Behavioural effects of allylglycine (2-amino-4-pentenoic acid) and 2-keto-4-pentenoic acid following focal injection into the rat cerebellum and caudate nucleus

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Convulsant action of (+)- or (−)-allylglycine (AG), which inhibits γ-aminobutyric acid (GABA) synthesis, probably depends on conversion of AG to 2-keto-4-pentenoic acid (2K4PA). D-Amino acid oxidase, which is localized to the hind-brain (Goldstein, 1966), converts (+)-AG to 2K4PA *in vitro* (Orlowski, Rheingold & Stanley, 1977) and decreases GABA concentration in hind-brain, but not fore-brain after systemic administration (Horton, Chapman & Meldrum, 1978). The widespread decrease in GABA concentration after (−)-AG is consistent with the metabolism of (−)-AG by enzymes of widespread distribution, although the exact enzyme involved is not known.

We now report behavioural effects of focal injection of (−)-AG, (+)-AG and 2K4PA in the caudate nucleus (CN) and in the fastigial nucleus (FN) of the cerebellum in male Wistar rats (175–200 g). At least 20 injections of each compound were made at each site.

Injection of (−)-AG (10–50 μg in 0.5–4 μl 0.9% NaCl soln.) into the FN produced wild running seizures with tonic limb extension (onset 15–37 min, duration 50–60 min). Injection of (+)-AG (25–200 μg in 0.5–4 μl 0.9% NaCl soln.) into the FN caused intermittent ipsilateral hind-limb lifting, which in some animals spread to involve the hind-quarters (onset 50–114 min, duration 120–180 min). 2K4PA (5–20 μg in 0.5–10 μl 50 mM sodium phosphate buffer pH 6.8) into the FN caused lifting of the ipsilateral fore-paw and splaying of the ipsilateral hind-limb while some animals fell to the contralateral side.

Injection of (−)-AG (25–50 μg) into the CN caused contralateral fore-paw myoclonus (onset 30–75 min, duration 120–180 min). Injection of (+)-AG (25–400 μg) into the CN had no effect. Injection of 2K4PA (5–20 μg) into CN caused abnormal limb posturing such as flexion, extension and limb clutching, but no myoclonus (onset 30–60 min, duration 55–90 min).

Vehicle injections in CN or FN produced behavioural changes lasting less than 5 minutes.

Abnormal motor activity after injection of (+)-AG into the FN but not CN emphasizes the role of D-amino acid oxidase in the metabolism of (+)-AG. The behavioural effects of 2K4PA injection into the FN were similar to (+)-AG but of shorter latency. The production of behavioural effects of (−)-AG in both FN and CN is consistent with a widespread metabolism of this isomer. However, injection of 2K4PA into either FN or CN did not reproduce exactly the behavioural effects of injection of (+)- or (−)-AG injected into the same sites.

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Differential actions of typical and atypical neuroleptic agents on two behavioural effects of apomorphine in the mouse

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Criteria which are considered important for neuroleptic testing are, firstly, the ability of a test to detect changes in mesolimbic function and, secondly, an ability to detect the actions of both the typical (e.g. butyrophenone, phenothiazine) and atypical neuroleptic agents (e.g. benzamide, clozapine). Two behavioural models based on the effects of apomorphine in the mouse, circling after unilateral nigrostriatal damage and climbing in normal animals, have been used for neuroleptic testing (Pycock, Tarsy & Marsden, 1975; Protais, Costentin & Schwartz, 1976). Both behavioural responses have been indicated as striatal effects, even though the actions of the atypical agents, such as sulpiride, are considered in terms of primary changes in mesolimbic function (Waldmeier

& 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