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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, $n \geq 6$.

depend as much on dopamine (DA) as 5-HT stimulation in the CNS. Thus a closely related syndrome is induced when L-DOPA is substituted for L-tryptophan and 5-HT and DA antagonists may have similar effects on both syndromes (Jacobs, 1974; Deakin & Green, 1978). Costain & Green (1978), however, found no effect of propranolol on the L-DOPA syndrome.

We have considered the possibility that high precursor doses used in previous hyperactivity studies may preclude a high sensitivity to antagonist drugs quality of effect as well as the sensitivity to antagonist drugs in these syndromes. A central role for propranolol in inhibiting behavioural syndromes which may be 5-HT mediated is confirmed and extended.

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Intravenous bicuculline in mice facilitates *in vivo* evaluation of drugs affecting GABA like mechanisms

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It has been established, both by receptor binding (Möhler & Okada, 1977) and neuropharmacologically (Curtis, *et al.*, 1971) that bicuculline antagonizes the action of GABA by competition for postsynaptic action γ-aminobutyric acid (GABA) by competition for postsynaptic receptors. Bicuculline in nonlethal doses in mice produces pronounced myoclonic seizures, a well-defined behavioural end-point, but one which has not been reported in the literature in a systematic way.

This study was designed to examine compounds having diverse modes of action on the GABA system. Groups of ten female CD_1 mice (body wt. 20–25 g) were premedicated with putative GABA-like compounds intravenously at 2 min or intraperitoneally at 30 min or 5 h, prior to intravenous bicuculline (0.55 mg/kg; pH 6.0; 0.2 ml/20 g body weight). The ensuing behavioural syndrome was evaluated for presence or absence of myoclonic seizures, tonic convulsions and mortality, as well as for the time of onset and the duration of seizure activity. The syndrome occurred in 90 ± 4 (±s.e. mean) % of control mice (n = 10 groups) with an onset of 6.5 ± 0.4 s and a duration of 8.2 ± 0.6 seconds. Mortality invariably followed tonic convulsions, but only occurred in 6 ± 3% of control mice. The antagonism of myoclonic seizures by compounds was assessed quantally to determine ED_{50} values.

The results in Table 1 show that at appropriate premedication times GABA transaminase inhibitors, except gabaculine at the doses tested, GABA agonists and the neuronal uptake inhibitors diaminobutyric acid and chlorpromazine, were all active in antagonizing bicuculline-induced myoclonic seizures. In those animals in which seizures were not completely blocked, the time to onset was lengthened and the duration of the behaviour was shortened. Since the benzodiazepines only have low potency in inhibiting bicuculline binding, the high activity of diazepam is interesting. In addition the potency of γ-vinyl GABA was higher than would be expected from a consideration of whole brain GABA levels (Jung *et al.*, 1977) suggesting that regional or subcellular distribution of the generated GABA may play a crucial role. It is concluded that this test allows ready detection of drugs having GABA-like effects *in vivo*.

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