Central hypotensive effect of α-methyldopa

SIR,—The hypotensive action of L-α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa) is rather difficult to demonstrate in laboratory animals. Only large doses of the drug, administered to conscious dogs (Goldberg, Da Costa & Ozaki, 1961; Kroneberg, 1963), to renal hypertensive rats (Muscholl, 1966) or to conscious normotensive rats (Henning, unpublished observations) significantly decrease blood pressure. As far as we know, an acute hypotensive effect has never been demonstrated in the anaesthetized cat. Although in man and animals the administration of α-methyldopa gives rise to decreased peripheral resistance, the mechanism of this effect is still poorly understood. Infusion of α-methyldopa into the brachial artery in man does not cause any increase of the blood flow of the corresponding forearm or hand (Henning & Johnsson, unpublished experiments). One of us (M. H.) finds that α-methyldopamine, which does not pass through the blood brain barrier, depletes noradrenaline from the peripheral sympathetic nerves but has no effect on the blood pressure of conscious rats. Therefore, a central effect of α-methyldopa might be the cause of the decrease of the peripheral resistance. The present communication affords evidence that in the cat a centrally mediated hypotensive effect may be demonstrated for α-methyldopa.

Recently, van Zwieten, Bernheimer & Hornykiewicz (1966) have demonstrated that the injection of low doses of reserpine into the vertebral artery of the cat much decreased the concentration of noradrenaline and dopamine in the brain without affecting the amine content of the heart. This effect was accompanied by a decrease in blood pressure which was probably of central origin. The same experimental method was used for our investigations on the central effect of α-methyldopa.

Cats of either sex (2·0–4·5 kg) were anaesthetized with chloralose (80 mg/kg intraperitoneally). The thorax was opened by severing the first three ribs from the left side of the sternum. The left subclavian artery and its side branches were carefully exposed. All side branches with the exception of the vertebral artery were ligated. A polyethylene catheter was introduced into the subclavian artery and pushed forward in the direction of the heart, until its tip reached the proximal end of the vertebral artery. Thus, solutions infused slowly into this catheter will chiefly flow into the vertebral artery and finally reach those regions in the brain where the pressure regulation centres are located. The blood flow in the subclavian artery most likely prevents the transition of the drugs administered via this route to the peripheral circulation. Artificial respiration was applied throughout the experiments via a tracheal cannula. The drug was dissolved in saline and infused either into the vertebral artery or into the right femoral vein over a period of approximately 1 hr. The blood pressure was taken from the left femoral artery and recorded by a Grass Polygraph via a Statham pressure transducer type P23Dc. About 3 hr after the end of the infusion the animals were killed. The noradrenaline content of the right ventricle of the heart and that of the brain (cerebellum removed) was measured (Bertler, Carlsson & Rosengren, 1958). The dopamine and 5-hydroxytryptamine (5-HT) contents of the brain were measured by the methods described by Carlsson & Lindqvist (1962) and Andén & Magnusson (1967), respectively. Control animals were sham operated. Saline was infused either into the vertebral artery or into the left femoral vein under the same circumstances as those used for the infusion of the drug.

In one series of experiments 20 mg/kg α-methyldopa, dissolved in 5–7 ml saline, was infused into the vertebral artery. As shown in Table 1 the

noradrenaline content of the brain was significantly lowered, whereas that of the heart (right ventricle) remained unaffected. The dopamine and 5-HT levels of the brain underwent no significant changes. Approximately 1-2 hr after the end of the infusion a slow but pronounced hypotensive effect was observed. The blood pressure was reduced on the average by 55 mm Hg (s.e.m. = 13, n = 6). The same low dose (20 mg/kg) of α-methyldopa *intravenously* infused, did not affect the blood pressure. However, the brain noradrenaline was depleted to approximately the same extent as observed after administration o the drug into the vertebral artery. The noradrenaline level of the heart remained normal. Intravenous infusion of a higher dose, 200 mg/kg, gave rise to a reduction of arterial blood pressure in 3 animals out of 4 (mean reduction 28 mm s.e.m. = 15).

The results demonstrate that the infusion of small doses of α-methyldopa into the vertebral artery causes a clearcut fall in blood pressure. Since intravenous infusion of the same low dose does not affect blood pressure, it is uncertain whether the accompanying reduction in brain noradrenaline is related to the hypotensive effect of α-methyldopa which was observed after infusion of the drug

TABLE 1. EFFECTS OF INFUSION OF α-METHYLDOPA ON BLOOD PRESSURE, HEART NORADRENALINE AND BRAIN NORADRENALINE, DOPAMINE AND 5-HYDROXYTRYPTAMINE

Treatment	Hypotensive effect 3 hr after treatment mm Hg	Heart noradrenaline μg/g	Brain		
			Noradrenaline μg/g	Dopamine μg/g	5-HT μg/g
Infusion of saline into vertebral artery (control). (Means ± s.e.m., 4 experiments)	none	1·05 ± 0·196	0·21 ±0·018	0·29 ± 0·034	0·24 ± 0·019
Infusion of α-methyldopa (20 mg/kg) into vertebral artery. (Means ± s.e.m., 6 experiments)	55 ± 13	1·17 ± 0·101	0·14* ± 0·014	0·24 ± 0·023	0·22 ± 0·013
Infusion of α-methyldopa (20 mg/kg) into femoral vein. (Means ± s.e.m., 4 experiments)	none	1·30 ± 0·218	0·13** ± 0·006	0·22 ± 0·010	0·20 ± 0·017
Infusion of α-methyldopa (200mg/kg) into femoral vein. (Means ± s.e.m., 4 experiments)	28 ± 15	0·86 ± 0·051	0·13* ± 0·008	0·15** ±0·013	0·12** ± 0·018

* Differs significantly from the control value (analysis of variance), $P < 0·005$.
** As above $P < 0·001$.

into the vertebral artery. It is remarkable that upon intravenous infusion of such a low dose (20 mg/kg) the noradrenaline in the brain is lowered, whereas that in the heart remains unaffected. Although the depletion in the brain is of the same order of magnitude as that observed after infusion of the drug into the vertebral artery, it may be possible that administration via the two different routes gave rise to depletion in different parts of the brain. Until now only the whole brain (after removal of the cerebellum) has been analysed.

For reserpine-induced depletion the heart seems more sensitive than the brain (Carlsson, 1965). The fact that a relatively high intravenous dose (200 mg/kg) of α-methyldopa shows but a slight hypotensive effect is in agreement with previous observations made in anaesthetized animals (for review, see Muscholl, 1966).

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Reversal of α-methyltyrosine-induced behavioural depression with dihydroxyphenylalanine and amphetamine

SIR,—The time course and the degree of behavioural depression following administration of α-methyltyrosine correlates with the reduced brain levels of noradrenaline and dopamine (Hanson, 1965; Moore, 1966). Nevertheless, many factors must be considered before this behavioural deficit can be causally related to a lack of brain catecholamines. For example, toxicity (Weissman & Koe, 1965) and direct depressant actions of α-methyltyrosine could contribute to the behavioural effects. However, with proper precautions it can be shown that these factors do not play a major role in the behavioural effects of this drug. Multiple injections of small doses of α-methyltyrosine produced behavioural depression and catecholamine depletion without concomitant toxicity (Rech, Borys & Moore, 1966). The importance of a direct depressant action of α-methyltyrosine was minimized by the finding that pretreatment with monoamine oxidase inhibitors reduced both the catecholamine-depleting and behavioural depressant effects of this drug without altering the concentration of α-methyltyrosine in the brain (Moore & Rech, 1967). Further efforts to implicate brain catecholamines in the central actions of α-methyltyrosine are described in this communication. It will be shown that both dihydroxyphenylalanine (L-dopa), which serves as an immediate precursor for dopamine and noradrenaline, and (+)-amphetamine, which mimics the actions of catecholamines, at least at peripheral sites, reverse α-methyltyrosine-induced behavioural depression.

Female rats (CD_1, Charles River Animal Farm), 175–200 g, were trained to perform in a shuttle box. Each trial was initiated by activating a small light on the side of the cage occupied by the animal. After 5 sec of light the grid floor on the same side of the cage was electrified for 5 additional sec. If the rat moved to the unlighted side during the initial 5 sec, the response was termed