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# Central hypotensive effect of α-methyldopa

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In cats under chloralose anaesthesia L-α-methyldopa (20 mg/kg) was infused for 1 hr into the left vertebral artery. One to 3 hr after the end of the infusion a gradual and significant lowering of mean arterial blood pressure was observed. The dopamine and noradrenaline contents of the brain were significantly reduced while brain 5-hydroxytryptamine and heart noradrenaline concentrations remained normal. The same low dose of L-α-methyldopa infused into a systemic vein did not affect the blood pressure. However, brain dopamine and noradrenaline were depleted to the same extent as observed after infusion into the vertebral artery. Intravenous infusion of a large dose of L-α-methyldopa (200 mg/kg) did not significantly alter mean arterial blood pressure but lowered brain dopamine, noradrenaline and 5-hydroxytryptamine levels. No effect on heart noradrenaline was observed. Infusion of saline or the D-isomer of α-methyldopa (20 mg/kg) into the vertebral artery had no effect on blood pressure or tissue monoamines.

THE mechanism underlying the antihypertensive action of L-α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa) in animals and in man has been subject to much research in recent years but still presents a number of unexplained features. The subject has been extensively reviewed by Sourkes (1965), Muscholl (1966), Holtz & Palm (1966) and Stone & Porter (1966; 1967).

It is commonly agreed that the hypotensive effect of α-methyldopa is mediated through interference with the sympathetic system in general. However, the exact site of action has not been established. Opinions differ as to the function of the peripheral sympathetic nerves after treatment with α-methyldopa, but there seems to be only a moderate impairment of peripheral adrenergic mechanisms (see reviews mentioned above; cf. also Haefely, Thoenen & Hürlimann, 1967; Haefely, Hürliman & Thoenen, 1967). On the other hand, several obvious effects of α-methyldopa on the central nervous system have been reported.

*In vivo*, the metabolism of catecholamines is affected by α-methyldopa in a number of different ways. Tissue levels of dopamine, noradrenaline and 5-hydroxytryptamine (5-HT) are decreased upon administration of the drug to animals (Smith, 1960; Porter, Totaro & Leiby, 1961; Hess, Ozaki & Udenfriend, 1960; Hess, Connamacher & others, 1961). The depletion of dopamine and noradrenaline occurs mainly through a stoichiometric exchange of these amines with the metabolites of α-methyldopa, i.e., α-methyldopamine and α-methylnoradrenaline, respectively (Carlsson & Lindqvist, 1962; Carlsson, 1964), whereas the lowering of 5-HT may be the result of inhibition of synthesis (Sharman & Smith, 1962; Roos & Werdinius, 1963; Burkard, Gey & Pletscher, 1964).

The interrelation of these biochemical changes and the functional effects of α-methyldopa is also subject to debate. Apparently, the drug must undergo decarboxylation to form α-methyldopamine and α-methylnoradrenaline or both, in order to exert its hypotensive and catecholamine depleting effects (Davis, Drain & others, 1963; Henning, unpublished

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experiments). Carlsson & Lindqvist (1962) suggested that the amines formed on metabolism of α-methyldopa may take over the function of dopamine and noradrenaline in the brain and later Day & Rand (1963) extended this assumption to the peripheral nerves as well. It has also been shown that in these nerves, α-methylnoradrenaline formed from α-methyldopa is released after electrical stimulation (Muscholl & Maître, 1963) and a number of investigators have stated that the activity of α-methylnoradrenaline on the adrenergic receptors is less than that of noradrenaline (Mueller & Horwitz, 1962; Day & Rand, 1964; Brunner, Hedwall & others, 1966; 1967). This release of a substitute or "false" transmitter of inferior quality has been proposed as an explanation for the hypotensive effect of α-methyldopa (Day & Rand, 1963; review by Muscholl, 1966). However, the time relation between the noradrenaline depletion and the decrease in blood pressure is poor, the latter effect being shorter-lasting than the former (Torchiana, Porter & others, 1965; Henning, 1967). This discrepancy implies that the false transmitter concept in its simplest outline is not sufficient to explain the antihypertensive action of α-methyldopa.

Considering the uncertainty about the site of action of the blood pressure lowering property of α-methyldopa, it was thought of interest to investigate whether a possible central nervous component significantly contributes to this action. In previous studies the administration of drugs into a vertebral artery in the cat has been used to investigate whether hypotensive effects of vasoactive drugs are mediated by the central nervous system (Zwieten, Bernheimer & Hornykiewicz, 1966; Reis & Zwieten, 1967; Sattler & Zwieten, 1967). In the present work a low dose of α-methyldopa has been infused into a vertebral artery in chloralose anaesthetized cats. The effects of this procedure on arterial blood pressure and tissue monoamines have been compared with those obtained after infusion of the same low dose of α-methyldopa into a systemic vein. Control experiments have been made with infusions of saline or the D-isomer of α-methyldopa. A significant lowering of blood pressure was seen only after administration of L-α-methyldopa into a vertebral artery although brain catecholamines were decreased both in this case and upon intravenous infusion. Part of the results have been reported in preliminary communications previously (Henning & Zwieten, 1967a,b).

## Experimental

### MATERIAL AND METHODS

The experiments were made on cats of either sex (2·0–4·5 kg) anaesthetized with chloralose (60–70 mg/kg i.p.). Artificial respiration was applied via a tracheal cannula. The blood pressure in the left femoral artery was recorded continuously by a Statham pressure transducer type P23Dc and a Grass Polygraph.

For infusion of solutions into the left vertebral artery, a polyethylene catheter was introduced into the left subclavian artery, which was exposed

after thoracotomy. All its side-branches were ligated with the exception of the vertebral artery. Solutions infused slowly into the catheter may be expected to flow into the vertebral artery since the blood flow in the subclavian artery prevents the infused solution entering the heart and thus into the peripheral circulation. Accordingly, the drugs reach the brain stem in high concentrations. The exact position of the catheter is shown in Fig. 1. Details of the surgical procedure have been described

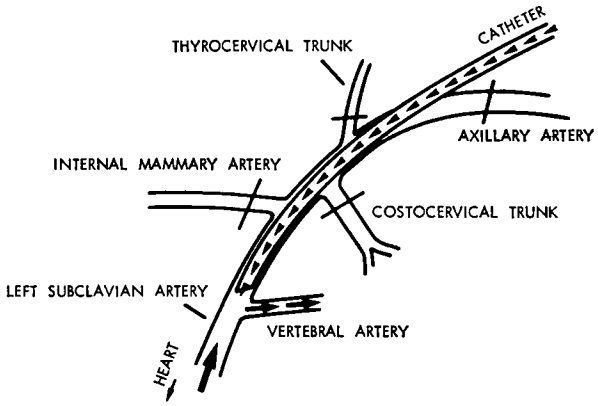


FIG. 1. Schematic representation of the technique used for infusion of drugs into the left vertebral artery. The left subclavian artery is exposed after thoracotomy. The axillary artery and all its side-branches except the vertebral artery are ligated. A polyethylene catheter is introduced into the subclavian artery so that the tip lies at the level of the vertebral artery.

previously (Zwieten & others, 1966; Reis & Zwieten, 1967; Henning & Zwieten, 1967a; Sattler & Zwieten, 1967). Drugs dissolved in saline (5–7 ml) were infused into the catheter over a period of about 1 hr. In a preliminary experiment (not included here) rapid injection of α-methyldopa into the catheter had no effect on blood pressure. For intravenous infusion we used the left femoral vein.

The animals were killed by cutting the great vessels to the heart about 3 hr after the end of the infusion. The amine contents of the brain (cerebellum removed) and of the right ventricle of the heart were measured. In some experiments the brain was sectioned immediately behind the mamillary bodies from the ventral surface and in front of the anterior corpora quadrigemina from the dorsal surface. The two parts of the brain, "forebrain" and "lower brain stem," were then analysed separately. Noradrenaline (Bertler, Carlsson & Rosengren, 1958), dopamine (Carlsson & Lindqvist, 1962), and 5-HT (Andén & Magnusson, 1967) were measured. α-Methyldopamine was determined by utilizing the observation (Carlsson & Lindqvist, 1962) that this amine behaves essentially like dopamine on the cation exchange resin columns used for separation of noradrenaline and dopamine, whereas it behaves like noradrenaline in the fluorimetric assay and can be distinguished in this way from dopamine.

## Results

*Blood pressure.* Changes in blood pressure observed upon the various treatments are represented in Fig. 2. Infusion of L-α-methyldopa 20 mg/kg into the left vertebral artery produced a decrease in mean arterial blood pressure which was slow in onset; usually no change in pressure was observed during the 1 hr infusion. Within the first hr after the end of the infusion a gradual fall in blood pressure occurred and 1 hr after the infusion had been terminated the average decrease in blood pressure was 17 mm Hg (s.e. 3·3, n = 10). During the following hours a further diminution in pressure was seen, the mean decrease 2 and 3 hr after the end of the infusion amounting to 27 mm Hg (s.e. 5·9, n = 10) and 36 mm Hg (s.e. 6·0, n = 10), respectively. Calculated in per cent of the pre-infusion blood pressure levels, which were about the same in the five series of experiments (Fig. 2), these decreases amounted to 12% (s.e.

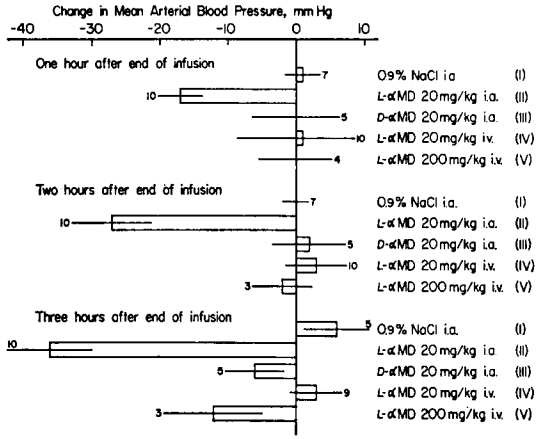


FIG. 2. Changes in mean arterial blood pressure after infusion of various drugs into the left vertebral artery (i.a.) or into the femoral vein (i.v.) of anaesthetized cats. The values are means with s.e.; number of experiments is indicated with the small figures.

Analysis of variance of the changes at each interval after the end of the infusion shows: After 1 hr (II) differs significantly from (I) and (IV) ($P < 0{\cdot}1\%$) and from (III) and (V) ($P < 1\%$). After 2 and 3 hr (II) differs significantly from (I), (III) and (V) ($P < 0{\cdot}1\%$) and from (V) ($P < 2{\cdot}5\%$). (I), (III), (IV) and (V) were not significantly different from each other at any interval ($P > 10\%$).

Initial blood pressure levels: (I) 135 mm Hg (s.e. 11·7), (II) 139 mm Hg (s.e. 5·5), (III) 137 mm Hg (s.e. 11·0), (IV) 150 mm Hg (s.e. 3·0), (V) 130 mm Hg (s.e. 5·8).

2·4), 19% (s.e. 3·8) and 27% (s.e. 4·1), respectively. In a few experiments the blood pressure was followed for as long as 4–5 hr after the end of the infusion and in these experiments no further decrease was observed.

The lowering of blood pressure after infusion of L-α-methyldopa in this dose was at all intervals statistically significant (analysis of variance; P values are given in Fig. 2) from the changes in the control experiments (infusion of saline or D-α-methyldopa) and after systemic infusion.

In another series of experiments L-α-methyldopa (20 mg/kg) was infused into the femoral vein. In this series the vertebral artery was also cannulated (sham operation) but no infusion was given. In control experiments D-α-methyldopa (20 mg/kg) or saline were infused into the left vertebral artery. These procedures provoked only small and variable changes in blood pressure which were not statistically different.

Intravenous infusion of a large dose of L-α-methyldopa (200 mg/kg) slightly lowered the blood pressure after 3 hr (mean decrease 12 mm Hg, s.e. 7·3, n = 4) but the change did not differ statistically from the control experiments.

*Tissue monoamines.* The levels of heart noradrenaline, whole brain noradrenaline, dopamine and 5-HT after the various types of treatment are given in Table 1. Control values were obtained from the animals infused with saline.

TABLE 1. LEVELS OF TOTAL BRAIN NORADRENALINE (NA), DOPAMINE (DA), 5-HYDROXYTRYPTAMINE (5-HT) AND α-METHYLDOPAMINE (α-M-DA) AND OF HEART NA AFTER VARIOUS TREATMENTS AS INDICATED. The values are means ± s.e. and number of experiments. P values were calculated by analysis of variance.

| Treatment | Total brain | | | | Heart (right ventricle) |
|---|---|---|---|---|---|
| | NA | DA | α-M-DA | 5-HT | NA |
| A. Controls (0·9% NaCl in vertebral artery) | 0·23<br>0·014<br>(10) | 0·37<br>0·033<br>(9) | 0·03<br>0·02<br>(3) | 0·29<br>0·017<br>(10) | 1·19<br>0·138<br>(9) |
| B. L-α-Methyldopa 20 mg/kg in vertebral artery .. .. .. .. .. | 0·16<br>0·010<br>(12) | 0·27<br>0·017<br>(12) | 0·28<br>0·040<br>(6) | 0·27<br>0·026<br>(10) | 1·48<br>0·137<br>(12) |
| C. D-α-Methyldopa 20 mg/kg in vertebral artery .. .. .. .. .. | 0·23<br>0·011<br>(6) | 0·28<br>0·021<br>(5) | — | 0·26<br>0·026<br>(5) | 1·82<br>0·406<br>(5) |
| D. L-α-Methyldopa 20 mg/kg in femoral vein .. .. .. .. .. | 0·17<br>0·013<br>(10) | 0·27<br>0·024<br>(9) | 0·27<br>0·022<br>(4) | 0·26<br>0·018<br>(10) | 1·34<br>0·117<br>(10) |
| E. L-α-Methyldopa 200 mg/kg in femoral vein .. .. .. .. .. | 0·13<br>0·008<br>(4) | 0·15<br>0·013<br>(4) | 0·65<br>0·078<br>(4) | 0·12<br>0·018<br>(4) | 0·86<br>0·051<br>(4) |
| | P % | P % | P % | P % | |
| A–B .. | <0·1 | <0·5 | <0·1 | >10 | n.s. |
| A–C .. | >10 | <5 | — | >10 | |
| A–D .. | <0·1 | <1 | <1 | >10 | |
| A–E .. | <0·1 | <0·1 | <0·1 | <0·1 | |
| B–C .. | <0·1 | >10 | — | >10 | |
| B–D .. | >10 | >10 | >10 | >10 | |
| B–E .. | >10 | <0·1 | <0·1 | <0·1 | |
| C–D .. | <0·5 | >10 | — | >10 | |
| C–E .. | <0·1 | <0·1 | — | <1 | |
| D–E .. | <10 | <0·1 | <0·1 | <0·5 | |

Three hr after an infusion of L-α-methyldopa (20 mg/kg) into a vertebral artery there was a significant, though moderate reduction of brain dopamine and noradrenaline while brain 5-HT and heart noradrenaline remained normal (for P values, see Table 1). Similarly, the intravenous infusion of the same dose of L-α-methyldopa also lowered brain dopamine and noradrenaline significantly, but brain 5-HT and heart noradrenaline

remained unaffected (for P values, see Table 1). There was no difference between the degree of amine depletion in these experiments and in those in which L-α-methyldopa was infused intra-arterially. When D-α-methyldopa was administered into the vertebral artery no significant changes were observed in the brain or heart amine contents. The intravenous infusion of a large dose of L-α-methyldopa (200 mg/kg) gave a significant reduction of all the amines studied in the brain (for P values, see Table 1). The noradrenaline content in the heart also seemed lower in this series than in the other four, but the difference was not significant.

When it was found that infusion of L-α-methyldopa into the vertebral artery and intravenous infusion of the same dose produced similar degrees of amine depletion, the lower brain stem and forebrain were analysed separately in some experiments. The results are summarized in Table 2.

TABLE 2. LEVELS OF NORADRENALINE (NA), DOPAMINE (DA) AND 5-HYDROXYTRYPTAMINE (5-HT) IN LOWER BRAIN STEM AND FOREBRAIN AFTER TREATMENTS AS INDICATED.

| Treatment | Lower brain stem | | | Forebrain | | |
|---|---|---|---|---|---|---|
| | NA | DA | 5-HT | NA | DA | 5-HT |
| Control (0·9% NaCl in vertebral artery) .. | 0·26<br>0·032<br>(6) | 0·08<br>0·005<br>(5) | 0·64<br>0·066<br>(6) | 0·24<br>0·016<br>(7) | 0·44<br>0·016<br>(6) | 0·27<br>0·017<br>(7) |
| L-α-Methyldopa 20 mg/kg in vertebral artery .. | 0·21<br>0·012<br>(6) | 0·09<br>0·023<br>(6) | 0·66<br>0·118<br>(5) | 0·18<br>0·010<br>(6) | 0·31<br>0·025<br>(6) | 0·27<br>0·031<br>(6) |
| L-α-Methyldopa 20 mg/kg in femoral vein .. | 0·23<br>0·033<br>(6) | 0·07<br>0·005<br>(5) | 0·58<br>0·067<br>(6) | 0·20<br>0·010<br>(6) | 0·32<br>0·025<br>(6) | 0·25<br>0·012<br>(6) |

No difference between the effect of intra-arterial or intravenous administration of α-methyldopa was observed.

In a few experiments the level of α-methyldopamine in the brain was also measured (Table 1). Intravenous and intra-arterial administration of L-α-methyldopa 20 mg/kg gave rise to similar concentrations of α-methyldopamine. After intravenous infusion of 200 mg/kg L-α-methyldopa the α-methyldopamine concentration in the brain was significantly higher than after the smaller dose (Table 1).

## Discussion

These results show that a small dose of L-α-methyldopa when infused into the vertebral artery lowers the mean arterial blood pressure of cats anaesthetized with chloralose. In a preliminary experiment it was found that a rapid injection of the same dose of α-methyldopa had no effect. Since infusion of saline or D-α-methyldopa into the vertebral artery had no influence on the blood pressure in identical experiments, it seemed that the effect of L-α-methyldopa was specific; it is generally agreed that the biological activity of α-methyldopa resides in the L-isomer (Porter & others, 1961; Sjoerdsma, 1961; Gillespie, Oates & others, 1962; Sjoerdsma, Vendsalu & Engelman, 1963). Furthermore, in our experiments the lowering of blood pressure after L-α-methyldopa was slow in

onset. The effect had probably reached its maximum about 3 hr after the infusion had been terminated, since no additional decrease occurred in the few experiments in which the blood pressure was followed for a further 1–2 hr. A similar time course is observed when large single doses of α-methyldopa are administered to conscious animals (Goldberg, DaCosta & Ozaki, 1961; Kroneberg, 1963; Davis & others, 1963; Torchiana & others, 1965; Henning, 1967) or to man (Schaub, Nager & others, 1962; Cannon, Whitlock & others, 1962; Onesti, Brest & others, 1964). The relative magnitude of the hypotensive response after infusion of L-α-methyldopa into the vertebral artery was about the same as that observed after systemic administration of much larger doses in conscious animals. In our experiments, the intravenous infusion of a relatively large dose of the drug failed to lower the blood pressure significantly. This observation is in agreement with most previous investigations. However, Miele (1966) observed a significant decrease of blood pressure in cats under urethane anaesthesia after oral administration of α-methyldopa.

In the present investigation, α-methyldopa significantly lowered whole brain dopamine and noradrenaline either after infusion into the vertebral artery, or after intravenous infusion, and the depletion was of the same moderate degree. Moreover, the levels of α-methyldopamine were about the same in these two types of experiments. When the lower brain stem was analysed separately there was still no significant difference in amine content after the two routes of administration. These findings are puzzling in view of the clear-cut effect on blood pressure after infusion into the vertebral artery. However, in view of the small number of animals investigated, the evidence is not conclusive. Possibly, a more extensive and detailed analysis of various parts of the brain stem might have disclosed a correlation between the lowering of blood pressure and the decrease in amine content. It seems reasonable to conclude, however, that there exists in the region supplied by the vertebral artery a structure which is influenced by infusion of α-methyldopa into this vessel in such a way as to bring about a reduction in blood pressure. The determination of the nature and exact localization of this effect requires further investigation. This component of the hypotensive effect of α-methyldopa is not necessarily related to the gross action of the drug on brain monoamines. A potentiation of anaesthesia by α-methyldopa seems rather unlikely since the intravenous infusion of 200 mg/kg does not affect blood pressure.

There is ample evidence for an effect of α-methyldopa on the central nervous system although the relative importance of this component for the hypotensive action has not been established. Thus, in animal experiments, the drug potentiates barbiturate narcosis and causes sedation and suppression of learned behaviour (Sourkes, 1965; Hanson & Henning, 1967). The α-methylated amine metabolites of α-methyldopa, α-methyldopamine and α-methylnoradrenaline, deplete the noradrenaline from sympathetically innervated organs but not from the brain; they have no antihypertensive effect in rats (Brunner & others, 1966; 1967; Henning,

1967). In man, α-methyldopa inhibits various haemodynamic reflexes involving both central and peripheral nervous mechanisms (Dollery & Harington, 1962; Sannerstedt, Varnauskas & Werkö, 1962; Mason & Braunwald, 1964; Shapiro & Krifcher, 1964). Clinical experience with the drug has also revealed a number of predominantly central nervous effects. These include sedation, psychiatric symptoms, Parkinsonism and abnormal lactation (Sourkes, 1965; Horwitz, Pettinger & others, 1967).

After infusion of the D-isomer of α-methyldopa the amine levels in the brain were the same as those observed after saline infusion. D-α-Methyldopa neither affected the blood pressure nor the concentration of monoamines in other species, or in man (Porter & others, 1961; Sjoerdsma, 1961; Gillespie & others, 1962; Sjoerdsma & others, 1963). It is not known whether in the cat D-α-methyldopa penetrates the blood-brain barrier to the same extent as does the L-isomer.

None of the treatments affected the noradrenaline content of the heart significantly. Thus, it appears that the brain is more sensitive to the noradrenaline-depleting action of small doses of α-methyldopa than is the heart. For reserpine-induced depletion, the opposite seems to be true (Carlsson, Rosengren & others, 1957; Carlsson, 1965). Central monoamine neurons generally appear to operate with a higher metabolic rate than the peripheral adrenergic nerves. The present observations may thus be interpreted to show that α-methyldopa depends more than does reserpine on the rate of metabolism for its catecholamine depleting action.

The results described in the present paper suggest that the blood pressure lowering effect of α-methyldopa may be, at least in part, of central origin. The exact mechanism of this effect remains unknown. The centrally mediated effect does not necessarily exclude the contribution of impaired peripheral sympathetic function to the hypotensive action of α-methyldopa.

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