Behavioural changes induced by N,N-dimethyltryptamine in rodents

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N,N-Dimethyltryptamine (DMT) produces psychotic states in man and has been considered as a causative agent in schizophrenia (Rodnight, 1975). Although DMT may act as a partial agonist at cerebral 5-hydroxytryptamine (5-HT) receptors (Bennett & Snyder, 1976) its mechanism of action remains unknown. We now report behavioural effects of DMT in rodents and their manipulation by drugs acting on cerebral monoamine pathways.

DMT (0.5–8.0 mg/kg i.p.) administered to male Swiss S mice (20–25 g) induced a dose-dependent hyperactivity syndrome comprising increased locomotor activity accompanied by prostration, hind-limb abduction, tremor, Straub tail, retropulsion, jerking and vocalization. Onset of activity occurred within 5 min but was of short duration (20–40 min). Pretreatment with pargyline HCl (75 mg/kg i.p.; 1 h previously) prolonged the duration of action of DMT (120–140 min) ($P < 0.05$) and was subsequently used in all experiments. Pargyline alone was without effect.

Total motor activity produced by DMT (2 mg/kg i.p.) plus pargyline HCl (75 mg/kg i.p.) was judged using groups of 3 mice in Animex activity meters. Pretreatment with the 5-HT receptor antagonists cyproheptadine HCl (10 mg/kg i.p.; 1 h previously) ($P < 0.0025$) and methergoline (5 mg/kg i.p.; 1 h previously) ($P < 0.05$) enhanced DMT-induced activity. In contrast, cinanserin HCl (10 mg/kg i.p.; 1 h previously), another 5-HT receptor antagonist, inhibited DMT-induced activity ($P < 0.05$). The α-adrenoceptor antagonist phenoxybenzamine (10 mg/kg i.p.; 1 h previously) had no effect on DMT-induced activity, whereas the β-adrenoceptor antagonist propranolol (20 mg/kg i.p.; 1 h previously) inhibited the hyperactivity ($P < 0.05$). The dopamine receptor antagonists haloperidol (1 mg/kg i.p.; 1 h previously) and pimozide (1 mg/kg i.p.; 3 h previously) both inhibited DMT-induced activity ($P < 0.0005$) suggesting that DMT might stimulate dopamine receptors. However, administration of DMT (2 mg/kg i.p.) plus pargyline HCl (75 mg/kg i.p.) failed to induce circling behaviour in mice with a 6-hydroxydopamine (16 μg in 4 μl 0.9% saline) induced lesion of one nigro-striatal pathway, although these animals circled contraversively to apomorphine (0.5 mg/kg s.c.) and ipsiversively to amphetamine sulphate (4 mg/kg i.p.).

Administration of DMT (0.5–35 mg/kg) to male Wistar rats (200–300 g) produced a similar dose-dependent behavioural syndrome to that seen in mice. This was again potentiated by pargyline HCl (75 mg/kg i.p.). Animals receiving DMT (15 mg/kg i.p.) plus pargyline HCl (75 mg/kg i.p.) were observed for the presence of the behavioural changes other than increased locomotor activity. Pretreatment with cyproheptadine HCl (10 mg/kg i.p.), methergoline (5 mg/kg i.p.), haloperidol (1 mg/kg i.p.), phenoxybenzamine (10 mg/kg i.p.) or propranolol (20 mg/kg i.p.) 1 h previously failed to prevent the onset of these other behavioural effects, although they did have similar effects on the hyperactivity to those observed in the mouse.

We suggest that the DMT-induced behavioural syndrome comprises two components. One consists of increased motor activity and can be manipulated by drugs acting on cerebral 5-HT and dopamine receptors. The other behavioural changes, however, do not appear to be mediated via a monoamine pathway.

References

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