brain under cold conditions, or an increase only in the hypothalamus (Simmonds, 1969).

The difference in results obtained may be related to the use of an inhibitor of catecholamine synthesis in Gordon's experiments, since it has been reported that α-methyl tyrosine can produce hypothermia (Papeschi & Randrup, 1973) and this may be the effect which is associated with the increased noradrenaline turnover, rather than the cold stress alone. To investigate this possibility we have attempted to relate hypothermia to brain catecholamine depletion in the rat after the administration of inhibitors of catecholamine biosynthesis (α-methyl tyrosine methylester, 400 mg/kg i.p.; 3-iodo-tyrosine, 200 mg/kg i.p.; and sodium diethyldithiocarbamate, 500 mg/kg i.p.). In addition, we have attempted to modify the effects of these drugs either by stimulating heat production after administration of thyroxine, or by inhibiting heat production with very large doses of methimazole, an inhibitor of thyroid hormone synthesis. We have found a relationship between hypothermia and dog brain catecholamine depletion, which is altered by exposing the animals to cold stress (4-5°) for 2 hours. This relationship is largely independent of drug treatment, except that α-methyl tyrosine produced a more marked hypothermia than was anticipated from the associated depletion of brain catecholamines.

It is thought that this relationship between hypothermia and central catecholamine depletion may explain some differences between interpretation of experimental results obtained by others. Also, it is suggested that this work may have implications for the feedback control of core temperature, and that it throws some doubt on the validity of using inhibition of brain catecholamine biosynthesis as a means of assessing central catecholamine turnover.

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The role of brain dopamine in the hyperactivity syndrome produced in rats after administration of L-tryptophan and a monoamine oxidase inhibitor

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Administration to rats of tranylcypromine (20 mg/kg) followed 30 min later by L-tryptophan (100 mg/kg) results in a characteristic syndrome of hyperactivity and hyperpyrexia, which appears to be due to the central action of the increased rate of brain 5-hydroxytryptamine (5-HT) synthesis produced by this treatment (Grahame-Smith, 1971a). The role of brain catecholamines in the production of this syndrome has now been studied.

Injection of 2 x 200 mg/kg α-methyl p-tyrosine (α-MPT) i.p., a tyrosine hydroxylase inhibitor, at 18 and 16 h before administration of the tranylcypromine (20 mg/kg) followed 30 min later by L-tryptophan (100 mg/kg) completely abolished the hyperactivity and hyperpyrexia. At this time brain noradrenaline (NA) and dopamine (DA) concentrations were both decreased about 75%, while brain tryptophan and 5-hydroxytryptamine (5-HT) rose to the concentrations observed in rats not pretreated with αMPT. The αMPT analogue α-methyl m-tyrosine which does not inhibit brain catecholamine synthesis did not inhibit hyperactivity. Administration of L-dopa (150 mg/kg) i.p., 1 h after the second injection of α-MPT restored brain DA concentrations to 75% of control values, did not restore brain NA concentrations but did bring back the hyperactivity response to tranylcypromine and tryptophan. Brain tryptophan and 5-HT concentrations rose as before. The dopamine-β-hydroxylase inhibitor, disulfiram (400 mg/kg) i.p., given 6 h before the tranylcypromine and L-tryptophan did not inhibit hyperactivity. Disulfiram caused a 75% depletion of brain NA concentrations but had no effect on brain DA levels. These findings suggested that dopamine might be involved in the post-synaptic responses to increased 5-HT release produced by tranylcypromine and tryptophan treatment.

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.