Br. J. Pharmac. (1978), **64**, 201–209.

THE EFFECTS OF PUTATIVE 5-HYDROXYTRYPTAMINE ANTAGONISTS ON THE BEHAVIOUR PRODUCED BY ADMINISTRATION OF TRANYLCYPROMINE AND L-TRYPTOPHAN OR TRANYLCYPROMINE AND L-DOPA TO RATS

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1 The putative 5-hydroxytryptamine (5-HT) receptor blocking drugs methysergide (10 mg/kg) and methergoline (5 mg/kg) were found to abolish some components of the hyperactivity syndrome, including head weaving and forepaw treading, which follow administration to rats of tranylcypromine (20 mg/kg) and L-tryptophan (100 mg/kg). Hyperactivity and hyper-reactivity were potentiated with a resultant increase in automated locomotor activity counts. In contrast (−)-propranolol (20 mg/kg) inhibited all features of the syndrome. The same results were obtained with these drugs when the behaviour was elicited by *p*-chloroamphetamine (10 mg/kg) or by tranylcypromine and tryptamine (10 mg/kg).

2 Methysergide and methergoline had similar effects on the syndrome produced by tranylcypromine and L-DOPA (50 mg/kg) whereas propranolol was without effect.

3 None of the putative 5-HT receptor antagonists affected brain 5-HT turnover as assessed by rate of accumulation of 5-HT following monoamine oxidase inhibition with tranylcypromine.

4 Microinjections of 5,7-dihydroxytryptamine into the spinal cord resulted in a 70% fall in cord 5-HT concentrations without an effect on brain 5-HT concentrations. The behavioural response to the putative 5-HT receptor agonist, 5-methoxy *N,N*-dimethyltryptamine (2 mg/kg), was potentiated in these animals suggesting that 5-HT receptors become supersensitive on denervation, and that some components of the behavioural syndrome are mediated by spinal cord 5-HT receptors.

5 Pretreatment with α-methyl *p*-tyrosine (2 × 200 mg/kg) delayed the onset of all components of the behaviour elicited by tranylcypromine/L-tryptophan by 60 min, indicating an involvement of catecholamines in the syndrome.

6 *p*-Chloroamphetamine-induced 5-HT depletion had no effect on any component of the tranylcypromine-L-DOPA behaviour.

Introduction

When rats are treated with an irreversible monoamine oxidase (MAO) inhibitor and L-tryptophan they display a complex series of behavioural changes which includes hyperactivity (Hess & Doepfner, 1961; Grahame-Smith, 1971a). The behaviour appears to be due to increased synthesis and 'spill-over' onto the post-synaptic receptors of brain 5-hydroxytryptamine (5-HT) (Grahame-Smith, 1971a); the behavioural changes have been used to investigate the way that various drugs alter 5-HT function in the central nervous system (see reviews of Green & Grahame-Smith, 1976a; Jacobs, 1976).

A similar behavioural syndrome follows administration of a MAO inhibitor and L-DOPA, and this behaviour has been used as an index of dopaminergic function (Everett, Weigland & Rinaldi, 1963; Green & Kelly, 1976). The similarity of the two behavioural syndromes suggests they may have a common neurochemical basis. However, attempts to demonstrate this have produced conflicting results.

The behavioural effects of MAO inhibitor plus tryptophan are dependent on 5-HT synthesis since inhibition of 5-HT synthesis with *p*-chlorophenylalanine inhibits the behaviour (Grahame-Smith, 1971a;

Jacobs, 1974). However, Green & Grahame-Smith (1974) reported that depletion of brain dopamine with α-methyl *p*-tyrosine inhibited the hyperactivity produced by MAO inhibitor plus tryptophan suggesting the involvement of a dopaminergic system. If this dopaminergic system is directly activated by the tranylcypromine/L-DOPA drug combination this could explain the similarity of the tranylcypromine/L-DOPA to the tranylcypromine/L-tryptophan syndrome.

In apparent contradiction of these results, Jacobs (1974; 1976) reported that α-methyl *p*-tyrosine was without effect on most features of the MAO inhibitor plus tryptophan syndrome. Furthermore, Jacobs (1974) observed that *p*-chlorophenylalanine inhibited some of the behavioural components not only of the MAO inhibitor plus tryptophan but also of the MAO inhibitor plus L-DOPA syndrome. He therefore concluded that the similarity of the two syndromes was due to 5-HT release.

Crow & Deakin (1977) suggested that the different behavioural components of the tranylcypromine/tryptophan syndrome might have different neurochemical bases. Conflicting experimental results might thus be explained by methods of quantification of the behaviour which emphasize different behavioural components, for example, automated recordings of activity (Grahame-Smith, 1971a) and ratings of head-weaving and forepaw treading etc. (Jacobs, 1974).

We have re-examined the effects of α-methyl *p*-tyrosine and *p*-chloroamphetamine on different components of the two syndromes in an attempt to clarify their neurochemical bases. We have used both automated activity recordings and ratings of components of the behaviour and have examined the effects of the three putative 5-HT antagonists, methysergide, methergoline and propranolol. Various behavioural and pharmacological findings suggest that both methysergide (Banna & Anderson, 1973) and methergoline (Ferrini & Glässer, 1965; Fuxe, Agnati & Everitt, 1975) are 5-HT receptor antagonists. More recently the β-adrenoceptor antagonist (−)-propranolol has been shown to inhibit the tranylcypromine/L-tryptophan hyperactivity (Green & Grahame-Smith, 1976b) and Middlemiss, Blakeborough & Leather (1977) reported that (−)-propranolol was as potent as methysergide in inhibiting 5-HT binding in brain.

On the basis of brain transection experiments Jacobs & Klemfuss (1975) suggested that the tranylcypromine and tryptophan syndrome is mediated by spinal cord 5-HT neurones. As a more direct test of this hypothesis, we investigated the effects of selective destruction of spinal cord 5-HT neurones by intra spinal microinjections of the neurotoxin 5,7-dihydroxytryptamine on the syndrome elicited by 5-methoxy *N*,*N*-dimethyltryptamine.

Methods

Adult male Sprague-Dawley derived rats weighing 150 to 220 g (Anglia Laboratory Animals, Alconbury, Huntingdon) were used.

Behavioural measurements

Hyperactivity was measured in groups of 3 animals by means of LKB Animex activity meters (sensitivity and tuning: 30 μA) as previously described (Grahame-Smith, 1971a; Green & Grahame-Smith, 1974). Results were collected as movements/min and the means of successive 5 min periods are plotted on the graphs.

The locomotor activity elicited by 5-methoxy *N*,*N*-dimethyl tryptamine (5-MeODMT) in the 5,7-dihydroxytryptamine (5,7-DHT) lesioned animals was measured during the period 10 to 20 min after 5-MeODMT administration on individual animals with LKB Animex meters and results are given as mean movements/min during this time.

The following behavioural changes were rated in individual animals during activity recording: hind-limb abduction, head weaving, Straub-tail, forepaw treading and hyper-reactivity and were scored on the following scale: 0-absent, 1-equivocal, 2-definite, 3-severe.

Biochemical measurements

Brain 5-HT was measured in whole brain and spinal cord (from immediately behind the cerebellum to approximately T5) by the fluorometric method of Curzon & Green (1970).

Lesion experiments

Rats were pretreated with protriptyline (25 mg/kg) 30 min preoperatively to prevent non-specific damage to noradrenaline neurones. The rostral spinal cord was exposed between C1 and C2 and stabilized by traction applied to the hind limbs, the head being held in a stereotactic frame. 5,7-DHT 6 μg in 2 μl of 2% w/v ascorbic acid in saline was injected bilaterally approximately 0.7 mm off the midline and 1.7 mm below the surface. No motor impairment was produced by this procedure.

Drugs

Drugs were obtained from the following sources; tranylcypromine (Smith, Kline & French); L-tryptophan, L-DOPA, *p*-chloroamphetamine, α-methyl *p*-tyrosine, tryptamine (Sigma); 5,7-dihydroxytryptamine creatine sulphate (Regis, Chicago); methysergide (Sandoz); methergoline (Farmitalia, Milan);

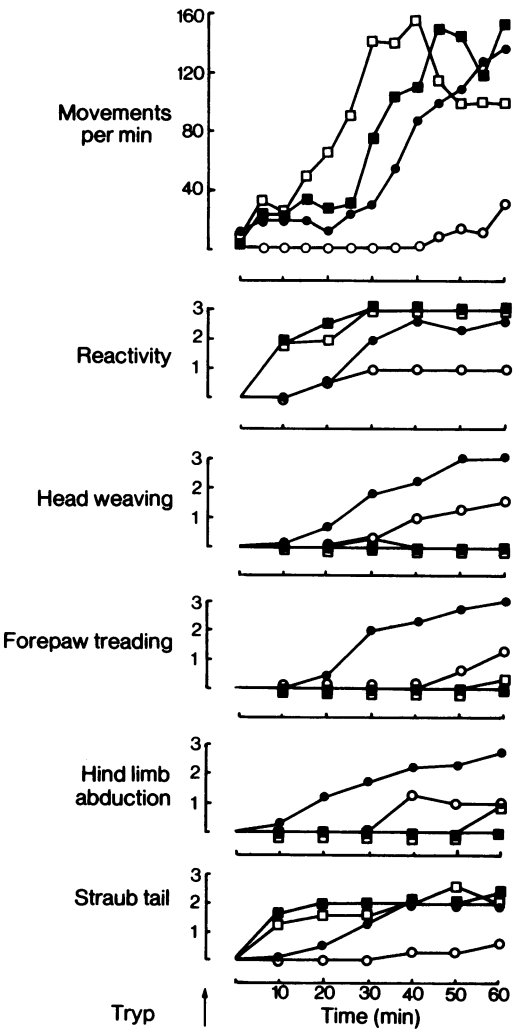

Figure 1 Effects of methysergide, methergoline and propranolol on behaviour elicited by tranylcypromine and tryptophan in rats: (●) saline pretreated; (○) (−)-propranolol (20 mg/kg) 45 min before tranylcypromine (20 mg/kg); (□) methysergide (10 mg/kg) with tranylcypromine (20 mg/kg); (■) methergoline (5 mg/kg) with tranylcypromine (20 mg/kg). Tryptophan (Tryp, 100 mg/kg) was injected 30 min after tranylcypromine in each group. Details of activity and behavioural ratings in text. Animals were grouped in 3s for activity recording. Individual animals were rated at same time as activity recording. Behavioural ratings show means of 6 saline pretreated animals and 3 in each of the drug pretreated groups. Differences between saline and drug pretreated animals are significant ($P < 0.05$, Fisher's exact probabilities test) for at least three time points on all measures except Straub tail.

(−)-propranolol (ICI); 5-methoxy *N,N*-dimethyltryptamine (Sigma).

All drugs except 5,7-dihydroxytryptamine (see Lesion methods above) were injected intraperitoneally. L-Tryptophan, *p*-chloroamphetamine and methysergide were dissolved in 0.9% w/v NaCl solution (saline). L-DOPA and α-methyl *p*-tyrosine were suspended in saline containing 1% carboxymethyl cellulose. Methergoline was dissolved in 0.7% w/v ascorbic acid in water and injected immediately. Control animals received the appropriate vehicle.

Results

Effects of methergoline, methysergide and (−)-propranolol on the behaviour produced by tranylcypromine and L-tryptophan

Rats were either pretreated with (−)-propranolol (20 mg/kg) 45 min before tranylcypromine (20 mg/kg) or were given methysergide (10 mg/kg) or methergoline (5 mg/kg) at the same time as tranylcypromine (20 mg/kg). L-Tryptophan (100 mg/kg) was injected 30 min after the tranylcypromine.

Methergoline (5 mg/kg) and methysergide (10 mg/kg) produced almost total inhibition of forepaw treading, headweaving, Straub-tail and hind limb abduction (Figure 1). However locomotor activity, which was well co-ordinated, was still present. The animals became extremely hyper-reactive (Figure 1). They 'piled together' in one corner of the cage and would suddenly rush around the cage before returning to the group. This response could be elicited reproducibly by sound or movement near the cage but also occurred without obvious stimulation. In consequence, while the behaviour produced by tranylcypromine and L-tryptophan was considerably altered by pretreatment by methergoline or methysergide, this change was not reflected in the Animex counts which showed no decrease (Figure 1).

In contrast to the effects of methergoline and methysergide, (−)-propranolol (20 mg/kg) pretreatment almost totally abolished all the behavioural changes including hyper-reactivity and the animals looked almost normal for the first 60 min (Figure 1). These changes were reflected in reduced Animex counts (Figure 1).

Effects of methergoline and (−)-propranolol on the behaviour produced by p-chloroamphetamine or tranylcypromine and tryptamine

Administration to rats of *p*-chloroamphetamine (10 mg/kg) rapidly induces the same behavioural changes as those observed after tranylcypromine and L-tryptophan and it seems likely that this behaviour is due

to 5-HT release (see Frey & Magnussen, 1968; Jacobs, 1976; Green & Kelly, 1976). A closely similar syndrome can also be produced by administration of MAO inhibitor and tryptamine (Foldes & Costa, 1975). We therefore investigated the effect of methergoline and propranolol on these behavioural changes.

When methergoline (5 mg/kg) was given 60 min before either *p*-chloroamphetamine (10 mg/kg) or tranylcypromine (10 mg/kg) followed by tryptamine (10 mg/kg) 30 min later, it abolished the same behavioural changes as when given before tranylcypromine/L-tryptophan but again spared the hyper-reactivity and sudden bursts of locomotor activity.

(−)-Propranolol (20 mg/kg) pretreatment abolished the behavioural changes produced by *p*-chloroamphetamine or tranylcypromine/tryptamine, as it did when given before tranylcypromine/L-tryptophan.

Effects of methergoline, methysergide and (−)-propranolol on the behavioural changes produced by tranylcypromine and L-DOPA

These experiments were conducted exactly as those studying the effects of the putative 5-HT receptor blocking drugs on the tranylcypromine/L-tryptophan behaviour (see above) except that L-DOPA (50 mg/kg) was given instead of L-tryptophan.

In agreement with Jacobs' (1974) observations, we found that methysergide inhibited several of the behavioural changes normally seen (Figure 2). Again the rats displayed marked hyper-reactivity and sudden bursts of co-ordinated locomotor activity around the cage, interspersed with periods of immobility. Methergoline pretreatment had the same effects as methysergide on this behavioural syndrome. It was observed that animals pretreated with either of these drugs died much more rapidly after tranylcypromine/L-DOPA administration. Ferrini & Glässer (1965) also noted that methergoline increased the toxicity of L-DOPA.

In contrast (−)-propranolol (20 mg/kg) given 45 min before the tranylcypromine did not abolish any of the behavioural changes occurring in this syndrome (Figure 2).

The effect of depleting brain 5-hydroxytryptamine with p-chloroamphetamine on the behaviour produced by tranylcypromine and L-DOPA

The original findings of Green & Kelly (1976) were confirmed and it was observed that all the behavioural changes such as forepaw treading and head weaving were still present in animals pretreated with *p*-chloroamphetamine (Figure 3). Furthermore these changes were still present 90 min after L-DOPA administration and did not diminish as might be expected if residual 5-HT were being further depleted.

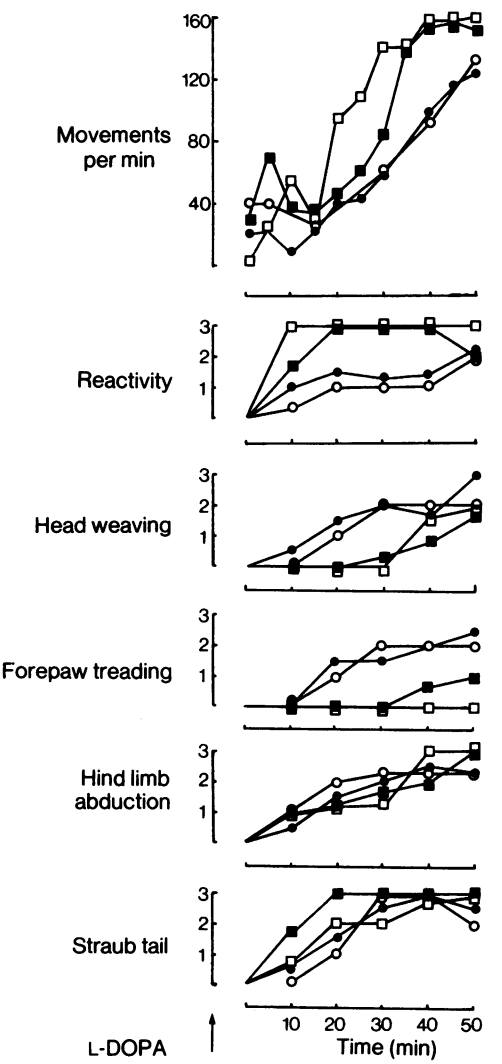

Figure 2 Effects of methysergide, methergoline and propranolol on behaviour elicited by tranylcypromine and L-DOPA in rats. Key as Figure 1. L-DOPA (50 mg/kg) injected 30 min after tranylcypromine in each group. Behavioural ratings show mean of 12 saline pretreated animals and 3 in each of the drug pretreated groups. Differences between methergoline or methysergide and saline pretreated animals are significant ($P < 0.05$, Fisher's exact probabilities test) for at least three time points on reactivity, head weaving and forepaw treading.

Effect of α-methyl p-tyrosine on the behaviour produced by tranylcypromine and L-tryptophan

We also investigated the effect of α-methyl *p*-tyrosine

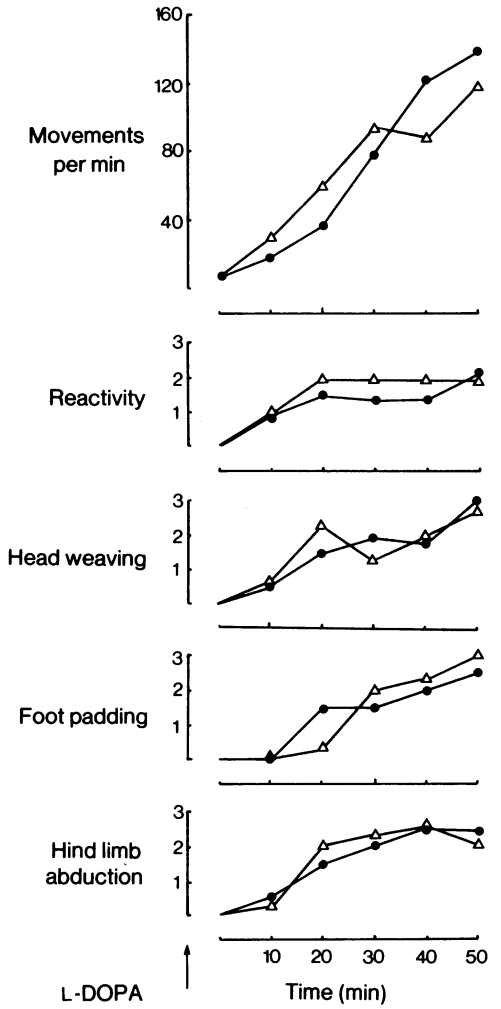

Figure 3 Lack of effect of *p*-chloroamphetamine pretreatment on behaviour elicited by tranylcypromine and L-DOPA: (●) saline controls; (△) *p*-chloroamphetamine (10 mg/kg) 24 h before tranylcypromine (20 mg/kg) injection. L-DOPA (50 mg/kg) injected 30 min after tranylcypromine; 3 animals per group.

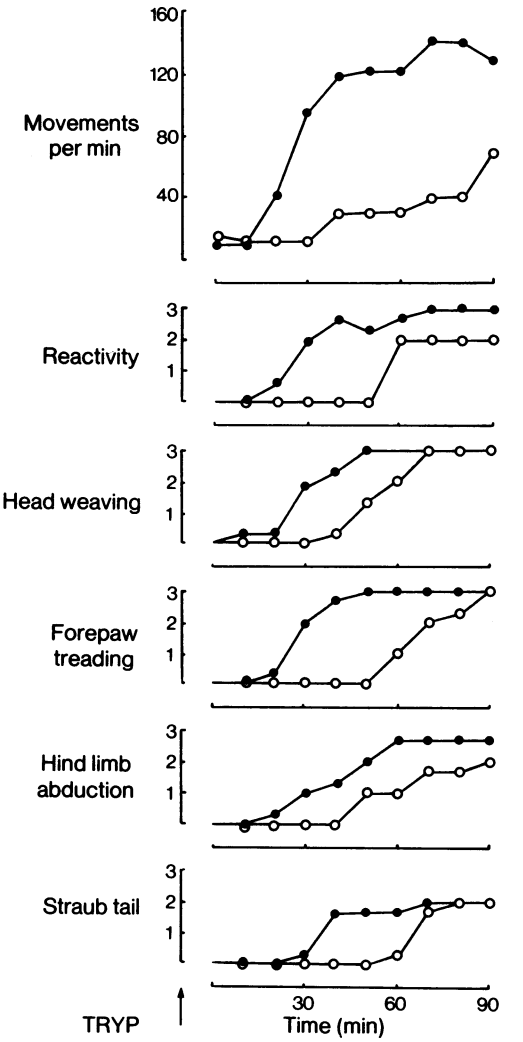

Figure 4 Effects of α-methyl *p*-tyrosine pretreatment on behaviour elicited by tranylcypromine and tryptophan: (●) saline controls; (○) α-methyl *p*-tyrosine (200 mg/kg) 18 and 16 h before tranylcypromine (20 mg/kg) injection. Tryptophan (Tryp, 100 mg/kg) 30 min after tranylcypromine. 3 animals per group. Differences between saline and α-methyl *p*-tyrosine pretreated animals significant on all measures for at least three time points ($P < 0.05$, Fisher's exact probabilities test).

pretreatment on the behaviour produced by tranylcypromine/L-tryptophan in view of the discrepancy between the observations of Green & Grahame-Smith (1974) and Jacobs (1974).

Rats were pretreated with α-methyl *p*-tyrosine (200 mg/kg) at 15 h 00 min and 17 h 00 min. At 09 h 00 min the next morning the animals were given tranylcypromine (20 mg/kg) followed by L-tryptophan (100 mg/kg) 30 min later.

We confirmed the previous observation (Green & Grahame-Smith, 1974) that α-methyl *p*-tyrosine pretreatment almost totally abolished the locomotor activity response. Furthermore, ratings of the individual behavioural components of the syndrome were also reduced. This effect lasted for approximately 60 min

after which time the α-methyl *p*-tyrosine pretreated animals gradually developed the full syndrome (Figure 4).

Effects of methergoline, methysergide and propranolol on the concentration and synthesis rate of 5-hydroxytryptamine in brain and spinal cord

None of the putative antagonists altered the steady state concentration of 5-HT in brain and spinal cord (Table 1). Neither did any of these compounds significantly alter the rate of 5-HT synthesis, measured as the rate of accumulation of 5-HT during the 60 min following MAO inhibition, as in the method described by Neff & Tozer (1968).

Effect of lesioning of the spinal cord 5-hydroxytryptamine neurones on the behaviour produced by 5-methoxy N,N-dimethyltryptamine

The descending 5-HT pathways to the cord were lesioned as described in the Methods. After 9 days, when 5-HT receptors have been shown to exhibit denervation supersensitivity (Trulson, Eubanks & Jacobs, 1976) the rats were injected with tranylcypromine (20 mg/kg) followed 30 min later by the 5-HT agonist 5-MeODMT (2 mg/kg) (Grahame-Smith, 1971b). Following administration of this 5-HT agonist the lesioned animals developed significantly more marked head weaving, Straub-tail and hind limb abduction (Table 2). There was an increase in forepaw treading which just failed to reach statistical significance ($P < 0.075$). The increase in these behavioural changes resulted in an increase in the activity meter counts. It was confirmed that the lesion resulted in a 70% reduction in cord 5-HT concentrations without reducing forebrain concentrations (Table 2).

Discussion

When rats were pretreated with methysergide and methergoline before tranylcypromine and L-tryptophan administration, the behavioural changes, which are dependent on increased brain 5-HT synthesis (Grahame-Smith, 1971a), were markedly altered. Foot padding, head weaving, and hind limb abduction were almost completely absent in these animals as has been previously reported (Crow & Deakin, 1977). However, hyper-reactivity was greatly potentiated and rats displayed sudden bursts of locomotion about the cage. Consequently the activity counts were increased although produced by a radically different behaviour in the methysergide and methergoline pretreated rats.

Administration of either *p*-chloroamphetamine or tranylcypromine and tryptamine results in the appearance of syndromes indistinguishable from those seen after tranylcypromine and L-tryptophan and there is evidence that these syndromes also result from release of brain 5-hydroxytryptaminergic systems (Foldes & Costa, 1975; Jacobs, 1976; Green & Kelly, 1976). These syndromes were affected by

Table 1 Effects of putative 5-hydroxytryptamine (5-HT)-receptor blocking drugs on 5-HT synthesis in brain and spinal cord

	Tissue amine concentration (μg 5-HT/g tissue)		*5-HT synthesis (μg g⁻¹ h⁻¹)*
	Saline injected	*Tranylcypromine injected*	
Brain			
Saline	0.42 ± 0.02 (10)	0.58 ± 0.03 (10)	0.16
Methysergide	0.41 ± 0.01 (5)	0.59 ± 0.03 (5)	0.18
Methergoline	0.44 ± 0.04 (9)	0.65 ± 0.02 (9)	0.21
Propranolol	0.45 ± 0.02 (8)	0.59 ± 0.02 (10)	0.14
Spinal cord			
Saline	0.96 ± 0.06 (9)	1.20 ± 0.11 (7)	0.24
Methysergide	0.96 ± 0.04 (9)	1.32 ± 0.18 (13)	0.36
Methergoline	0.94 ± 0.02 (4)	1.26 ± 0.04 (9)	0.32
Propranolol	0.93 ± 0.02 (4)	1.30 ± 0.03 (6)	0.37

For basal 5-HT concentrations, rats were injected with (−)-propranolol (20 mg/kg), 45 min before death, or with methysergide (10 mg/kg) or methergoline (5 mg/kg) 60 min before death and 5-HT concentrations measured. For synthesis rates the rats were injected with tranylcypromine (20 mg/kg) 45 min after propranolol or 60 min after methysergide or methergoline and the concentration of 5-HT measured 60 min after the injection of the MAO inhibitor. There are no statistically significant drug effects as assessed by *t*-tests. Figures are means ± s.e. mean.

methysergide and methergoline in the same way as the tranylcypromine/L-tryptophan syndrome.

Lesioning of the spinal cord 5-HT tracts by discrete injection of 5,7-DHT resulted in an enhanced behavioural response to the 5-HT agonist, 5-MeODMT, which is consistent with the view of Jacobs & Klemfuss (1975) that the syndrome is predominantly mediated by spinal 5-HT systems and with other evidence that 5-HT receptors become supersensitive on denervation (Trulson *et al.*, 1976; Hole, Fuxe & Johnson, 1976).

Methergoline and methysergide were effective in blocking those behavioural changes that appeared to be spinal in origin (Straub tail, hind limb abduction, forepaw treading and head weaving) leaving intact the hyperactivity (locomotion) and hyper-reactivity. Propranolol on the other hand was very effective in inhibiting all aspects of the behavioural changes.

We can only speculate on the reasons for these observations. One possibility is that all the behaviour is 5-hydroxytryptaminergic and that propranolol blocks 5-HT receptors in all parts of the CNS whereas methergoline and methysergide do not block those nonspinal 5-HT receptors which mediate hyper-reactivity. Electrophysiological experiments indicate that many 5-hydroxytryptaminergic responses are unaffected by methergoline and methysergide (Haigler & Aghajanian, 1977). Alternatively, the hyper-reactivity component may not involve 5-HT release and thus not be blocked by methergoline or methysergide. However, the global efficacy of propranolol on the behavioural components could not then be simply explained in terms of 5-HT receptor antagonism.

None of the putative antagonists (including propranolol) altered the steady state of 5-HT in the brain or spinal cord. Neither did they alter the rate of 5-HT synthesis in these two tissues and no selective effects of methysergide or methergoline on spinal cord metabolism were observed. Previously, Fuxe *et al.* (1975) found a small increase in 5-HT synthesis following methergoline. Our results showed a similar tendency but this failed to reach statistical significance. These observations suggest that the situation in 5-hydroxytryptaminergic systems is quite different from that in the dopaminergic system where receptor blockade with neuroleptics increases turnover (Sharman, 1963).

α-Methyl *p*-tyrosine antagonized the behaviour produced by tranylcypromine/L-tryptophan for 60 min after tryptophan administration. Foldes & Costa (1975) found that intraventricular administration of 6-hydroxydopamine also abolished this behaviour. It seems clear therefore that the tranylcypromine/L-tryptophan behaviour is dependent not only on increased 5-HT synthesis but also intact brain catecholaminergic function.

Since catecholaminergic systems are directly activated by tranylcypromine/L-DOPA it might be expected that 5-hydroxytryptaminergic mechanisms would not be involved in the behavioural effects of this drug combination. The lack of effect of *p*-chloroamphetamine-induced 5-HT depletion on the tranylcypromine/L-DOPA behaviours is in accordance with this view (Figure 3). However, the putative 5-HT receptor antagonists methergoline and methysergide blocked some components of the syndrome whereas propranolol was completely ineffective.

Table 2 Behavioural effects of tranylcypromine plus 5-methoxy *N,N*-dimethyltryptamine in control and spinal 5,7-dihydroxytryptamine-lesioned animals

	Control	*Lesioned*	P (*t-test*)
No. of observations	10	5	
Head weaving	1.5 ± 1.0	2.8 ± 0.4	<0.02
Forepaw padding	1.8 ± 1.0	2.8 ± 0.4	NS
Hind limb abduction	1.7 ± 0.5	2.8 ± 0.4	<0.01
Straub tail	1.5 ± 0.7	2.8 ± 0.4	<0.01
Reactivity	1.4 ± 0.8	2.2 ± 0.4	NS
Locomotor counts/min	79.0 ± 19.0	123.0 ± 18.0	<0.01
Temperature °C	36.6 ± 0.4	38.0 ± 0.8	<0.02
Conc. of 5-HT in spinal cord	0.53 ± 0.10	0.14 ± 0.01	<0.01
Conc. of 5-HT in brain	1.01 ± 0.23	0.87 ± 0.12	NS

Experimental details of lesioning of spinal cord and behavioural scoring are given in Methods section. NS: not significantly different from control. Means ± s.e. means.

The evidence that propranolol does have activity as a 5-HT antagonist, apart from that presented here, is quite strong. Weinstock, Weiss & Gitter (1977) observed that propranolol not only inhibited 5-hydroxytryptophan-induced head twitches in mice but also blocked the contraction produced by 5-HT in the rat fundus strip preparation. Middlemiss *et al.* (1977) reported that this drug had almost the same potency as methysergide in inhibiting *in vitro* 5-HT binding to rat brain synaptic membranes. It seems likely therefore that tranylcypromine/L-DOPA behaviours do not involve 5-HT release. If this is the case then the ability of methergoline and methysergide to antagonize some of the tranylcypromine/L-DOPA behaviours must depend on actions in addition to 5-HT receptor blockade. This conclusion is supported by the recent demonstration that methergoline and other 5-HT receptor antagonists significantly antagonize dopamine-sensitive adenylate cyclase (Enjalbert, Hamon, Bourgoin & Brockaert, 1978).

We thank Smith, Kline and French for tranylcypromine, Farmitalia for methergoline and ICI for propranolol.

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(*Received October 18, 1977.*
Revised June 2, 1978.)