallucinogens of the phenylalkylamine and indolealkylamine classes respectively; 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), an analogue of DMT, has more potent psychological effects than DMT (Shulgin, 1970). There are close structural similarities between mescaline and the catecholamines and between the methylated indoles and serotonin as well as preferential pharmacological actions for the two classes of hallucinogens on these neurotransmitters.

Mescaline is a weak blocker of serotonin uptake (Ross and Renyi, 1967) and only slightly decreases serotonin turnover (Anden, Corrodi, Fuxe and Meek, 1974; Tonge and Leonard, 1969), while DMT and 5-MeO-DMT are strong blockers of serotonin uptake (Anden, Corrodi and Fuxe, 1971; Horn, 1973) and significantly decrease serotonin turnover (Bradley and Briggs, 1974; Fuxe, Holmstedt and Jonsson, 1972). There is also evidence that DMT may cause serotonin to be released from presynaptic stores (Meek and Fuxe, 1971) and that 5-MeO-DMT mimics the excitatory effects of serotonin at presynaptic receptors (Bradley and Briggs, 1974). Reduced serotonin turnover caused by the indoles may be related to the fact that both DMT and 5-MeO-DMT directly inhibit the firing of serotonergic neurones in the midline raphe nuclei (Aghajanian, Foote and Sheard, 1970; deMotigny and Aghajanian, 1977). Mescaline inhibits some of these neurones only indirectly and increases the firing of other raphe neurones (Haigler and Aghajanian, 1973). Thus, in terms of net synaptic action on serotonin, mescaline would act as an antagonist on serotonergic neurones, while both DMT and 5-MeO-DMT would act as an agonist.

Mescaline has significant effects on catecholaminergic systems, including producing presynaptic release of dopamine (Friedhoff, Coupet and Hadfield, 1969) and blocking norepinephrine uptake (Dengler, Speigel and Titus, 1961). Recently, DMT has been shown to stimulate the release of dopamine (Haubrich and

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Wang, 1977; Waldmeier and Maitre, 1977), but it has no effect on noradrenergic systems (Anden *et al.*, 1971). Hallucinogens of the two chemical classes might be expected to have different behavioural effects corresponding to their different neuropharmacological actions.

Previous work has shown that mescaline can both facilitate and disrupt conditioned avoidance responding in rats, with the facilitatory effect occurring in rats with low performance levels and the disruptive effect in rats with high performance levels (Gorelick and Bridger, 1977). Tolerance develops to this disruptive effect of mescaline (Bridger, Mandel and Stoff, 1973; Smythies, Sykes and Lord, 1966), but not to the facilitatory effects of either mescaline or *d*-lysergic acid diethylamide (LSD) (Stoff, Mandel, Gorelick and Bridger, 1974). Recently, it has been found that there is no tolerance to LSD-produced depression of raphe unit activity (Trulson, Ross and Jacobs, 1977), one of the most prominent actions of LSD in the CNS.

The effects of the drug to which tolerance does not develop may serve as a useful animal model for endogenously produced mental illness. Since DMT (Saavedra and Axelrod, 1972; Wyatt, Saavedra and Axelrod, 1973) and, perhaps, 5-MeO-DMT (Mandel and Walker, 1974) occur in human tissue, it would be of interest to find out whether these compounds have facilitatory effects in the same paradigms as mescaline or LSD. *N,N*-dimethyltryptamine and 5-MeO-DMT have been shown to disrupt conditioned avoidance responding in rats with high performance levels (Smythies, Bradley, Johnston and Leonard, 1967; Stoff, Moja, Gillin and Wyatt, 1977), but have not previously been tested at performance levels or in strains where mescaline or LSD have facilitatory effects.

In the first experiment, DMT, 5-MeO-DMT and mescaline were given to naive rats of five strains (Long-Evans Hoods, Fischer 344/mai, Zivic-Miller, Roman Low Avoider and Roman High Avoider) during acquisition of shuttlebox escape-avoidance behaviour. Since these strains differ in their ability to acquire avoidance behaviour (see review by Ray and Barrett, 1975), performance level was also a variable in this experiment. In the second experiment, the dose response effects of DMT was studied in experienced, stably performing Long-Evans rats who had achieved a high or low baseline avoidance rate in the shuttlebox.

APPARATUS

The experimental task was a dual-chambered shuttlebox divided into two equal-sized compartments. There were minor stimulus modifications between Experiments 1 and 2, previously described in detail elsewhere (Gorelick and Bridger, 1977; Stoff *et al.*, 1977). In both experiments, there was a brief adaptation period during which time the rat was free to make pretrial crossovers (PTCs); a discriminative stimulus came on 5 sec before scrambled electric foot shock (negative reinforcer) and a shuttlebox crossing during this interval terminated the stimulus and prevented shock onset (conditioned avoidance response [CAR]), but a crossing more than 5 sec after stimulus onset terminated both stimulus and shock (escape response); the intertrial interval was 20 sec during which time the rat was free to make intertrial crossovers (ITCs). Response latencies and shuttlebox crossings were automatically measured.

EXPERIMENT 1 (ACQUISITION OF CONDITIONED AVOIDANCE RESPONSE [CAR])

Methods

Animals

The animals consisted of five different strains of rats: (1) Long–Evans Hooded (Marland Farms)—HOODs—(n = 45), Charles River derived CD Sprague–Dawley (Zivic Miller Laboratories)—ZMs—(n = 41), (3) Fischer 344s (Microbiological Associates)—F344s—(n = 143), (4) Roman Low Avoiders (National Institutes of Health)—RLAs—(n = 38) and (5) Roman High Avoiders (National Institutes of Health)—RHAs—(n = 39). All rats were experimentally naive, male and 200–250 g. They were maintained on *ad libitum* food and water in individual wire mesh cages on a 09:00–21:00 light–dark cycle.

Procedure

Drug testing during acquisition of CAR

Separate groups of F344s were injected (i.p., 0.1 ml/100 g) with different doses of DMT (0.5–4.0 mg/kg), 5-MeO-DMT (0.125–4.0 mg/kg), mescaline (9.9–39.6 mg/kg) or saline. Similarly, separate groups of HOODs were given DMT (2.0–16.0 mg/kg), 5-MeO-DMT (0.25–16.0 mg/kg), mescaline (39.6 mg/kg) or saline. Separate groups of ZMs, RLAs and RHAs each received one dose of drug—DMT 4.0 mg/kg, 5-MeO-DMT 4.0 mg/kg, mescaline 39.6 mg/kg or saline.

Drugs were freshly dissolved in saline, adjusted to pH 5–6 and injected intraperitoneally in a volume of 0.1 ml/100 g body weight. Two minutes after DMT, 5-MeO-DMT or saline and 10 min after mescaline, rats were placed in the shuttlebox and given a 3.0-min adaptation period followed by a 100-trial acquisition test.

Results

Strain differences during acquisition of CAR

A between groups one-way analysis of variance among the saline-treated rats of the 5 strains showed that there were significant differences on acquisition

Table 1. Mean (±S.E.) number of conditioned avoidance responses during shuttlebox acquisition after mescaline, DMT and 5-MeO-DMT in 5 rat strains

Drug	Dose (mg/kg)	RHAs	F344s	ZMs	RLAs	HOODs
Saline	—	68 ± 10 (n = 9)	58 ± 9 (n = 11)	43 ± 6 (n = 11)	9 ± 4 (n = 11)	2.6 ± 1.3 (n = 10)
Mescaline	39.6	79.2 ± 2.8 (n = 10)	0.6 ± 0.3 (n = 6)	71 ± 7 (n = 10)	21 ± 5 (n = 9)	27 ± 7 (n = 7)
DMT	4.0	70 ± 5 (n = 10)	26 ± 5 (n = 10)	21 ± 6 (n = 10)	3.3 ± 1.6 (n = 8)	4.6 ± 2.9 (n = 10)
5-MeO-DMT	4.0	58 ± 6 (n = 10)	16 ± 4 (n = 11)	20 ± 4 (n = 10)	7 ± 4 (n = 10)	0.8 ± 0.3 (n = 9)

RHAs = Roman High Avoiders; F344s = Fischer 344; ZMs = Zivic–Miller; RLAs = Roman Low Avoiders; HOODs = Long-Evans Hooded.

of the CAR (F = 17.4, d.f. = 4, 47, $P < 0.01$). Table 1 presents the mean (±S.E.) number CARs for each of these strains. It can be seen from Table 1 that the CAR order from highest to lowest, was: RHAs > F344s > ZMs > RLAs > HOODs. Analogous effects to the CAR measure were obtained using response latency as the dependent variable. Among the 5 strains, there were no significant differences on either measure of activity, pretrial and intertrial crossings.

Effects of mescaline, DMT and 5-MeO-DMT on acquisition of CAR for the different strains

One-way analyses of variance among the four groups in Table 1 (mescaline 39.6 mg/kg, DMT 4 mg/kg, 5-MeO-DMT 4 mg/kg, saline) were statistically significant on CAR for F344s (F = 14.0, d.f. = 3, 34, $P < 0.01$), ZMs (F = 16.0, d.f. = 3, 37, $P < 0.01$), RLAs (F = 3.2, d.f. = 3, 34, $P < 0.01$), and HOODs (F = 46.5, d.f. = 3, 32, $P < 0.01$); there were no significant differences for RHAs (F = 1.7, d.f. = 3, 35, $P > 0.05$).

Post hoc tests using Dunnett's t showed that mescaline facilitated the CAR in rat strains with relatively low behavioral baselines: HOODs (t = 7.4, $P < 0.01$), RLAs (t = 2.4, $P < 0.05$), ZMs (t = 3.3, $P < 0.01$) but disrupted the CAR in F344s who responded at a relatively high baseline (t = 6.3, $P < 0.01$).

The indole hallucinogens showed a uniform disruptive effect, occurring in F344s for DMT (t = 3.6, $P < 0.01$) and 5-MeO-DMT (t = 4.6, $P < 0.01$), and in ZMs for DMT (t = 2.7, $P < 0.05$) and 5-MeO-DMT (t = 2.8, $P < 0.05$). Analogous effects to the CAR measure were obtained using response latency as the dependent variable. There were no significant effects on intertrial motor activity for any of these drugs.

Dose response effects of DMT, 5-MeO-DMT and mescaline during acquisition of CAR in F344s and HOODs

One-way analyses of variance showed dose-related disruption on the CAR in F344s among various doses of DMT (F = 2.6, d.f. = 4, 44, $P < 0.05$) (Fig. 1), 5-MeO-DMT (F = 4.2, d.f. = 6, 66, $P < 0.01$) (Fig. 1), and mescaline (F = 10.6, d.f. = 3, 27, $P < 0.01$) (Fig. 2). Trend analyses (modified for unequal n: following Winer, 1971, pp. 181) indicated significant linear

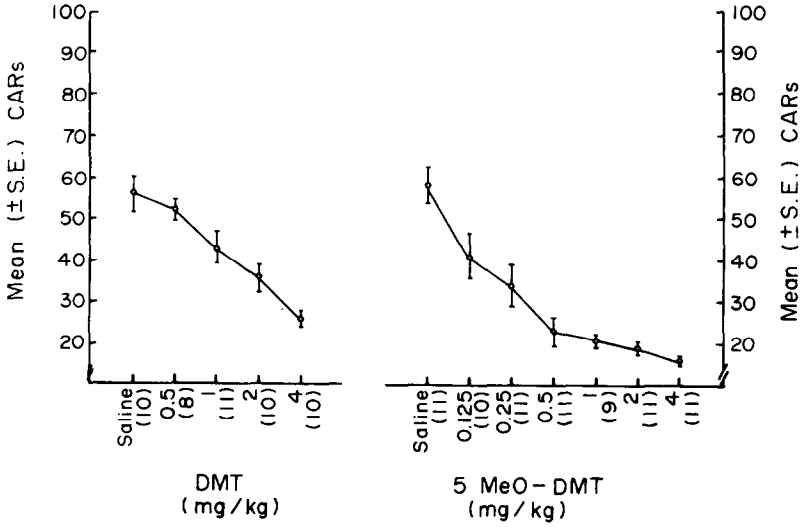

Fig. 1. Dose response effects of DMT and 5-MeO-DMT on acquisition of conditioned avoidance response (CAR) in Fischer 344 rats.

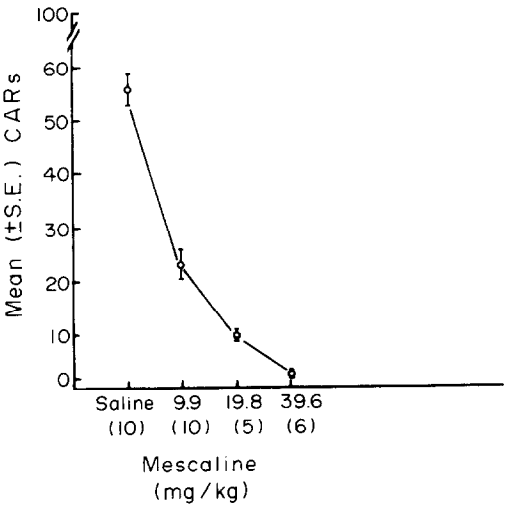

Fig. 2. Dose response effects of mescaline on acquisition of conditioned avoidance response (CAR) in naive Fischer 344 rats.

components for DMT ($F = 8.1$, $P < 0.01$), 5-MeO-DMT ($F = 23.5$, $P < 0.01$) and mescaline ($F = 25.8$, $P < 0.01$) such that a linear regression equation can predict, respectively, 77.6%, 89%, 80.7% of variation in the drugs' effects. Inspection of Figure 1 indicates that 5-MeO-DMT's disruptive effect occurred at the lowest dose used (0.125 mg/kg) and the degree of disruption produced by this dose of 5-MeO-DMT was about equivalent to the effect of DMT 1.0 mg/kg; 5-MeO-DMT had an effect about 8 times more potent than DMT. Figure 2 shows that F344s are very sensitive to the disruptive effects of mescaline since the lowest dose tested (9.9 mg/kg) resulted in at least a two-fold decrease in conditioned avoidance responding; the highest dose tested (39.6 mg/kg) completely blocked escape responding, as well as the CAR.

In HOODs, none of the doses of DMT (2–8 mg/kg) or 5-MeO-DMT (0.25–4 mg/kg) influenced the CAR. Higher doses of 5-MeO-DMT caused convulsions and tremors in hooded rats. The toxic effects of 5-MeO-DMT have previously been described in detail (Gillin, Tinklenberg, Stoff, Stillman, Shortlidge and Wyatt, 1976).

EXPERIMENT 2 (PRETRAINED POOR AND GOOD AVOIDERS)

Methods

Animals

The animals were 18 male Long–Evans hooded rats (Marland Farms) weighing 410–610 g. Every rat was previously trained in the shuttlebox to stable baseline avoidance rates. The baseline rates were not permanently affected by prior drug treatments, nor by 6-day rest periods interposed to allow drug effects to wear off. Rats were maintained on *ad libitum* food and water in individual wire mesh cages on a 09:00–18:00, light-dark cycle.

Procedure

Dose response testing of DMT on pretrained poor and good avoiders

Rats were trained (100 trials escape/avoidance sessions per day) until they achieved a stable baseline avoidance performance which was greater than 88% CARs (good performers, $n = 8$) or less than 6% (poor performers, $n = 10$). The training procedure and criterion for stability has been described in detail elsewhere (Gorelick and Bridger, 1977). After reaching criterion, different doses of DMT (2, 4, 8 or 16 mg/kg) were given in random order according to a repeated measures design.

Results

Goof performers

In good performers, DMT significantly decreased avoidance performance ($F = 12.7$, $P < 0.01$) in a dose-dependent way (see Fig. 3). It can be seen from Figure 3 that the threshold dose for disruption was 4 mg/kg which is about four times higher than the threshold dose for disruption during acquisition in F344s (see Fig. 1). DMT did not influence the number of PTCs, but ITCs increased for the two highest doses (i.e. 8, 16 mg/kg).

Poor performers

In poor performers, DMT had no significant effect on avoidance performance ($F = 1.5$, $P < 0.05$), but did significantly lengthen response latency ($F = 3.5$, $P < 0.01$). *Post hoc* tests (Newman–Keuls) showed

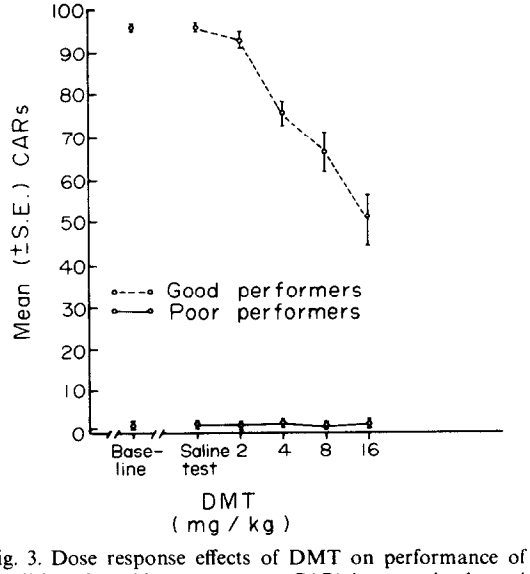

Fig. 3. Dose response effects of DMT on performance of conditioned avoidance response (CAR) in pretrained good and poorly performing hooded rats.

that this effect was due to a significant difference between the 16 mg/kg group and all the other groups.

DISCUSSION

The findings of this study show that the indolealkylamine hallucinogens, DMT and 5-MeO-DMT, have a psychopharmacological profile on rat shuttlebox avoidance that is different from mescaline, the prototype of the phenylalkylamine hallucinogens. The differential effects are strain and/or baseline-dependent.

In three rat strains (HOODs, RLAs, ZMs) who respond at relatively low conditioned avoidance response (CAR) baselines during acquisition, mescaline has facilitatory effects on the CAR (Experiment 1). The dose-dependent response of this effect in hooded rats has already been reported (Bridger *et al.*, 1973). Further, mescaline facilitated the CAR in another shuttlebox situation where the baseline response rate was low; i.e. pretrained hooded rats which were poor stable CAR performers (Gorelick and Bridger, 1977). Unlike mescaline's facilitatory effect during acquisition of the CAR, DMT and 5-MeO-DMT disrupted the CAR in ZMs or had no effect in HOODs (Experiment 1). Facilitation of responding by mescaline, but not by DMT, has also been reported by Schoenfeld (1976) who found that mescaline, but not DMT, restored behaviour suppressed by electric shock.

Mescaline has previously been found to disrupt the CAR in shuttlebox situations where the baseline response rate was relatively high: ie, in pretrained hooded rats who were good stable CAR performers (Gorelick and Bridger, 1977) or during acquisition in F344s (here in Experiment 1; also Gorelick and Bozewicz, 1977). Mescaline-like disruptive effects were found for DMT and 5-MeO-DMT in these situations, for both DMT and 5-MeO-DMT during acquisition in F344s (Experiment 1) and for DMT in good performers (Experiment 2). Thus, the effects of DMT and 5-MeO-DMT seem to be uniformly disruptive of the CAR.

N,N-dimethyltryptamine and 5-MeO-DMT's inability to produce a facilitatory effect on shuttlebox avoidance during acquisition (Experiment 1) or in poor performers (Experiment 2) may be related to the weaker effect of indole hallucinogens on catecholamines as compared with muscaline (see introduction). This assumes that mescaline's facilitatory effect is mediated by catecholamines. Support for this assumption comes from the finding that the facilitatory effect is stress related, may be blocked by alpha-methyl-para-tyrosine (Gorelick, 1975), and catecholamines are involved in behavioural activation (Brodie and Shore, 1957). The indoles, DMT and 5-MeO-DMT share, with mescaline, the ability to stimulate central serotonin receptors and this may be related to the disruptive effect which these three agents produce.

There are some additional points worth mentioning: (i) strain-related differences in avoidance learning were found to be very high in RHAs and F344s and very low in RLAs and HOODs (see Table 1). This confirms the findings of others (e.g. Barrett and Ray, 1970; Coyle, Wender and Lipsky, 1973); (ii) strain-related differences in sensitivity to drugs were found: RHAs were insensitive to all three drugs and F344s were the most sensitive rat strain to mescaline and DMT (see Table 1) [i.e. the lowest dose of mescaline (9.9 mg/kg) severely hindered avoidance behaviour in F344s (see Fig. 2) but, at comparable performance levels, the same dose had no effect in hooded rats who were good avoiders (Gorelick and Bridger, 1977) and the threshold dose of DMT causing disruption was 1 mg/kg in F344s and 4 mg/kg in hooded rats (compare Figs 1 and 3)]; (iii) in terms of mg/kg, DMT is at least 9 times more potent than mescaline in disruption of avoidance behaviour (compare Figs 1 and 2) and 5-MeO-DMT is about 8 times more potent than DMT (see Fig. 1). The relative potency of these three hallucinogens in disrupting avoidance behaviour (5-MeO-DMT > DMT > mescaline) parallels their relative potency on psychological and perceptual measures in humans, stimulation of serotonin receptors (Anden *et al.*, 1971; Fuxe *et al.*, 1972), as well as preferential pre- versus postsynaptic depression of raphe firing (deMontigny and Aghajanian, 1977).

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