Monoamine-depleting properties of a new and very potent enzyme-activated irreversible inhibitor of aromatic aminoacid decarboxylase: α-monofluoromethyldopa

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Inhibitors of aromatic aminoacid decarboxylase (AADC) previously studied have not proved to be sufficiently potent and/or specific to substantially decrease concentrations of endogenous catechol- or indoleamines (Bartholini & Pletscher, 1975).

Recently, a new, enzyme-activated, irreversible inhibitor of AADC, namely DL-α-monofluoromethyldopa (MFMD, RMI 71963), has been synthesised. Its biochemical effects, both *in vitro* and *in vivo*, have now been investigated and evidence is presented that with this compound essentially complete depletion of monoamines can be achieved through blockade of their synthesis at the decarboxylation step.

Male CD, albino mice (20–25 g) and male Sprague Dawley rats (200–250 g) were used. AADC activity and serotonin were determined as described by Palfreyman, Danzin, Bey, Jung, Ribereau-Gayon, Aubry, Vevert & Sjoerdsma (1978) and catechol derivatives by HPLC with electrochemical detection (Wagner, Palfreyman & Zraïka, unpublished).

In vitro, MFMD (1–50 μM) inhibited AADC purified from hog kidneys. For example, at a concentration of 5 μM, the enzyme was inhibited irreversibly by 50% in less than 2 min (see also Kollonitsch, Patchett, Marburg, Maycock, Perkins, Doldouras, Duggan & Aster, 1978). In experiments using mice, tissues were removed from animals injected i.p. with MFMD (0.25 to 250 mg/kg). There was marked time- and dose-related inhibition of AADC activity in kidney, heart and brain and with doses of 100 mg/kg there was total inhibition in all tissues examined in less than one hour. Administration of MFMD (50–250 mg/kg i.p.) to mice or rats and removal of tissues after 6 h resulted in a dose-related decrease in catecholamines and dihydroxyphenylacetic acid concentrations of brain, heart and kidney and an increase in the dopa concentrations. Similarly, serotonin concentrations were reduced in all three tissues. Following a single i.p. injection of MFMD (100 mg/kg) the catecholamine content of the three tissues remained decreased for up to 4 days. Five doses of MFMD (100 mg/kg i.p.) given every 12 h reduced the catecholamine concentrations of the brain, heart and kidney to almost undetectable levels; for example, a 97%, 94% and 83% depletion of noradrenaline, dopamine and serotonin respectively was seen in the brain of these MFMD treated mice. In the rat, MFMD (25 mg/kg s.c. every day for three days) diminished brain catecholamines by more than 80%. A comparison of the routes of administration of MFMD in rats showed oral and s.c. administration to be almost equieffective to the i.p. route for catecholamine depletion of brain and heart.

That MFMD produces its catechol- and indoleamine depleting effect solely by inhibition of their synthesis at the decarboxylase step is strongly suggested by a lack of inhibitory effect of MFMD on tyrosine and dopamine hydroxylation. Additionally the compound does not have a reserpine-like effect nor does it affect the reuptake or release of [^{3}H]-noradrenaline in rat cortical synaptosomes *in vitro*.

MFMD thus represents a new, specific and very potent inhibitor of AADC that should prove useful as a pharmacological tool and may have therapeutic applications.

References

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