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.

References

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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