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BEHAVIOURAL CHANGES INDUCED BY *N,N*-DIMETHYLTRYPTAMINE IN RODENTS

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1 *N,N*-Dimethyltryptamine (DMT) in pargyline pretreated rodents induced a dose-dependent behavioural syndrome consisting of hyperactivity, prostration and hindlimb abduction, mild tremor, Straub tail, retropulsion and jerking.

2 In rats pretreated with pargyline, the behavioural syndrome induced by DMT differed from that induced by L-tryptophan or quipazine, in the lack of forepaw treading and head-weaving and in the presence of only mild tremor.

3 The hyperactivity component of the DMT-induced behavioural syndrome in pargyline-pretreated mice was potentiated by cyproheptadine, methergoline, and mianserin, inhibited by cinanserin, haloperidol, pimozide, methiothepin and propranolol, and not affected by 501C67-sulphate and methysergide.

4 The maximal behavioural changes induced by DMT in rats, other than hyperactivity, were unaffected by pretreatment with cyproheptadine, methysergide, and cinanserin. However, propranolol reduced the intensity of all behavioural effects apart from body jerking, and methergoline decreased the duration of prostration. Phenoxybenzamine and haloperidol, in contrast, enhanced prostration.

5 DMT plus pargyline did not induce circling behaviour in mice with a unilateral 6-hydroxydopamine lesion of the nigro-striatal pathway.

6 The DMT-induced behavioural syndrome appears to consist of two components, (a) hyperactivity and (b) other behavioural changes. They differ in their response to drugs affecting brain monoamines. The hyperactivity component may be expressed via dopamine mechanisms, but the other behavioural changes are not. The two behaviours do not respond consistently to drugs believed to alter brain 5-hydroxytryptamine function.

Introduction

Of the methylated indoleamines (such as dimethylserotonin(bufotenin), psilocybin and 5-methoxy-*N,N*-dimethyltryptamine), *N,N*-dimethyltryptamine (DMT) is of particular interest because it has been suggested that it is a 'schizotoxin'. DMT has been shown to produce psychedelic effects when administered to normal subjects (Szara, 1956; Kaplan, Mandel, Stillman, Walker, Van den Heuval, Gillin & Wyatt, 1974). DMT can be synthesized in the tissues of both man and animals (Axelrod, 1962; Mandell & Morgan, 1971; Saavedra & Axelrod, 1972; Mandel, Prasad, Lopez-Ramos & Walker, 1977), and no apparent tolerance seems to develop on repeated administration of this drug to the cat (Gillin, Cannon & Magyar, 1973) or squirrel monkey (Cole & Pieper, 1973). On the basis of this evidence, DMT has been considered as a possible causative agent in schizophrenia (Rodnight, 1975; Gillin, Kaplan, Stillman & Wyatt, 1976).

The simple behavioural effects of DMT in animals have received less attention than studies of its effects on complex behaviour such as operant behaviour (Cole & Pieper, 1973; Kovacic & Domino, 1976). The mechanism of action of DMT also is in doubt, although some studies have suggested direct 5-hydroxytryptamine (5-HT) receptor stimulation by DMT. For example, DMT has been reported to cause hyperextension of the hindlimb of acute spinalised rats which is believed to be dependent on 5-HT receptor activity (Anden, Jukes & Lundberg, 1964; Anden, Corrodi & Fuxe, 1971).

In the present study, we have investigated the behavioural effects of systemically administered DMT in rodents and, because of its possible action on 5-HT mechanisms, have compared them with the actions of the 5-HT receptor agonist quipazine and L-tryptophan (a precursor of 5-HT). We have also studied the effect of a range of 5-HT and other monoamine recep-

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tor antagonists on the behavioral syndrome provoked by DMT.

A preliminary account of this work was given to the British Pharmacological Society (Jenner, Marsden & Thanki, 1978).

Methods

DMT-induced behavioural syndrome in rodents

Wistar rats (200 to 300 g) and Swiss S or P strain mice (20 to 30 g) of either sex were used in all experiments. Rats were observed in individual plastic cages (35 cm × 23 cm × 17 cm). Mice were observed in groups of three in similar cages. Animals were allowed 20 to 30 min habituation in their cages before injection with either pargyline (75 mg/kg i.p.) or distilled water. Two hours later DMT (0.5 to 35 mg/kg i.p.) or control solution (the vehicle in which DMT was dissolved) were injected and the animals were observed subsequently for up to 3 h. DMT base (Sigma) was dissolved in a few drops of 0.5 N HCl and distilled water and the pH of the solution was adjusted to 6.0 to 6.5 with 0.1 N NaOH. Pargyline hydrochloride (Abbott Laboratories) was dissolved in distilled water.

The intensity of each behaviour was assessed in at least 5 rats at each dosage level using the following scoring system. Absent = 0, present but mild intensity = +, moderate intensity = ++, intense = +++. In addition, each animal was given an overall

Table 1 Source, dose and administration schedule for monoamine antagonists used as potential modulators of the *N,N*-dimethyltryptamine (DMT) behavioural syndrome

Drug	*Source*	*Dose (mg/kg) and route*	*Solution*	*Injection time before DMT (h)*
Cyproheptadine hydrochloride	Merck, Sharp & Dohme	10 i.p.	In distilled water after warming	1
Methergoline	Farmitalia	5 i.p.	With twice the amount of tartaric acid + 6 drops of 70% alcohol then to volume with distilled water (pH 3.8)	1
Cinanserin hydrochloride	Squibb	10 i.p.	Distilled water	1
Mianserin hydrochloride	Organon	20 i.p.	Distilled water	1
501C67-sulphate	Burroughs Wellcome	10 i.p.	Distilled water boiled for 30–40 min	2*
Methysergide hydrogen maleinate	Sandoz	10 s.c. or i.p.	0.9% saline, vigorous shaking	10 min before or after
Phenoxybenzamine hydrochloride	Smith, Kline & French Labs	10 i.p.	Ampoule solution diluted with distilled water	1
Propranolol hydrochloride	I.C.I.	20 or 40 i.p.	Distilled water	1
Haloperidol	Searle	1 i.p.	Ampoule solution diluted using distilled water	
Pimozide	Janssen	1 i.p.	In distilled water with an equal weight of tartaric acid	3
Methiothepin	Roche Products	1 i.p.	In distilled water	1
α-Methyl-*p*- tyrosine methyl ester hydrochloride	Sigma	200 i.p.	In distilled water	2*

Unless otherwise stated, weights of drugs are expressed in terms of the salt. Fresh solutions of these drugs were prepared on the day of the experiment. Experiments with each drug were repeated at least six times and Student's *t* test was employed for comparison of Animex counts.

* Pargyline pretreatment given 1 h before DMT. In all other cases it was given 2 h before DMT.

score (0 to 4) to indicate the intensity of the entire syndrome. The scores presented represent the maximal intensity observed. Locomotor hyperactivity produced by DMT in rats and mice was studied using Animex activity meters (LKB Farad).

The effect of antagonists on DMT-induced hyperactivity in Animex experiments is presented as the difference between the counts recorded in the 2 h period following DMT administration in animals receiving DMT alone, compared to those animals also pretreated with an antagonist. This approach ignores the potential effect of antagonists on basal motor function, but has been adopted to overcome the problem of presenting all control data and the numerous internal comparisons involved. However, the effect of antagonists on basal activity was small since spontaneous activity was already reduced by pargyline pretreatment. Further, DMT administration in the presence or absence of antagonist pretreatment, revealed identical effects of antagonist drugs to those reported. For animals given pargyline (75 mg/kg) 2 h previously, a standard dose of 15 mg/kg DMT was adopted for all behavioural experiments in rats while 2 mg/kg DMT was used in mice (both doses i.p.). The effects of various receptor antagonists were studied, whose source, dose and injection schedule are summarised in Table 1. The doses of monoamine antagonists used are high, but are those known to prevent 5-HT-mediated effects in other behavioural models.

In order to assess whether any of the behavioural effects of DMT were due to intraperitoneal irritation and whether the inhibitory action of some drugs might be due to a local anaesthetic-like action, some animals were pretreated with procaine hydrochloride (20 mg/kg i.p.) 1 h before DMT administration, or with the long-acting bupivacaine (20 mg/kg i.p.) 60 or 10 min before DMT. These treatments were, however, without effect on the intensity or duration of the behavioural syndrome induced by DMT.

Comparison of 5-hydroxytryptamine behavioural syndromes in rats

In rats that had been given pargyline (75 mg/kg) 2 h previously, the effects of L-tryptophan (150 mg/kg i.p.) and quipazine (20 mg/kg i.p.) were observed and compared with those of DMT (15 mg/kg i.p.). L-Tryptophan (Sigma Chemical Co) was dissolved in 0.9% w/v NaCl solution (saline) by adding a few drops of 1 M HCl. Quipazine maleate (Miles Laboratories) was dissolved in distilled water.

Effect of DMT in mice with unilateral 6-hydroxydopamine nigro-striatal lesions

6-Hydroxydopamine hydrochloride (6-OHDA) (16 μg in 4 μl ice-cold saline) was injected directly into one striatum of hand-held mice while under ether anaesthesia (von Voigtlander & Moore, 1973). Two weeks after surgery, animals received apomorphine hydrochloride (0.5 mg/kg s.c.) or amphetamine sulphate (4 mg/kg i.p.). Only animals showing strong contraversive turning to apomorphine and strong ipsiversive turning to amphetamine were used in subsequent studies. Turns were counted for 1 min every 5 min for 30 min after injection of each drug. The effect of pargyline (75 mg/kg i.p.) alone, DMT (4 mg/kg i.p.) alone and in combination were tested in these animals.

Statistics

Hyperactivity data for control and drug-treated animals obtained using Animex activity meters were compared by Student's *t* test. Alterations in the behavioural scoring systems were assessed by the Mann-Whitney U test for non-parametric data.

Results

DMT-induced behavioural syndrome in rat

The main components of the behavioural syndrome produced by DMT are listed in Table 2. Other behavioural effects observed were backward walking (retropulsion), abdominal contractions and some vocalisation. The syndrome appeared within 5 min of injection and was maximal by 15 min. The intensity and duration of each component was dose-dependent in the presence of a monoamine oxidase inhibitor (MAOI), pargyline. Pargyline (75 mg/kg i.p.) itself did not induce the behavioural effects produced by DMT but increased the duration and intensity of the DMT-induced syndrome.

In rats pretreated with pargyline, DMT (5 mg/kg i.p.) produced a splaying of the hindlimbs (hindlimb abduction). This effect was not sufficiently severe to interfere with normal movement which appeared enhanced. Other behavioural changes were absent at this dose.

DMT (10 mg/kg i.p.) produced an initial increase in controlled motor activity and small stereotyped movements (grooming and sniffing). However, the subsequent onset of prostration made movement difficult. Animals lay on their abdomens making swimming movements of the limbs. Mild tremor and abdominal contractions were also obvious at this dose. The syndrome lasted for about 80 to 90 min.

DMT (15 mg/kg i.p.) impaired normal motor function by the production of marked prostration. However, the animals exhibited bursts of rapid swimming movements interspersed with periods of immobility. The swimming movements of the limbs were recorded as an increase in total activity on activity meters and

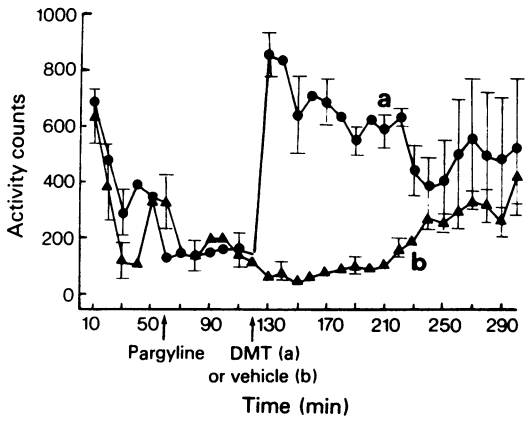

Figure 1 The time course of behavioural hyperactivity induced by *N,N*-dimethyltryptamine (DMT) in pargyline pretreated rats recorded by Animex activity meters. Most of the activity recorded consisted of swimming movements of the limbs, tremor and body jerking. Individual rats were placed in Animex activity cages and allowed 1 h to acclimatise. Pargyline (75 mg/kg i.p.) was then administered followed 1 h later by DMT (a, 15 mg/kg i.p.) or vehicle (b). Activity was recorded at 10 min intervals over the next 3 h period. Results are expressed as the mean 6 experiments; vertical lines show s.e. mean.

lasted for some 120 min (Figure 1). This hyperactivity did not represent an increase in controlled locomotion, which was grossly inhibited. Whole body jerks and Straub tail were also apparent at this dose and the incidence of wet dog shakes (WDS) and stereotyped movements increased. The animals reacted violently to loud auditory stimuli exhibiting rapid limb movements and jumping motions.

Following DMT (20 mg/kg i.p.) body jerking became more marked with greater immobility due to prostration and limb abduction. The frequency of all behavioural components was further increased and some forepaw treading was observed. The behavioural syndrome lasted for about 140 to 160 min.

DMT (35 mg/kg i.p.) produced almost total immobility and profound prostration. Whole body jerks were prominent and increased in frequency. Other behavioural effects were also intensified and the syndrome lasted for 180 to 200 min.

Thus, with increasing doses of DMT, animals pretreated with pargyline showed progressive increase in prostration with subsequent enhanced impairment of motor function and appearance and intensification of other behavioural effects.

Comparison of the DMT-induced behavioural syndrome with that induced by L-tryptophan or quipazine

The behavioural syndromes produced by DMT (15 mg/kg i.p.) and that produced by L-tryptophan (150 mg/kg i.p.) or quipazine (20 mg/kg i.p.) in the presence of pargyline were, in general, very similar (Table 3). However, the onset of L-tryptophan-induced behavioural syndrome was slow (30 to 40 min) compared to that of DMT (0 to 5 min) and quipazine (0 to 5 min). L-Tryptophan and quipazine caused marked tremor, whereas this was slight following DMT. Forepaw treading and head-weaving in L-tryptophan and quipazine-treated animals were perhaps the two main factors, apart from tremor, distinguishing the effects of these drugs from those of DMT.

Table 2 Behavioural changes induced in rats by *N,N*-dimethyltryptamine (DMT, 5 to 35 mg/kg i.p.), following pargyline pretreatment (75 mg/kg i.p. 2 h beforehand)

Behavioural components	*Vehicle control solution*	*DMT* 5 mg/kg	*DMT* 10 mg/kg	*DMT* 15 mg/kg	*DMT* 20 mg/kg	*DMT* 35 mg/kg
Prostration	0	+	++	++/+++	+++	+++
Hyperactivity	0	+	++	++/+++	+++	+++
Tremor	0	0	0/+	0/+	+	+
Whole body jerks	0	0	0/+	0/+	+	+/++
Grooming and sniffing	0/+	0/+	+	+	+/++	++
Straub tail	0	0	+	+/++	+++	+++
Wet dog shakes	+	+	+	++	++	++
Overall score	0	1	2	3	4	4

Animals were assessed for each individual behavioural component according to the following scoring system:— absent = 0; present (but mild intensity) = +; moderate intensity = ++; intense = +++. Animals were also given an overall score (0–4) as an indication of the intensity of the entire behavioural syndrome. The scores represent the maximal intensity observed in 2-3 h following DMT administration.

The effect of monoamine receptor antagonists on DMT-induced behavioural syndrome in rats

The components of the behavioural syndrome produced by DMT were individually scored (as previously described) in control animals and in those pretreated with monoamine receptor antagonists. Table 4 contains the *maximum* scores obtained during at least 2 h of observation.

Methysergide, cyproheptadine and cinanserin pretreatment did not alter the maximal intensity of the DMT-induced syndrome compared to animals receiving DMT alone. Phenoxybenzamine and haloperidol pretreated animals exhibited greater prostration and less hyperactivity than the DMT-treated control group. Methergoline pretreated animals initially developed the control DMT-induced behavioural response but from 50 min onwards showed less prostration but greater hyperactivity than animals receiving DMT alone. Propranolol (40 mg/kg i.p.) produced a marked reversal of the DMT-induced effects. Thus, apart from body jerking, the animals appeared almost indistinguishable from animals receiving propranolol alone. Propranolol (20 mg/kg) was almost without effects on the DMT-induced syndrome.

DMT-induced hyperactivity in mice

Mice placed in activity cages showed initial exploratory activity which declined after approximately 30 min as the animals became accustomed to the new environment. Pretreatment with pargyline (75 mg/kg i.p.) reduced this exploratory phase (Figure 2). DMT was administered to animals 2 h after introduction into the activity cages, when habituation was complete. DMT alone in the dose range 0.5 to 8.0 mg/kg produced no change in total motor activity.

DMT (0.5 to 8.0 mg/kg) in animals pretreated with pargyline (75 mg/kg 2 h beforehand) caused a dose-dependent hyperactivity of rapid onset, maximal by 10 min and lasting approximately 120 min (Figures 2 and 3). At low doses (for example 2 mg/kg) animals showed an increase in controlled motor activity, but at higher doses this was disrupted by other behavioural effects, particularly prostration. The increase in activity measured at these higher doses therefore consists mainly of the effects of DMT in inducing swimming movements of the limbs, body jerking and tremor. At a dose of DMT 10 mg/kg some mice died.

In subsequent experiments, animals were pretreated with pargyline (75 mg/kg i.p.) and were given an intraperitoneal dose of DMT 2 mg/kg which produced about a 50% increase in total activity.

The effect of 5-hydroxytryptamine receptor antagonists on DMT-induced hyperactivity in mice

Some 5-HT receptor antagonists increased and others decreased the hyperactivity syndrome produced following administration of DMT (2 mg/kg i.p.) plus pargyline (Figure 4). Mianserin (20 mg/kg i.p.), cyproheptadine (10 mg/kg i.p.) and methergoline (5 mg/kg i.p.) caused increases in activity induced by DMT of 100, 60 and 170% respectively. Cinanserin (10 mg/kg i.p.), on the other hand, reduced DMT-induced hyperactivity by about 40%. 501C67-sulphate (10 mg/kg i.p.) and methysergide (10 mg/kg s.c.) had no effect.

Table 3 Comparison of the behavioural effects produced by administration of *N,N*-dimethyltryptamine (DMT, 15 mg/kg i.p.), L-tryptophan (150 mg/kg i.p.) or quipazine (20 mg/kg i.p.) to rats pretreated with pargyline (75 mg/kg 2 h beforehand)

Behavioural components	*DMT (15 mg/kg i.p.)*	*L-Tryptophan (150 mg/kg i.p.)*	*Quipazine (20 mg/kg i.p.)*
Prostration	+ +/+ + +	+ +/+ + +	+ +/+ + +
Hyperactivity	+ +/+ + +	+ +/+ + +	+ +
Tremor	+*	+ + +	+ + +
Whole body jerks	+/+ +	0/+	0/+
Grooming and sniffing	+	0/+	0/+
Straub tail	+/+ +	+ +	+/+ +
Wet dog shakes	+ +	+ + +	+ +
Reciprocal forepaw treading	0/+*	+ +/+ + +	+ +/+ + +
Head weaving	0/+*	+ +/+ + +	+ +/+ + +
Onset	0–5 min	30–40 min	0–5 min
Duration	120 min	120 min	100 min

Behaviour was assessed as described in the footnote to Table 2.
* $P < 0.05$ compared to L-tryptophan and quipazine-induced behavioural syndromes.

Table 4 The effect of monoamine antagonists on the behavioural syndrome induced by *N,N*-dimethyltryptamine (DMT 15 mg/kg i.p.) in rats pretreated with pargyline (75 mg/kg i.p. 2 h beforehand)

	Control	*Cyproheptadine*	*Methergoline*	*Methysergide*	*Cinanserin*	*Propranolol*	*Phenoxybenzamine*	*Haloperidol*
Behaviour component	+ *DMT*	+ *DMT*	+ *DMT*	+ *DMT*	+ *DMT*	+ *DMT*	+ *DMT*	+ *DMT*
Prostration	+ + / + + +	+ + / + + +	+ + / + + +[1]	+ + / + + +	+ + / + + +	+*	+ + +*	+ + +*
Hyperactivity	+ + / + + +	+ + / + + +	+ + +*	+ + / + + +	+ + / + + +	0/+*	0/+*	+/+ +*
Tremor	0/+	0/+	0/+	0/+	0/+	0*	0/+	0/+
Whole body jerks	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+
Grooming and sniffing	+	+	0/+	+	+	0*	+	+
Straub tail	+/+ +	+/+ +	+	+/+ +	+/+ +	+/0*	+/+ +	+/+ +
Overall score	3	3	2-3	3	3	1-2	3	3

Behaviour was assessed as described in the footnote to Table 2. The scores represent the maximum response exhibited during the period of behavioural observation.

* $P < 0.05$ compared to animals receiving DMT alone.

[1] Significantly reduced ($P < 0.05$) by 50 min.

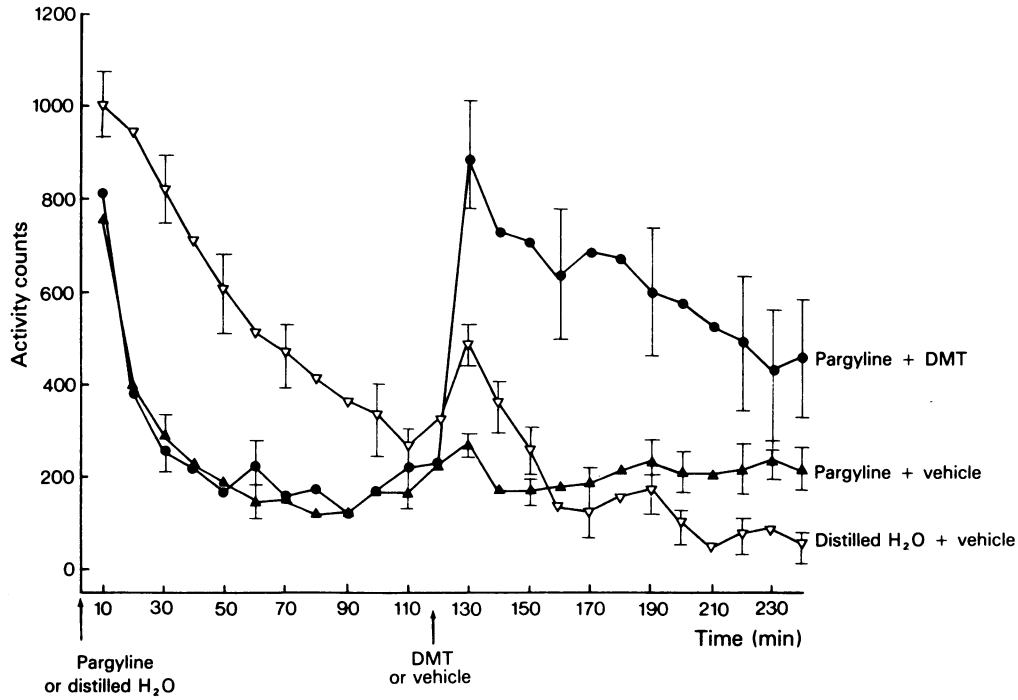

Figure 2 The time course of behavioural activity induced by *N,N*-dimethyltryptamine (DMT) in pargyline pretreated mice recorded by Animex activity meters. Most of the activity recorded consisted of swimming movements of the limbs, tremor and body jerking. Groups of 3 mice were injected with either pargyline (▲, ● 75 mg/kg i.p.) or distilled water (▽), placed in Animex activity cages and allowed 2 h to become accustomed to the environment. Animals then received DMT (● 2 mg/kg i.p.) or vehicle (▲, ▽) and activity was recorded at 10 min intervals over the following 2 h period. Results are expressed as the mean for at least 8 batches of animals; vertical lines show s.e. mean.

Effects of adrenoceptor and dopamine receptor antagonists on DMT-induced hyperactivity in mice

Phenoxybenzamine, an α-adrenoceptor antagonist, had no effect on DMT-induced hyperactivity syndrome, whereas the β-adrenoceptor antagonist, propranolol, caused slight inhibition (Figure 5).

Two potent dopamine receptor antagonists, namely, haloperidol (1 mg/kg i.p.) and pimozide (1 mg/kg i.p.) considerably reduced DMT-induced hyperactivity, as did methiothepin (1 mg/kg i.p.), a neuroleptic with potent dopamine, 5-HT and noradrenaline receptor antagonist properties (Figure 6). Pretreatment of mice with α-methyl-*p*-tyrosine (AMPT; 200 mg/kg i.p. 2 h before DMT), an inhibitor of tyrosine hydroxylase and catecholamine synthesis, did not affect DMT-induced hyperactivity.

DMT in unilateral 6-hydroxydopamine nigro-striatal lesioned mice

Apomorphine (0.5 mg/kg s.c.) induced contralateral circling (5.0 ± 0.4 turns/min, 15 min after injection) in mice with unilateral 6-OHDA-induced lesions of the nigro-striatal pathway, whereas amphetamine (4 mg/kg i.p.) induced ipsilateral circling (5.5 ± 0.6 turns/min, 30 min after injection).

Neither pargyline (75 mg/kg i.p.) alone, DMT (4 mg/kg i.p.) alone nor pargyline (75 mg/kg i.p.) plus DMT (4 mg/kg i.p.) produced consistent turning in either direction (Figure 7).

Discussion

N,N-dimethyltryptamine (DMT), like other hallucinogenic indoleamines, has an inhibitory action on the firing of 5-hydroxytryptaminergic raphe neurones and on neurones in the amygdala and ventral lateral geniculate receiving an identified 5-hydroxytryptaminergic input suggesting agonist activity (Aghajanian & Haigler, 1975). In addition, DMT alters rat spinal reflexes in a manner identical to 5-HT, again suggesting agonist properties of this compound (Anden *et al.*, 1971). Thus, DMT might be expected to cause a behavioural syndrome in rodents like that produced by

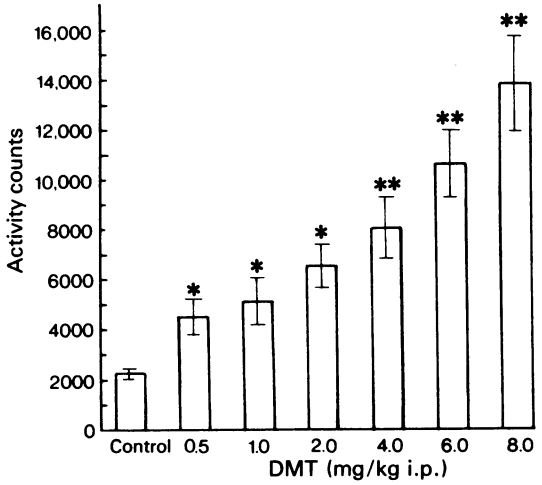

Figure 3 Induction of behavioural hyperactivity in mice pretreated with pargyline (75 mg/kg i.p.), following a range of doses of *N*,*N*-dimethyltryptamine (DMT, 0.5–8.0 mg/kg i.p.) as described in the legend to Figure 2. Activity for the 2 h period following DMT administration is expressed as the mean for at least 9 batches of mice; vertical lines show s.e. mean. * $P < 0.0025$; ** $P < 0.0005$.

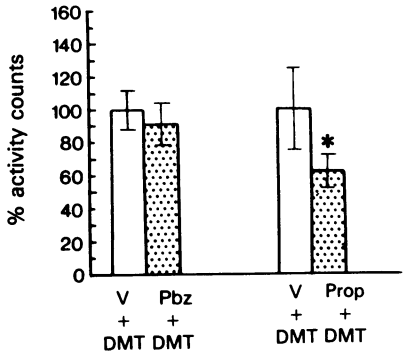

Figure 5 The effect of the adrenoceptor antagonists, phenoxybenzamine and propranolol, on behavioural hyperactivity induced by *N*,*N*-dimethyltryptamine (DMT, 2 mg/kg i.p.) in mice pretreated with pargyline (75 mg/kg i.p.) as described in the legend to Figure 4. Propranolol and phenoxybenzamine pretreatment is described in Table 1. V = vehicle; Pbz = phenoxybenzamine (10 mg/kg i.p.); Prop = propranolol (20 mg/kg i.p.). Groups of control and antagonist pretreated animals were run in parallel to avoid day to day variation in motor activity. Results are expressed as the mean for at least 7 batches of mice; vertical lines show s.e. mean. * $P < 0.05$.

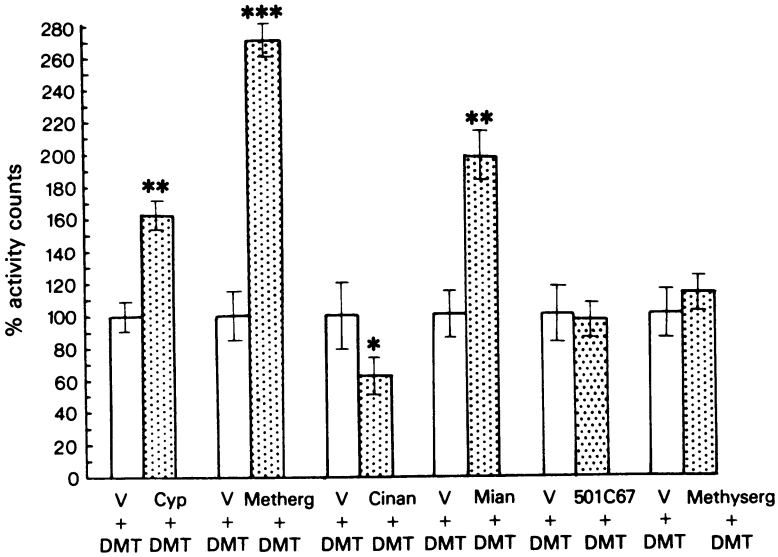

Figure 4 The effect of 5-hydroxytryptamine (5-HT) receptor antagonists on behavioural hyperactivity induced by *N*,*N*-dimethyltryptamine (DMT, 2 mg/kg i.p.) in mice pretreated with pargyline (75 mg/kg i.p.) as described in the legend to Figure 2. Activity following antagonist administration was recorded for 2 h after DMT administration (stippled column) and is presented as a percentage of activity measured in animals receiving pargyline plus DMT alone assessed at the same time (open column). Animals were pretreated with 5-HT antagonists (all given i.p.) as detailed in Table 1. V = vehicle; Cyp = cyproheptadine (10 mg/kg); Metherg = methergoline (5 mg/kg); Cinan = Cinanserin (10 mg/kg); Mian = mianserin (20 mg/kg); 501C67 sulphate (10 mg/kg); Methyserg = methysergide (10 mg/kg). Animals receiving DMT plus pargyline alone were run in parallel with groups also receiving a 5-HT antagonist to avoid day to day variations in motor activity. Results are expressed as the mean for at least 8 batches of animals; vertical lines show s.e. mean. * $P < 0.05$; ** $P < 0.005$; *** $P < 0.0005$.

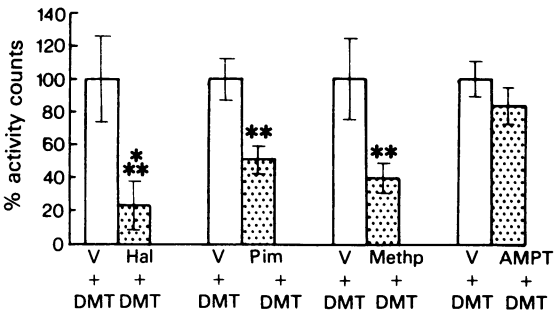

Figure 6 The effect of haloperidol, pimozide, methiothepin and α-methyl-*p*-tyrosine (all given i.p.) on hyperactivity induced by *N,N*-dimethyltryptamine (DMT 2 mg/kg i.p.) in mice pretreated with pargyline (75 mg/kg i.p.) as described in the legend to Figure 4. V = vehicle; Hal = haloperidol (1 mg/kg); Pim = pimozide (1 mg/kg); Methp = methiothepin (1 mg/kg); AMPT = α-methyl-*p*-tyrosine (200 mg/kg). Groups of control and antagonist pretreated animals were run in parallel to avoid day to day variation in motor activity. Results are expressed as the mean ± 1 s.e. mean for at least 4 batches of mice. ** $P < 0.005$; *** $P < 0.0005$.

5-HT agonists or precursors. Indeed, the administration of DMT to rodents pretreated with the MAOI, pargyline, produced a behavioural syndrome of rapid onset, characterized by hyperactivity, hind-limb abduction, prostration, mild tremor, Straub tail, abdominal contractions and jerking. The use of pargyline enhanced the intensity of the syndrome and increased its duration. In the absence of pargyline the syndrome was not obviously dose-dependent. This suggests that metabolism by MAO is a major pathway in rodents for DMT degradation as for other indoleamines (Lu, Wilson, Moore & Domino, 1974; Domino, 1975 and references therein).

The DMT-induced syndrome does contain many of the behavioural components seen following the administration of other presumed 5-HT agonists, L-tryptophan, tryptamine, α-methyltryptamine, 5-methoxy-*N,N*-dimethyltryptamine, *p*-chloro-amphetamine or quipazine all in the presence of a MAOI (Grahame-Smith, 1971; Foldes & Costa, 1973; Jacobs, 1974, 1976; Crow & Deakin, 1977; Deakin & Green, 1978; Sloviter, Drust & Connor, 1978; Marsden, 1978).

Our own comparison of the DMT-induced syndrome with that induced by either L-tryptophan or quipazine revealed a close resemblance in many aspects although wet-dog shakes, head-weaving and reciprocal fore-paw treading was rarely observed in DMT-treated animals. This evidence taken overall suggests that DMT exerts its behavioural effects via an agonist action on cerebral 5-HT receptors.

However, a number of aspects of DMT action are difficult to explain in terms of this simple hypothesis.

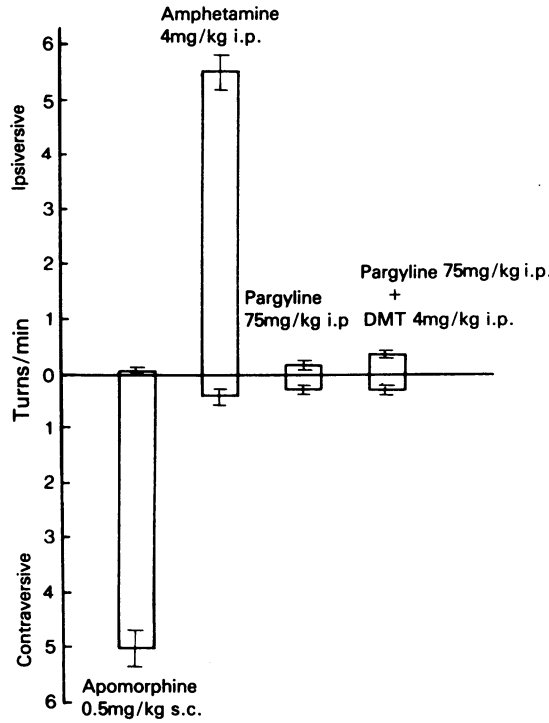

Figure 7 Turning behaviour induced by apomorphine, amphetamine, pargyline, and pargyline plus *N,N*-dimethyltryptamine (DMT) in mice with unilateral 6-hydroxydopamine (16 μg/4 μl 0.9% saline) lesions of the nigro-striatal dopamine pathway. Turning was assessed 15 min after apomorphine (0.5 mg/kg s.c.), 30 min after amphetamine (4 mg/kg i.p.), 1 h after pargyline (75 mg/kg i.p.) and at intervals up to 2 h following DMT (2 mg/kg i.p.) plus pargyline (75 mg/kg i.p.). Results are expressed as the mean number of turns observed in 1 min for at least 12 mice; vertical lines show s.e. mean.

Thus, the ability of some 5-HT antagonists to enhance DMT-induced hyperactivity would not be expected if this compound acts as a post-synaptic 5-HT agonist. Furthermore, the ability of DMT to act as a cerebral post-synaptic 5-HT agonist would appear weak, as judged by receptor binding experiments with [^{3}H]-5-HT (Bennett & Snyder, 1976). It might, therefore, be argued that DMT causes hyperactivity by a direct action on cerebral dopamine pathways. Indeed, biochemical evidence suggests that DMT alone stimulates dopamine release (Waldmeier & Maitre, 1977; Haubrich & Wang, 1977; Smith, 1977). This would be in agreement with the present finding that dopamine antagonists do inhibit DMT-induced hyperactivity. However, other evidence suggests it is unlikely that DMT has any direct actions on cerebral dopamine pathways, either presynapti-

cally or on post-synaptic receptors. Thus, pretreatment of animals with AMPT failed to alter the DMT-induced behavioural response. Further, neither in our study nor in that of Trulson, Stark & Jacobs (1977) did DMT produce any turning behaviour in rodents with unilateral 6-OHDA-induced nigrostriatal lesions. It has also been demonstrated that DMT only weakly displaces [^{3}H]-apomorphine or [^{3}H]-dopamine from their receptor binding sites (Burt, Creese & Snyder, 1976; Whitaker & Seeman, 1977) although it is fairly potent in displacing [^{3}H]-haloperidol; nor does DMT stimulate dopamine-sensitive adenylate cyclase *in vitro* (von Hungen, Roberts & Hill, 1975).

It is therefore difficult to attribute the ability of DMT to induce hyperactivity in rodents to a direct agonist action on either cerebral dopamine or 5-HT receptors. It would appear these effects are mediated indirectly by other mechanisms. The failure of phenoxybenzamine to alter any of the components of DMT syndrome suggests that α-adrenoceptors are not involved. The ability of propranolol to inhibit DMT-induced hyperactivity may be because propranolol interacts directly with brain 5-HT receptors (Green & Grahame-Smith, 1976; Middlemiss, Blakeborough & Leather, 1977; Weinstock, Weiss & Gitter, 1977). Alternatively, an action of DMT at β-adrenoceptors is feasible since another hallucinogenic indole (lysergic acid diethylamide) has been shown to act in this manner (Dolphin, Enjalbert, Tassin, Lucas & Bockaert, 1978).

A single action of DMT on cerebral 5-HT receptors also does not appear responsible for the other behavioural changes it causes. Thus, of the antagonists used, only metergoline or propranolol had any inhibitory action on these behaviours. Other 5-HT antagonists were without effect. Such findings are in agreement with the observation that propranolol and methergoline reverse prostration, head-weaving and fore-paw treading induced by L-tryptophan plus MAOI or 5-methoxy-*N*,*N*-dimethyltryptamine (Deakin & Green, 1978; Sloviter *et al.*, 1978).

In addition, a differential action of 5-HT antagonists has also been demonstrated against the behavioural syndrome induced by the 5-HT agonist 6-chloro-2-[1-piperazinyl]-pyrazine (MK 212). While methysergide and methergoline effectively blocked the behavioural changes, cyproheptadine, cinanserin and the peripheral 5-HT antagonist, xylamidine tosylate, were without activity (Clineschmidt, McGuffin & Pflueger, 1977)..

A number of possibilities exist to explain the selective inhibitory action of some 5-HT antagonists on the DMT-induced syndrome. Perhaps of greatest importance is the fact that most, if not all, of the 5-HT antagonists employed have more than one pharmacological action. In addition, little or nothing is known of the differing ability of these compounds to penetrate to the site of action of DMT (or central 5-HT receptors). It has also been demonstrated that these behaviours when produced by other presumed 5-HT agonists may originate from different areas of the central nervous sytem. Thus, while the hyperactivity and hind-limb abduction produced by L-tryptophan plus a MAOI are dependent on forebrain structures, the other behavioural components originate in the pons, medulla and spinal cord (Jacobs & Klemfuss, 1975). Indeed, spinal transection experiments can further subdivide the site of origin of some behavioural components. The importance of the spinal cord mechanism is demonstrated by the observation that 5,7-dihydroxytryptamine lesion of the 5-HT pathways in spinal cord enhances some of the behavioural changes induced by 5-methoxy-*N*,*N*-dimethyltryptamine (head-weaving, hind-limb abduction, Straub tail) (Deakin & Green, 1978).

The differing anatomical basis for the behavioural components may explain the differential effects of various 5-HT antagonists. Thus, Deakin & Green (1978) have proposed that the ability of methergoline and methysergide to block some components of the behavioural syndrome while enhancing hyperactivity may be because these drugs do not block supra-spinal 5-HT receptors. Indeed, electrophysiological experiments indicate that many 5-HT responses are unaffected by methergoline or methysergide (Haigler & Aghajanian, 1977). Alternatively, the disparity in the data may be explained by the existence of different 5-HT receptor populations in brain with differing functional purpose and differing agonist-antagonist selectivity. Peripheral pharmacological experiments have indicated the existence of at least two types of tryptaminergic or 5-hydroxytryptaminergic receptors (Woolley & Shaw, 1957; Winter & Gessner, 1968; Clineschmidt & Lotti, 1974; Franhuijzer & Bonta, 1974), and this is supported by the differential effect of drugs on hypothermia produced by the intracerebroventricular injection of 5-HT in rabbits (Girault & Jacob, 1979).

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