5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT) given after tranylcypromine produces hyperactivity and hyperpyrexia similar to that seen after tranylcypromine and L-tryptophan, but with a different time course, and it has been proposed that 5-MeODMT acts as a 5-HT analogue, at sites stimulated by 5-HT (Grahame-Smith, 1971b). Pretreatment of rats with α-MPT inhibited the hyperactivity normally produced by the administration of tranylcypromine (20 mg/kg) and 5-MeODMT (1 mg/kg and 5 mg/kg).

The results of these experiments are interpreted tentatively as follows. At some point between the post-synaptic receptor sites for 5-HT initiating the production of the hyperactivity syndrome and the total brain mechanisms responsible for the expression of this syndrome, lie a group of dopaminergic neurones, the activity of which is dependent upon adequate dopamine concentrations. The depletion of dopamine thus breaks the neuronal sequences necessary for the behavioural expression of 5-HT receptor site stimulation.

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The role of brain 5-hydroxytryptamine in the hyperactivity produced in rats by lithium and monoamine oxidase inhibition

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The administration to male Wistar rats of 3 M Eq/kg LiCl (s.c.) twice daily for three days followed on day 4 by a monoamine oxidase (MAO) inhibitor, either tranylcyprome (20 mg/kg) or pargyline (75 mg/kg), results in a characteristic hyperactivity syndrome identical to that produced by tranylcypromine and L-tryptophan (Grahame-Smith, 1971). Plasma lithium concentrations 16 h after the last injection of LiCl were 1.10 ± 0.43 mEq/l ($n = 6$). At least three injections of 3 mEq/kg LiCl were necessary before any hyperactivity was apparent, though one dose of 10 mEq/kg LiCl 5 h before tranylcypromine also caused hyperactivity with plasma lithium concentrations of 5.16 ± 0.30 mEq/l ($n = 6$).

When p-chlorophenylalanine (300 mg/kg) was given i.p., on the first two days of LiCl treatment (3 mEq/kg twice daily), the hyperactivity produced by MAO inhibition was abolished. Since p-chlorophenylalanine in this dose inhibits brain 5-hydroxytryptamine (5-HT) synthesis and also inhibits the hyperactivity resulting from L-tryptophan administration and MAO inhibition (Grahame-Smith, 1971a), this result suggests a role for 5-HT in hyperactivity produced by lithium treatment and MAO inhibition.

The rate of brain 5-HT synthesis was increased 70% by lithium pretreatment as judged by the rate of 5-HT accumulation after MAO inhibition (Table 1) and by the rate of 5-hydroxy-indole acetic acid accumulation after probenecid (200 mg/kg). This increase in brain 5-HT synthesis could not be related to an increase of brain tryptophan contrary to the report of Perez-Cruet, Tagliamonte, Tagliamonte & Gessa (1971).

Table 1 Effect of lithium on rate of rat brain 5-hydroxytryptamine synthesis

Treatment	*Brain 5-hydroxytryptamine (μg 5-HT/g brain wet wt.)*	
	NaCl	*LiCl*
Control	0.54 ± 0.02 (9)	0.55 ± 0.02 (12)
Tranylcypromine (20 mg/kg)	0.80 ± 0.05 (12)	0.99 ± 0.09 (11)
Pargyline (75 mg/kg)	0.82 ± 0.03 (9)	1.03 ± 0.04 (11)
Mean rate of 5-HT synthesis after MAO inhibition (μg/g)/h	0.27	0.46

Measurement of 5-HT was made 1 h following injection of saline (controls) or the monoamine oxidase inhibitors.

Measurement of 5-HT was made 1 h following injection of saline (controls) or the monoamine oxidase inhibitors.

From previous data on the quantitative relationship between increased synthesis of brain 5-HT and hyperactivity produced by L-tryptophan and MAO inhibition (Grahame-Smith, 1971), the degree of increase of 5-HT synthesis after lithium and MAO inhibition did not account completely for the hyperactivity. In addition, one dose of LiCl (3 mEq/kg), 5 h before tranylcypromine, followed 30 min later by L-tryptophan (50 mg/kg), potentiated the hyperactivity. This dose of LiCl did not effect brain 5-HT synthesis.

Lithium pretreatment did not potentiate the hyperactivity produced by 5-methoxy-*N,N*-dimethyltryptamine, which is thought to stimulate post-synaptic 5-HT receptor sites (Grahame-Smith, 1971b), indicating that lithium does not alter the post-synaptic response to 5-HT.

It seems likely that chronic lithium treatment not only causes an increase in 5-HT synthesis but may also increase that proportion of the 5-HT synthesized which is available for functional activity. The precise mechanisms by which lithium produces these effects is not yet known.

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Mechanism of the early pressor effect of centrally administered propranolol in the conscious rabbit

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In a previous communication (Dollery, Lewis, Myers & Reid, 1973) we reported that the intracerebroventricular (ICV) propranolol in the conscious rabbit produced a transient rise in mean arterial pressure (MAP) followed by a prolonged fall. Destruction of central noradrenergic (NA) neurones with intracisternal 6-hydroxydopamine (6-OHDA) diminished the early rise and abolished the fall. The hypotensive effect was thought to be due to adrenoceptor blockade since it was shown only by the (−)-isomer. The early rise in MAP, however, followed ICV injection of both isomers. In the following experiments we have further investigated the mechanism of this early pressor effect in the conscious rabbit.

ICV (+)-propranolol (500 μg) produced a maximum rise in MAP of 76.2 ± 8.7 mmHg and increase in heart rate (HR) of 103 ± 36 b/min at 5 minutes. Pretreatment with ICV desmethylimipramine (DMI−1.25 mg), a tricyclic compound which inhibits the uptake of noradrenaline into NA neurones (Uptake$_1$) reduced the early rise in MAP following ICV (+)-propranolol to 8.6 ± 9.4 mmHg at 5 minutes. The central injection of DMI (1.25 mg) caused an increase in MAP (35.9 ± 8.3 mmHg) and HR (50 ± 14 b/min) at 5 min with a return to near baseline at 30 minutes. These observations are consistent with those of Lewis, Rawlins & Reid (1972) that ICV NA and 6-OHDA both raise MAP in this preparation, supporting the hypothesis that central NA neurones are concerned with the maintenance of arterial pressure. The possibility that ICV (+)-propranolol causes a rise in MAP and HR by releasing endogenous stores of NA was therefore studied.

ICV pre-treatment with the alpha-adrenoceptor blocking agent yohimbine (150 μg) 30 min before the central administration of (+)-propranolol resulted in a significantly diminished pressor response (increase in MAP 14.0 ± 6.8 mmHg and HR 38 ± 15 b/min) at 5 minutes. Depletion of central NA by the ICV injection of reserpine (100 μg) 24 h previously, reduced the rise in MAP and HR following ICV (+)-propranolol to 17.1 ± 8.0 mmHg and 0 ± 10 b/min respectively, at 5 minutes.

These results are consistent with the hypothesis that propranolol is taken up into NA neurones via Uptake$_1$ and causes the release of endogenous NA which has a central pressor effect. It appears therefore that central NA neurones participate in both the early pressor and late hypotensive actions of ICV propranolol.

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