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.

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The mode of action of α-methyldopa

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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

in mean pressure of rapid onset (90 min after methyldopa treatment mean systolic pressure reduced from 190·4 ± 2·5 to 147·5 ± 2·00 mmHg (2 mg/kg) and from 191·2 ± 2·2 to 138·4 ± 2·9 mmHg (4 mg/kg)). The mechanism of the central hypotensive action of α-methyldopa appeared to be similar to that when given peripherally since it was abolished by the higher doses of Ro4-4602 but not by the lower doses. Disulfiram and sodium diethyldithiocarbamate (DDC) are potent inhibitors of dopamine-β-hydroxylase (Goldstein, Anagnoste, Lauber & McKereghan, 1964) and when administered to hypertensive rats at a dose of 100 mg/kg caused falls in mean systolic blood pressure (190·7 ± 1·8 to 159·4 ± 2·3 and 183·5 ± 1·9 to 151·8 ± 2·4 mmHg respectively). In hypertensive rats pre-treated with either disulfiram or DDC (100 mg/kg) the antihypertensive effect of α-methyldopa administered either centrally or peripherally was completely abolished. These observations strongly suggest that α-methyldopa exerts its antihypertensive effect by a central mechanism as suggested by Henning (1969). However, the abolition of the antihypertensive action of α-methyldopa by disulfiram and DDC is inconsistent with the postulate of Farmer (1965), that the antihypertensive effect is due to accumulation of α-methyldopamine, but is consistent with the false neurohumoral transmitter theory to explain the central action of α-methyldopa in relieving hypertension.

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The effects of different anaesthetics on responses of brain stem neurones to iontophoretically applied transmitter substances

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Anaesthesia is known to alter the responsiveness of neurones in the c.n.s. to substances applied microiontophoretically (Bloom, Costa & Salmoiraghi, 1965; Johnson, Roberts & Straughan, 1969; Crawford, 1970).

The effects of tribromoethanol, urethane and pentobarbitone anaesthesia on the responses of spontaneously active single neurones in the brain stem of cerebellectomized rats to microiontophoretic applications of acetylcholine (ACh), L-noradrenaline (NA) and 5-hydroxytryptamine (5-HT) were examined. The results were compared with those from decerebrate unanaesthetized control preparations.

The types of responses of brain stem neurones to ACh, (−)-NA and 5-HT in anaesthetized animals resembled those from the unanaesthetized control preparations.