TABLE 1. *Concentration of DOPAC and 5-HIAA in the optic lobes of* Octopus. *Values are in μg/g of fresh tissue and corrected for recoveries (mean ±S.E.M.).* $^{**}P<0.001$; $^{*}P<0.025$

	Dose mg/kg	Time h	DOPAC μg/g	5-HIAA μg/g
control	—	—	2·82±0·30 (17)	0·97±0·23 (10)
pargyline	100	3	0·29±0·03 (5)**	0·12±0·06 (5)*

REFERENCES

BLASCHKO, H. & HAWKINS, J. (1952). Observations on amine oxidase in cephalopods. *J. Physiol. Lond.*, **118**, 88–93.

JUORIO, A. V. (1971). Catecholamines and 5-hydroxytryptamine in nervous tissues of cephalopods. *J. Physiol. Lond.*, **216**, 213–226.

Further evidence for a central hypotensive action of α-methyldopa

L. FINCH* and G. HAEUSLER

Department of Experimental Medicine of F. Hoffmann-La Roche & Co Ltd., Basle, Switzerland

It was proposed that α-methyldopa exerts its hypotensive effect by the formation of α-methylnoradrenaline which was assumed to be a less potent false transmitter in the peripheral sympathetic nervous system (Day & Rand, 1963). However, it has been shown in the cat that adrenergic transmission is not or only slightly affected by α-methyldopa (Haefely, Hürlimann & Thoenen, 1967). More recently, Henning (1969) came to the conclusion that the decarboxylation of α-methyldopa within the central nervous system is essential for the hypotensive effect of the drug.

In conscious genetic hypertensive rats, the blood pressure started to decrease 1 h after the intraperitoneal injection of α-methyldopa (300 mg/kg) and the maximal fall of approximately 60 mmHg was attained 3 h later. This hypotensive effect of α-methyldopa was not prevented by the destruction of peripheral adrenergic nerve endings with 6-hydroxydopamine. Furthermore, in genetic hypertensive rats the responses to stimulation of the entire sympathetic outflow (Gillespie & Muir, 1967) were not influenced by pretreatment with α-methyldopa (300 mg/kg I.P.). Although α-methylnoradrenaline was 10 times less potent than noradrenaline in causing vasoconstriction in isolated perfused renal artery preparations of normotensive rats, the vasoconstrictor responses due to periarterial nerve stimulation were only slightly affected by pretreatment with α-methyldopa (300 mg/kg I.P.). These results rule out the possibility that the mechanism underlying the hypotensive effect of α-methyldopa is solely peripheral in nature.

A central hypotensive mechanism is supported by the finding, that destruction of adrenergic neurons in the brain by intraventricular injection of 6-hydroxydopamine markedly reduces the α-methyldopa-induced hypotension. Furthermore, α-methyldopa (100 mg/kg I.V.) significantly reduced the pressor responses which were produced by stimulation of the rat posterior hypothalamus. The onset of this inhibitory effect corresponded with the hypotensive effect of α-methyldopa. FLA-63, a selective dopamine-β-hydroxylase inhibitor, reversed the effect of α-methyldopa. Very similar results were obtained for the pressor responses produced by stimulation of the mid-brain reticular formation.

In the urethane anaesthetized cat, stimulation of the posterior hypothalamic area produced a rise in blood pressure which was strongly reduced by treatment with

α-methyldopa (100 mg/kg I.V.). Furthermore, the increases in discharges recorded from the splanchnic and renal sympathetic nerves during this stimulation were markedly reduced by treatment with α-methyldopa.

It is concluded that α-methyldopa exerts its hypotensive effect via a central mechanism and requires intact adrenergic neurones within the brain probably for the conversion of α-methyldopa to α-methylnoradrenaline.

REFERENCES

DAY, M. D. and RAND, M. J. (1963). A hypothesis for the mode of action of α-methyldopa in relieving hypertension. *J. Pharm. Pharmac.* **15**, 221–224.

GILLESPIE, J. S. and MUIR, T. C. (1967). A method of stimulating the complete sympathetic outflow from the spinal cord to blood vessels in the pithed rat. *Br. J. Pharmac.*, **30**, 78–87.

HAEFELY, W., HÜRLIMANN, A. and THOENEN, H. (1967). Adrenergic transmitter changes and response to sympathetic nerve stimulation after differing pretreatment with α-methyldopa. *Br. J. Pharmac.*, **31**, 105–119

HENNING, M. (1969). Studies on the mode of action of α-methyldopa. *Acta. physiol scand.* Suppl. **322**, 1–37

The mode of action of α-methyldopa

M. D. DAY, A. G. ROACH* and R. L. WHITING

Department of Pharmacy, University of Aston in Birmingham, Birmingham B4 7ET

The mode of action of α-methyldopa in relieving hypertension has not yet been established with certainty. The false neurohumoral theory of Day & Rand (1963, 1964) possibly fits the observed effects of the drug most satisfactorily. However, this theory has been weakened, firstly, by the observation that the sympathetic nerve blocking action of α-methyldopa on the cat's nictitating membrane appears to be due to the formation of α-methyldopamine rather than α-methylnoradrenaline (Farmer, 1965). Secondly, Henning (1969) has shown that peripheral inhibitors of dopa decarboxylase do not affect the antihypertensive effect of α-methyldopa whilst inhibition of central decarboxylase abolishes it. We have reinvestigated the mechanism of action of α-methyldopa using conscious rats made hypertensive by unilateral nephrectomy, DOCA implantation and substitution of 1·0% NaCl solution for drinking water.

The mean systolic blood pressure of a group of six hypertensive rats (187·1 ± 3·1 mmHg) was markedly reduced by intraperitoneally administered α-methyldopa (200 mg/kg). The peak effect occurred after 4·5 h and was a reduction of 57·1 ± 2·1 mmHg. The antihypertensive action of this dose of α-methyldopa was unaffected by a dose regimen of Ro4-4602 (3 doses of 50 mg/kg given i.p. 0·5 h before, 1·5 h and 3·5 h after α-methyldopa administration) known to inhibit peripheral decarboxylase (Bartholini & Pletscher, 1968). However, when Ro4-4602 was administered in a regimen (3 doses, 200 mg/kg i.p. given in the same pattern as the lower dosage), known to inhibit central as well as peripheral dopa decarboxylase, then the antihypertensive effect of α-methyldopa was abolished. The higher dose level of Ro4-4602 given alone itself caused a significant fall in mean systolic blood pressure in hypertensive rats (186·1 ± 1·8 to 150·0 ± 0·8 mmHg after 6·75 h) but this too was abolished with concomitant treatment with α-methyldopa, thus demonstrating a mutual antagonism between the two compounds. α-Methyldopa was administered centrally via indwelling intracerebroventricular cannulae into hypertensive rats in doses (2 mg/kg and 4 mg/kg) which when given peripherally did not affect mean blood pressure. These small central doses of α-methyldopa caused a pronounced fall