Inhibition of peripheral sympathetic function by α-monofluoromethyldopa, an irreversible inhibitor of aromatic amino acid decarboxylase

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α-Monofluoromethyldopa (MFMD, RMI 71963) is a selective, enzyme-activated, irreversible inhibitor of aromatic amino acid decarboxylase (AADC) which depletes catecholamines in brain and peripheral tissues of rats (Jung, Palfreyman, Ribereau-Gayon, Wagner & Zraïka, 1979). The effects of MFMD on the function of the sympathetic nervous system have been investigated *in vivo* and *in vitro*.

Male Sprague-Dawley rats (200–300 g) were pretreated with MFMD, 100 mg/kg, i.p. daily for 3 days or 250 mg/kg i.p. 24 h before being anaesthetized with sodium pentobarbitone and pithed. Pressor responses to stimulation of the entire sympathetic spinal outflow (1 and 4 Hz; 1 ms for 5 s; Gillespie & Muir, 1967) and to tyramine (25 and 100 μg/kg, i.v.) were reduced compared with control preparations. Catecholamine levels were significantly ($P < 0.05$) reduced in the hearts of the MFMD-treated animals but were unchanged in the adrenal glands. In animals adrenalectomized immediately before pithing pressor responses to nerve stimulation and to tyramine, but not to noradrenaline (0.2 and 0.8 μg/kg, i.v.), were inhibited following pretreatment with low doses of MFMD (2.5 and 25 mg/kg, i.p. daily for 3 days). Infusion of dopamine (0.1 mg kg^{-1} min^{-1} for 5 min) reversed both the depletion of catecholamines and the inhibition of sympathetic nervous function caused by MFMD.

MFMD (10 and 30 mg/kg, orally or 3 and 10 mg/kg, i.p., daily for 3 days) lowered the blood pressure of spontaneously hypertensive rats (Okamoto-Akoia strain).

Responses of rat portal vein or atria to field stimulation of the intramural sympathetic nerves were recorded *in vitro*. Stimulation parameters were: vein, 20 Hz for 10 s every 2 min, pulse width 1 ms; atria, 20 Hz for 3 s every 2 min, pulse width 0.5 mseconds. Responses of preparation taken from animals pretreated with MFMD (25 mg/kg, i.p., daily for 3 days) were significantly reduced compared to control tissues. Contractions of portal vein to field stimulation were augmented ($P < 0.05$) following incubation with dopamine (10 μM for 30 min, followed by 15 min washout) in the MFMD treated tissues, but not in control tissues or in preparations from animals treated with reserpine (2 mg/kg, s.c., daily for 2 days). Responses of untreated portal veins (but not atria) were gradually but significantly reduced ($P < 0.01$) during 150 min incubation with MFMD (20 μM) and with repeated nerve stimulation (parameters as above). At concentrations up to 600 μM, MFMD had no α-adrenoceptor antagonist activity in rat portal vein preparations, nor β-adrenoceptor antagonist activity in rat atria.

The results demonstrate that inhibition of peripheral sympathetic function can be achieved by depletion of catecholamines resulting from blockade of their biosynthesis at the decarboxylation step. MFMD thus represents a novel addition to the several groups of compounds whose principal property is to depress the activity of peripheral adrenergic neurones.

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References

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