R.W.K. is an MRC scholar. G.P.L. acknowledges financial support from the Wellcome Trust. NMDA was kindly supplied by Dr. J. Watkins, University of Bristol.

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On the importance of mesolimbic mechanisms for the control of apomorphine induced climbing behaviour in the mouse

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Climbing behaviour in the mouse has been forwarded as a model for detecting dopamine agonist and antagonist activity (Costall, Naylor & Nohria, 1978; Protais, Costentin & Schwartz, 1976). On the basis of electrolesion studies Protais, *et al.*, (1976) have suggested that the striatum plays a major role in the control of apomorphine induced climbing whilst Costall, Naylor & Nohria (1979) have suggested an additional role for the nucleus accumbens (ACB). The present studies utilised the 6-hydroxydopamine (6-OHDA) lesion technique to analyse further the relative roles of the ACB and striatum in apomorphine induced climbing.

6-OHDA (0.25—4.0 μg/1 μl) was injected into the ACB (2.3 mm anterior to bregma, ±1.0 mm lateral, 3.7 mm below the skull surface) and caudate-putamen (16 μg/4 μl) (1.0 mm anterior to bregma, ±2.0 mm lateral, 3.5 mm below the skull surface) of male albino mice (B.K.W., 35–40 g) using standard stereotaxic techniques (Costall, *et al.*, 1979). 6-OHDA was injected alone or after pretreatment with tranylcypromine (5.0 mg/kg i.p.) and desmethylimipramine (DMI, 25 mg/kg i.p.). Climbing was measured as 'the climbing index' (Costall, *et al.*, 1978). On completion of the behavioral studies (4–6 weeks) the dopamine (DA) and noradrenaline (NA) content of the mesolimbic areas (ACB and tuberculum olfactorium) and the striatal DA content were determined fluorometrically (Chang, 1964; Laverty & Sharman, 1965).

Intra-ACB 6-OHDA (0.25–4.0 μg) caused a dose-dependent depletion of mesolimbic DA (maximum depletion of approximately 60% occurring at 2–4 μg) without a significant change in mesolimbic NA or striatal DA levels (in the absence of tranylcypromine and DMI mesolimbic NA and striatal DA levels were slightly reduced by 2 or 4 μg 6-OHDA). Behaviourally, mice exhibited an increased climbing response to apomorphine (doses selected from range 0.625–1.0 mg/kg s.c., tested on alternate days for 36 days) which was maximum 7–10 days after intra-ACB 6-OHDA and persisted for the duration of the experiment. The maximal increase in response to apomorphine (a four-fold increase in sensitivity) was attained using 6-OHDA (2 μg). The tranylcypromine and DMI pretreatment generally enhanced the behavioural changes caused by 6-OHDA (0.25–2.0 μg) but this did not achieve statistical significance. Intrastriatal 6-OHDA, causing a depletion of striatal dopamine of approximately 85% (without altering mesolimbic DA or NA levels), failed to modify apomorphine climbing. All climbing responses were specifically antagonised by haloperidol (0.0125–0.05 mg/kg i.p.).

The importance of mesolimbic DA systems for the induction of climbing behaviour is indicated by the enhanced response to apomorphine after discrete denervation of the ACB and the reduced climbing observed after electrolesions of the same nucleus (Costall, *et al.*, 1979). Whilst we do not exclude a striatal involvement, the present results emphasise the potential contribution of mesolimbic mechanisms to the climbing response to apomorphine.

This work was supported by a grant from the Wellcome Trust. The authors thank Dr. D.H. Fortune for his supervision of the biochemical studies.

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β-Adrenoceptor antagonists in L-tryptophan and L-DOPA induced behavioural syndromes

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Evidence that propranolol and certain other β-adrenoceptor antagonists may also possess significant antagonist activity at 5-HT receptors is growing and comes from studies *in vitro* (Schechter & Weinstock, 1974; Middlemiss, Blakeborough & Leather, 1977) and from inhibition of behavioural syndromes thought to result from raised brain 5-HT activity. Propranolol and related antagonists have been shown to block head-twitch responses in mice (Weinstock, and increase the risk of non-specific neurotransmitter effects. We have, therefore, re-examined the effects of propranolol's isomers on L-tryptophan and L-DOPA induced hyperactivity using precursor doses, 3–6 and 10–20 times lower, respectively, than were commonly used in the above studies.

Reliable hyperactivity, in activity meters, was produced, and with approximately equal intensity, by L-tryptophan (15 mg/kg) and L-DOPA (5 mg/kg). Moreover, both syndromes were highly sensitive to the blocking effects of (−)-propranolol and in both cases, at doses only marginally above the peripheral β-blocking dose. The effect was highly stereospecific. Methysergide potentiated both syndromes and haloperidol was potent in blocking both syndromes (Table 1).

These studies suggest, therefore, that the size of precursor load may be important in determining the Weiss & Gitter, 1977) and the characteristic hyperactivity syndrome in rats which follows monoamine oxidase inhibition and L-tryptophan (Green & Grahame-Smith, 1976). Although the effects of propranolol in the latter are stereospecific they are, however, only reported at doses well in excess of peripheral β-adrenoceptor blocking doses.

This hyperactivity syndrome is complex and may

Table 1 Effect of antagonists on rat hyperactivity. Receptor antagonists or saline were administered to groups of three male rats (Alderley Park strain, 180–200 g) simultaneously with tranylcypromine (TCP) (20 mg/kg) followed thirty minutes later by L-tryptophan (L-TRYP) (15 mg/kg) or L-DOPA (5 mg/kg). All injections were i.p. Hyperactivity was measured on 'Columbus' activity meters, 40–60 min after precursor load

	Rat Hyperactivity			
	TCP + L-TRYP		*TCP + L-DOPA*	
	M.E.D. (mg/kg)	*Effect*	*M.E.D. (mg/kg)*	*Effect*
(−)-Propranolol	0.8	Inhibition	0.8	Inhibition
(+)-Propranolol	25.0	None	25.0	None
Haloperidol	0.2	Inhibition	0.3	Inhibition
Methysergide	15.0	Potentiation	2.5	Potentiation

Results expressed as the minimum effective dose (M.E.D.) of antagonist to give $P < 0.05$ by Student's 't' test relative to controls, $n \geq 6$.