These results lend support to the hypothesis that propranolol may be a central 5-HT antagonist in animals.

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Behavioural and biochemical studies in rats with N-methyl-D-aspartic acid and kainic acid

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Both kainic acid and N-methyl-DL-aspartate are excitatory amino acids believed to act at receptors for acidic amino acids. Of these two, kainate is believed to be excitotoxic at glutamate receptors (Olney, Rhee & Ho, 1974) and is widely used as a neurotoxic tool to produce models of neurological disorders associated with nervous degeneration, such as Huntington's chorea (Coyle, Schwarcz, Bennett & Campochiaro, 1977). N-Methyl-DL-aspartate is also a potent excitatory amino acid with some reported toxic properties (Olney, 1978). However, the active form of this compound is likely to be the D-isomer (Curtis & Watkins, 1963; Johnston, Curtis, Davies & McCulloch, 1974), and we have therefore explored the possible behavioural and neurotoxic properties of N-methyl-D-aspartate (NMDA) in comparison with those of kainic acid following acute and chronic injection into the rat globus pallidus.

Bilateral injections of NMDA (12 and 30 nm), kainic acid (2.3 nm) or vehicle (1.5 μl 0.05 M phosphate buffer, pH 7.2) were made stereotaxically into the globus pallidus of male Porton rats (A + 6.5, L ± 2.5, V − 1.0).

Animals were allowed to recover from surgery and behavioural and biochemical analyses conducted at 10 days. In a further series of animals, bilateral guide cannulae were mounted in the skull above the globus pallidus.

Acute bilateral injection of both NMDA and kainic acid (range 0.2–4 nm) induced a dose-dependent stimulation of motor activity. The lower doses of both amino acids produced sniffing and a mild locomotor response which was active for up to an hour ($P < 0.05$ for line crossing in an open field in comparison with vehicle-injected controls). The higher doses of NMDA and kainic acid produced various forms of hyperactivity and dyskinetic reactions including posturing, teeth grinding and torticollis. These behaviours were interposed between bursts of running seizure.

Chronically, both kainic acid and NMDA injected animals showed increased locomotor activity, with greater incidences of line crossing and rearing in the perimeter of an open field ($P < 0.01$ compared to vehicle-injected controls). Whereas acutely both amino acids exhibited similar potency for inducing hyperactivity, chronically 5–10 times the injected dose of NMDA was required to give the equivalent behavioural response as kainic acid.

Biochemically kainic acid (2.3 nm) induced a spectrum of changes within the injection site including reduced glutamate decarboxylase (GAD) (33% of control, $P < 0.001$) and choline acetyltransferase (ChAT) activity (55% of control, $P < 0.01$) and decreased concentrations of GABA and glutamate (39% of control, $P < 0.01$). NMDA (12 and 30 nm) caused a significant increase in glutamate concentrations ($P < 0.01$) and a reduction in ChAT activity ($P < 0.01$). The higher dose of NMDA caused a small, but significant decrease in pallidal GAD activity ($P < 0.05$).

Whilst the behavioural effects of these two excitant amino acids were similar, the biochemical profiles differed. Kainic acid is an agonist at glutamate receptors, while NMDA may be selective for aspartate receptors (Watkins, 1978). These two agents may provide useful tools to distinguish between the roles of glutamate and aspartate receptors within the central nervous system.

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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.