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Antihypertensive effect of methyldopa in metacorticoid immunosympathectomized rats

SIR,—It is now generally accepted that methyldopa (α-methyldihydroxyphenylalanine) is an effective antihypertensive agent. Day & Rand (1963) proposed that methyldopa lowered the blood pressure by acting as a weak false sympathetic neurotransmitter. This hypothesis is inconsistent with the observation that administration of methyldopa did not inhibit the effect of sympathetic nerve stimulation (Stone, Ross, Wenger, Ludden, Blessing, Totaro & Porter, 1962; Varma & Benfey, 1963) and did not reduce the release of noradrenaline after stimulation of sympathetic nerves (Davies, 1966). Indeed, Nickerson (1965) pointed out that "the role of catecholamine depletion or, indeed, of any action on catecholamine metabolism in the antihypertensive effect of methyldopa, requires re-evaluation".

Since almost complete destruction of the peripheral sympathetic system can be produced in mammals by immunosympathectomy (Levi-Montalcini & Booker, 1960; Levi-Montalcini & Angeletti, 1962), it became possible to test whether the antihypertensive action of methyldopa is due to a reduction in peripheral sympathetic activity and whether a fully active sympathetic system is essential for experimental hypertension.

Immunosympathectomy was produced by subcutaneous injection of 0·2 ml of 61,000 anti-units/ml of bovine anti-serum to nerve-growth factor (kindly supplied by Dr. R. K. Richards, Abbott Laboratories, Chicago) in 1–2 days-old Sprague-Dawley rats. The effectiveness of this treatment producing immunosympathectomy has been described by Iversen, Glowinski & Axelrod (1966). The treated and untreated litter mate controls were raised together. Noradrenaline (equivalent) was assayed biologically on isolated rabbit aortic strip (Helmer, 1961). Treated rats exhibited marked ptosis of the eye lids. The daily urinary excretion of catecholamine (as noradrenaline equivalent) was $2{\cdot}1 \pm 0{\cdot}5$ μg/kg in treated rats and $5{\cdot}6 \pm 1{\cdot}2$ μg/kg in normal rats. Myocardial noradrenaline in 3 treated rats was $0{\cdot}22 \pm 0{\cdot}22$ μg/g and in 3 normal controls was $1{\cdot}26 \pm 0{\cdot}23$ μg/g. The responses of the isolated atria of untreated rats (6 preparations) to tyramine were negligible. Approximately 2 months after birth, the rats were used for inducing metacorticoid hypertension. Rats were anaesthetized with an intraperitoneal injection of pentobarbitone sodium (30 mg/kg), one kidney was removed and a 20 mg desoxycorticosterone acetate pellet contained in 50 mg beeswax was implanted under the skin. Animals were maintained on 1% sodium chloride instead of water. The systolic blood pressure in the unanaesthetized rat was determined by the tail cuff method by means of an Electrosphygmograph (E & M Instruments). Methyldopa (200

mg/kg, once daily) was injected intraperitoneally into the hypertensive rats and the effect of this treatment on the blood pressure was measured (Table 1).

The control blood pressures of the immunosympathectomized rats and their litter mate controls were not different from each other. The incidence of hypertension in the immunosympathectomized rats was higher and the severity of hypertension in the 2 groups was identical. Methyldopa lowered the blood pressure in all metacorticoid hypertensive rats. The antihypertensive effect of methyldopa in both groups was also similar. After stopping the administration of methyldopa, the recovery of the blood pressure to pretreatment level was faster in control rats than in immunosympathectomized rats. The sedative effect of methyldopa was apparent in both groups of animals.

TABLE 1. EFFECT OF METHYLDOPA ON THE SYSTOLIC PRESSURE OF NORMAL AND IMMUNOSYMPATHECTOMIZED METACORTICOID HYPERTENSIVE RATS

	Immunosympathectomized	Normal control
No. of rats	12	12
Mean control systolic pressure, mm Hg	121 ± 7·2	123 ± 5·3
No. of hypertensive rats	7	3
Mean systolic pressure, mm Hg	194 ± 5·4	182 ± 1·5
Mean systolic pressure after treatment with methyldopa*, mm Hg	128 ± 5·3	142 ± 7·0
Mean systolic pressure 2 weeks after stopping methyldopa	175 ± 4·8	200 ± 5·7

* Only 6 rats were treated with methyldopa (200 mg/kg/day i.p. for 7 days).

These results suggest that experimental hypertension can be produced after almost complete destruction of the peripheral sympathetic system which follows immunosympathectomy. Since methyldopa lowered the blood pressure in metacorticoid hypertensive rats and since its antihypertensive action was not reduced by the absence of an active peripheral sympathetic system, it is suggested that the antihypertensive action of methyldopa, at least in part, is unrelated to the peripheral sympathetic system. The possibility that the residual sympathetic system in the immunosympathectomized rats (Levi-Montalcini & Angeletti, 1962; Iversen & others, 1966) may account for the observed effects of methyldopa is unlikely but cannot be excluded.

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