& Mâitre, 1976). Therefore, the present study compared the effects of atypical neuroleptics with those of classical agents, such as haloperidol, in the circling and climbing models in the mouse.

Unilateral electrolytic lesions were induced in the caudate-putamen of male mice (1.0 mm anterior to Bregma, 2.3 mm lateral, 3.5 mm vertical from skull surface; 1.5 mA for 15 s). After 14 days circling was measured in revs/2 minutes. Climbing was measured in cages lined with wire mesh: the time spent in a single climb, or in the 30 min following the first climb, were determined (see Costall, Naylor & Nohria, 1978).

Apomorphine (0.25–2 mg/kg s.c.) induced dose-dependent circling behaviour in the mouse: the intensity of asymmetry also increased with the dose. The circling behaviour induced by apomorphine (0.5 mg/kg s.c.) was antagonized by a typical neuroleptic such as haloperidol in a dose-dependent manner, and in a dose range of 0.0125–0.05 mg/kg i.p.: the larger dose caused complete inhibition of circling. However, an atypical agent such as sulpiride, in doses up to 20 mg/kg i.p., failed to antagonize circling behaviour. These findings contrast with the differential effects of such neuroleptic agents on the climbing behaviour induced in the mouse by apomorphine (1.0 mg/kg s.c.) (climbing behaviour was dose-dependent in the range 0.5–1.5 mg/kg s.c. apomorphine: stereotypy developed at larger doses and reduced the circling response). Climbing behaviour was specifically inhibited, dose-dependently, by haloperidol (0.025–0.1 mg/kg i.p.) and by sulpiride (2.5–10 mg/kg i.p.), the larger dose of each drug causing complete antagonism of climbing behaviour.

Although typical neuroleptic agents may be exerting their effects via similar mechanisms in both behavioural models, the data obtained with agents such as sulpiride indicates a difference in the mechanisms by which apomorphine induces circling and climbing behaviour. It is suggested that whilst circling behaviour may be dependent on striatal changes, climbing behaviour may involve a different type of apomorphine sensitive structure within the striatum and/or mesolimbic areas. Of the two models described, climbing behaviour would appear to be a more suitable model for detecting the different types of clinically active antischizophrenic agent.

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The effects of (+)-amphetamine and apomorphine on visually determined behaviour in the marmoset

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Administration of (+)-amphetamine (0.5–8.0 mg/kg) to marmosets results in a dose-dependent increase in small head movements (checking) but no change in locomotion. Apomorphine (0.063–1.0 mg/kg) increases locomotion but a moderate increase in checking is seen only between 0.125 and 0.5 mg/kg. The nature of the checking response has been analyzed in terms of visual stimulus control, using 8 adolescent marmosets. We used a large, diffusely lit, cardboard drum with four small windows positioned close to the floor. In order to provide an interesting visual scene, the drum was placed in front of cages of marmosets. Windows could be covered with a cardboard ring around the outside of the drum. Animals were observed through an eyehole in the lid of the drum. Observations were made at 5 min intervals, twice before and for 30 min after each injection. For each observation the position of the animals' head relative to the windows was classified every second over 50 s when the windows were uncovered and 50 s when covered. In this way the frequency and duration of visits to each window was determined and an assessment of the effect of the external visual environment made from the difference in behaviour when the windows were covered and uncovered.

A dose of (+)-amphetamine (4 mg/kg) which causes persistent checking behaviour, was compared with

saline control injections as well as with (+)-amphetamine (0.25 mg/kg) which does not increase checking. Control and 0.25 mg/kg treated animals spent about 25/50 s at windows when they were uncovered but less than 5/50 s when covered. But 10 min after injection with (+)-amphetamine (4 mg/kg), the time spent at uncovered windows fell to less than 10/50 s ($P < 0.01$, 2-tailed matched pair t test, compared with controls). This indicates a decrease in the influence of the external environment during amphetamine induced checking.

In contrast, the time spent at uncovered windows was not decreased by apomorphine (0.25 mg/kg) which does stimulate checking, when compared with 0.063 mg/kg apomorphine, which does not, or to controls. However, the time spent at covered windows was increased slightly by apomorphine ($P < 0.05$, 0.063 mg/kg; $P < 0.01$, 0.25 mg/kg). This probably reflects increased locomotion around the perimeter of the drum.

Thus it would appear that the persistent checking induced by amphetamine is not visually determined and is, in fact, incompatible with visually determined behaviour, whereas the moderate checking and the increase in locomotion induced by apomorphine does not prevent the external visual control of behaviour.

Inter-relationships between behavioural and neurochemical indices of supersensitivity in dopaminergic neurones

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There is considerable biochemical and behavioural evidence to suggest that supersensitivity of dopamine (DA) receptors develops in denervated rat striata following lesions of the nigrostriatal pathway (Ungerstedt, 1971). However, such lesions have not resulted in systematic changes in the activity of DA stimulated adenylate cyclase in striatal homogenates (Iversen, 1977). We have attempted therefore to inter-relate the rotational response to apomorphine with DA depletion, receptor sensitivity and DA stimulated adenylate cyclase activity in rat striatal homogenates after unilateral 6-hydroxydopamine lesions of the nigrostriatal pathway.

Rats were lesioned unilaterally in the medial forebrain bundle with a range of 6-hydroxydopamine concentrations (1–9 μg in 4 μl saline containing ascorbate, 1 mg/ml) and tested 14 days later in an automated rotameter for rotational response to 0.05 mg/kg of subcutaneously administered apomorphine (Waddington & Crow, 1978). Mean contralateral rotation was 298 turns/hour. Twenty-one days post-lesion rats were stunned and decapitated and striata stored at −40°C for subsequent assays. Mean DA depletion (assayed by the method of Coyle & Henry, 1973) was 83% ($n = 19$) in denervated striata. There was a significant correlation ($r = 0.68$; $P < 0.01$) between the degree of DA depletion and apomorphine-induced turning with a strong suggestion that DA depletions below 60% did not result in a rotational response. DA receptor sensitivity, assessed by [^{3}H]-spiperone binding (Reisine *et al.*, 1977) was elevated by 42% (range −28% to 186%; $P < 0.01$) in striatal preparations after nigrostriatal lesions with a significant correlation ($r = 0.58$; $P < 0.05$) between increases in spiperone binding and apomorphine induced turning with the regression line intersecting the axes near the origin. After 6-hydroxydopamine lesions adenylate cyclase activity was significantly increased ($P < 0.05$) with stimulation by DA (100 μM) but was unchanged in the presence of DA (10 μM) or under basal conditions. There was no significant correlation between adenylate cyclase activity and DA depletion, spiperone binding or rotational response to apomorphine.

These results suggest that in the rat behavioural manifestations of DA supersensitivity may not be exhibited below 60% DA depletion in denervated striata. However, as the regression line relating spiperone binding to rotational behaviour passes through the origin, the binding index of DA receptor supersensitivity may be directly proportional to the behavioural index of supersensitivity.

A.J.C. and J.L.W. are MRC scholars.

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