

STUDIES ON THE HYPOTENSIVE ACTION OF α -METHYLDOPAMINE

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1 Intraventricular α -methyldopamine (50-200 μ g) produced a dose-related fall in blood pressure in conscious spontaneously hypertensive rats. Pretreatment with intraventricular 6-hydroxydopamine prevented this hypotensive effect of α -methyldopamine.

2 The hypotensive effect of α -methyldopamine was prevented by intraventricular injection of phentolamine or desmethylinipramine, but not by intraperitoneal injection of haloperidol.

3 Pretreatment with U-14,624, a selective central dopamine- β -hydroxylase inhibitor, prevented the hypotensive effect of α -methyldopamine.

4 α -Methyldopamine was considerably less potent than noradrenaline as a pressor agent in the pithed rat, but noradrenaline and α -methylnoradrenaline were found to be equipotent.

5 α -Methyldopamine (1-5 mg i.c.v.) reduced pressor responses elicited by electrical stimulation of the midbrain reticular formation in cats anaesthetized with chloralose.

6 It is concluded that the hypotensive action of α -methyldopamine in conscious animals involves intact central α -adrenergic neurones and a central adrenergic uptake mechanism for the formation of α -methylnoradrenaline.

Introduction

Carlsson & Lindqvist (1962) suggested that decarboxylation products of α -methyldopa, α -methyldopamine (MDA) and α -methylnoradrenaline might take over the function of normal transmitters in the brain. Day & Rand (1963, 1964) extended this hypothesis to propose that α -methyldopa exerted its hypotensive effect by the formation of α -methylnoradrenaline which was assumed to be a less potent transmitter than noradrenaline in the peripheral sympathetic nervous system. However, there is evidence for only a moderate impairment of peripheral transmission (Haefely, Hurlimann & Thoenen, 1967; Henning & Svensson, 1968; Finch, 1971; Finch & Haeusler, 1973) and Trinker (1971) has reported that α -methylnoradrenaline and noradrenaline are equipotent in the anaesthetized dog and pithed rat.

Henning & Van Zwieten (1968) proposed a central site of action for α -methyldopa since the hypotensive effect of the drug was far greater when administered into the vertebral artery than when given intravenously, and other workers (Henning, 1969; Ingenito, Barrett & Procita, 1970; Heise & Kroneberg, 1973; Finch & Haeusler, 1973) have provided evidence supporting this view.

The present study provides evidence that the hypotensive effect of MDA involves stimulation of

central α -adrenoreceptors and requires an intact central adrenergic uptake mechanism.

Methods

Measurement of arterial blood pressure in conscious spontaneously hypertensive rats

Spontaneously hypertensive rats (SHR) which originated from a hypertensive mutant of the Japanese strain (Roche Basle) by brother-sister mating, were used for these experiments. Rats were anaesthetized with chloral hydrate (200 mg/kg i.p.). A polypropylene cannula (Portex PP25 tip welded to a PP50 catheter) was introduced down the right carotid artery until the tip was positioned in the thoracic aorta, and the cannula was exteriorised at the back of the neck. An intraventricular cannula (Hayden, Johnson & Maickel, 1966) was inserted into the lateral cerebral ventricles via a trephine hole drilled 1 mm lateral and 1 mm posterior to the bregma and was fixed using dental acrylic cement. Blood pressures were recorded 1-2 days later in conscious unrestrained rats, with a Statham pressure transducer and a Devices M2 recorder. Drugs were injected intraventricularly (i.c.v.) in volumes not greater than 20 μ l using a microlitre syringe with

the needle cut down so that the tip extended 0.5 mm beyond the cannula guide into the lateral ventricles of the brain.

Pithed rat preparation

Pithed rat preparations were used to study the pressor response to noradrenaline, α -methylnoradrenaline and MDA injected intravenously.

Experiments on anaesthetized cats

Cats of either sex (2-3 kg) were anaesthetized with chloralose (60 mg/kg i.v.). The femoral artery and vein were then cannulated and a Statham pressure transducer connected to the arterial cannula. The animal's head was fixed in a David Kopf stereotaxic apparatus and a bipolar electrode introduced via a trephine hole in the skull into the midbrain reticular formation using the following co-ordinates: A = 5.0, L = 1.0-2.0, V = -0.5 (Snider & Niemer, 1961).

A trephine hole was drilled in the skull 7 mm posterior and 5 mm lateral to the bregma. Drugs were injected into the lateral cerebral ventricles with a microlitre syringe, the needle of the syringe penetrating 14 mm below the top of the skull.

At the end of each experiment, Trypan blue dye was injected through the ventricular cannulae and the brain examined for ventricular staining. Groups of 4-6 animals were used for these experiments.

Drugs

Desmethylinipramine hydrochloride (Ciba Geigy), haloperidol (Janssen), 6-hydroxydopamine hydrobromide (F. Hoffman La Roche, Basle), (\pm)- α -methyl-dopamine hydrobromide (synthesized by Janssen & Roche Products), (-)-methylnoradrenaline hydrochloride (Hoechst), (-)-noradrenaline acid tartrate (Hoechst), phentolamine mesylate (Rogitine, Ciba-Geigy) U-14,624 (1-phenyl-3-(2-thiazolyl)-2-thiourea) Aldrich chemicals). Noradrenaline, α -methylnoradrenaline, MDA and 6-hydroxydopamine refer to base weight; all other drugs refer to the salt. Haloperidol was dissolved in 1% lactic acid, U-14,624 was given by the intraperitoneal route injected as a suspension, 18 h before the experiments were performed. 6-Hydroxydopamine was administered to conscious rats by intraventricular route at 2 day intervals (3 x 250 μ g) and experiments performed 7 days later. 6-Hydroxydopamine and MDA were dissolved immediately before use in 0.01 N HCl. α -Methylnoradrenaline and noradrenaline (for intravenous use) were stored in 0.1 N HCl and diluted in 0.9% w/v NaCl

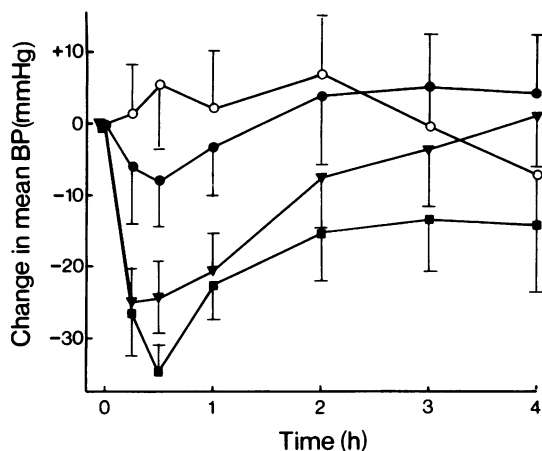


Figure 1 The effect of various doses of α -methyl-dopamine on the resting blood pressure of conscious, unrestrained spontaneously hypertensive rats. Vehicle of 20 μ l 0.01 N HCl (○); intraventricular α -methyl-dopamine, 50 μ g (●); 100 μ g (▼); 200 μ g (■). Vertical bars show the s.e. mean ($n = 8$ for all groups).

solution (saline) immediately before use. In the conscious rat experiments drugs for intraventricular administration were all dissolved in 0.01 N HCl immediately before use and the same volume of 0.01 N HCl was injected into the vehicle control animals.

Results

Hypotensive action of α -methyl-dopamine in conscious hypertensive rats

Conscious spontaneously hypertensive rats were used in groups of 8 for this study. The mean arterial blood pressure was recorded directly via a catheter introduced into the aortic arch. MDA (50-200 μ g i.c.v.) caused a dose-related fall in mean arterial blood pressure, the maximal fall being measured at 30 min (Figure 1). After the fall in blood pressure the pressure rose to values approaching control blood pressure values by the end of the 4 h experimental period.

An intraventricular injection of phentolamine (200 μ g/rat) 1 h before the injection of MDA (150 μ g i.c.v.) completely abolished the hypotensive action of intraventricular MDA (150 μ g) (Table 1).

Administration of intraventricular 6-hydroxydopamine (3 x 250 μ g) in doses shown to produce central sympathectomy and depletion of catecholamines (Uretsky & Iversen, 1970; Haesler, Finch & Thoenen, 1972) greatly reduced

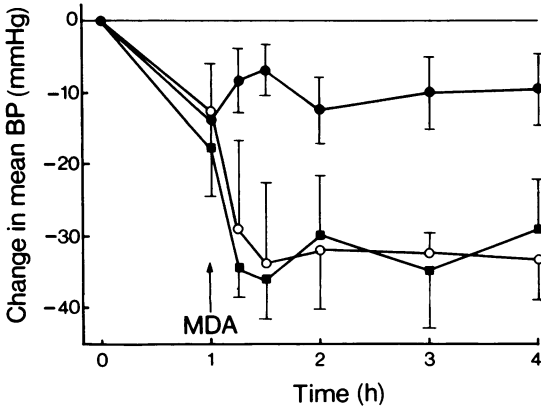


Figure 2 The effect of haloperidol on the hypotensive action of intraventricular α -methyldopamine (MDA) in conscious unrestrained spontaneously hypertensive rats. α -Methyldopamine (150 μ g i.c.v.) in rats pretreated with vehicle (lactic acid 1% i.p.) (○); α -methyldopamine (150 μ g i.c.v.) in rats pretreated with haloperidol (0.5 mg/kg i.p.) 1 h previously (■); haloperidol (0.5 mg/kg i.p.) alone (●). Vertical bars show s.e. mean. ($n = 8$ for all groups).

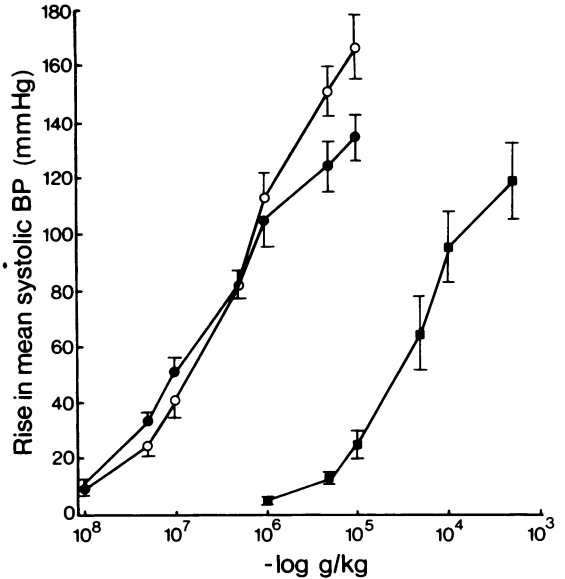


Figure 3 The pressor responses to intravenous noradrenaline (○), α -methylnoradrenaline (●) and α -methyldopamine (■) in pithed rats. The vertical bars show s.e. mean ($n = 7$ for all groups).

the hypotensive action of intraventricular MDA (150 μ g) (Table 1).

Administration of intraventricular desmethylimipramine (200 μ g/rat) 1 h before administration of MDA (150 μ g i.c.v.) completely abolished the hypotensive action of MDA (Table 1).

In rats pretreated with U-14,624 (200 mg/kg i.p.) 18 h previously, a dose known to inhibit

central dopamine- β -hydroxylase in the rat (Johnson, Boukma & Kim, 1970), the hypotensive action of the MDA (150 μ g i.c.v.) was completely abolished (Table 1).

Administration of haloperidol (0.5 mg/kg i.p.) to rats 1 h before intraventricular injection of

Table 1 The hypotensive effect of intraventricular α -methyldopamine (MDA) in conscious spontaneously hypertensive rats: modification by pretreatment with phentolamine, desmethylimipramine (DMI), 6-hydroxydopamine (6-OHDA) and U-14, 624

Treatment	(n)	Mean resting BP	Change in mean BP (mmHg) \pm s.e. mean					
			0.25 h	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h
0.01 NHCl vehicle i.c.v.	8	140.3 \pm 8.9	+1.3 \pm 7.1	+5.6 \pm 9.2	+2.2 \pm 8.0	+7.2 \pm 8.9	-0.3 \pm 6.4	-7.2 \pm 6.6
MDA (150 μ g i.c.v.)	8	145.3 \pm 5.4	-24.1 \pm 7.3	-26.9 \pm 5.7	-13.8 \pm 6.5	-10.3 \pm 5.3	-8.5 \pm 8.4	-10.0 \pm 7.7
Phentolamine (200 μ g i.c.v.)	8	141.3 \pm 13.2	+11.8 \pm 13.0	+20.7 \pm 10.1	+10.5 \pm 10.6	+22.1 \pm 12.1	+15.0 \pm 11.8	+17.1 \pm 10.3
MDA (150 μ g i.c.v.) 1h after phentolamine (200 μ g)	8	133.8 \pm 10.1	+8.4 \pm 9.3	+3.9 \pm 9.6	+1.2 \pm 11.2	+14.0 \pm 7.6	+9.0 \pm 5.8	+11.5 \pm 4.8
MDA (150 μ g i.c.v.) 1h after DMI (200 μ g i.c.v.)	8	148.0 \pm 7.6	-1.0 \pm 6.6	+2.9 \pm 7.4	+1.9 \pm 9.3	0.3 \pm 6.8	-6.0 \pm 6.8	-4.2 \pm 5.8
MDA (150 μ g i.c.v.) after 6-OHDA (3 x 250 μ g i.c.v.)	8	142.0 \pm 6.9	+5.0 \pm 5.0	-3.8 \pm 7.6	-1.0 \pm 8.3	-5.0 \pm 7.4	+2.3 \pm 9.4	+5.2 \pm 10.6
MDA (150 μ g i.c.v.) 18 h after U-14, 624 (200 mg/kg i.p.)	8	138.2 \pm 6.8	-4.3 \pm 6.7	-7.5 \pm 6.1	-3.1 \pm 5.8	+2.7 \pm 6.4	-2.8 \pm 7.0	+10.1 \pm 7.8

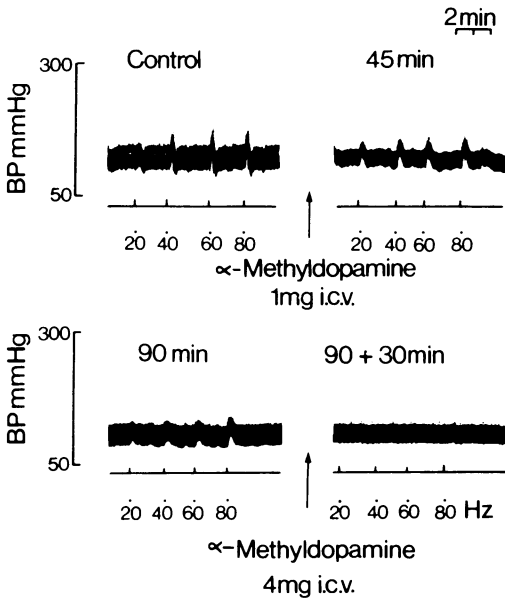


Figure 4 The effects of intraventricular α -methyl-dopamine (MDA) on the hypertensive action of stimulation of the mid brain reticular formation of a cat anaesthetized with chloralose. Stimulations were carried out for periods of 10 s at an intensity of 30 V, 0.1 ms duration at 20, 40, 60 and 80 Hz. Following control responses, 1 mg MDA was injected; after 90 min a further dose of 4 mg was injected.

MDA (150 μ g i.c.v.) failed to alter the hypotensive action of MDA (Figure 2). However, the lactic acid (1%) solvent of haloperidol, produced a prolonged fall in blood pressure (10 mmHg) in all animals.

Pressor effects of noradrenaline, α -methylnoradrenaline and α -methyl-dopamine in pithed rats

The pressor effect of these three catecholamines was studied in pithed rats. Noradrenaline and α -methylnoradrenaline were found to be equipotent, whilst MDA was approximately 100 times less potent than noradrenaline (Figure 3) and the maximum pressor response was less than that for noradrenaline.

Effect of α -methyl-dopamine on centrally induced pressor responses in chloralose-anaesthetized cats

Electrical stimulation of the midbrain reticular formation in cats anaesthetized with chloralose induced an immediate rise in blood pressure. Graded responses were obtained by increasing the

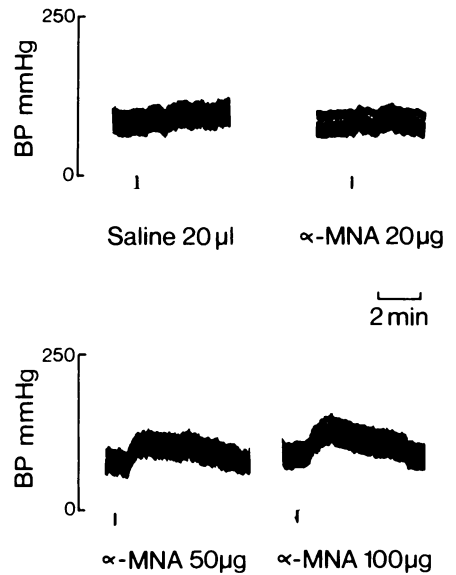


Figure 5 The effect of various doses of α -methyl-noradrenaline (α -MNA) administered intraventricularly on the resting blood pressure of a cat anaesthetized with chloralose. No change in blood pressure was observed with the vehicle (20 μ l saline).

frequency of stimulation and maximal responses were observed at 80 Hz. Intraventricular MDA (1 mg + 4 mg cumulative), caused the responses to be reduced and then abolished after a period of 120 min (Figure 4). No reduction in these responses to electrical stimulation occurred when the vehicle alone (20 μ l 0.01 N HCl) was injected, and stimulations carried out for a similar time period.

Effect on intraventricular α -methylnoradrenaline in chloralose-anaesthetized cats

Intraventricular injections of α -methylnoradrenaline (20-100 μ g) gave dose-related rises in blood pressure with no ensuing depressor response, even during a 3 h recording period (Figure 5).

Discussion

The results of the present study demonstrate the ability of intraventricular MDA to lower the blood pressure in conscious spontaneously hypertensive rats. This hypotensive action of intraventricular MDA was prevented by intraventricular pretreat-

ment with 6-hydroxydopamine in doses known to cause extensive depletion of central catecholamines (Uretsky & Iversen, 1970; Haeusler *et al.*, 1972). Pretreatment with intraventricular desmethylimipramine, which prevents uptake of catecholamines into central adrenergic neurones (Carlsson, Fuxe, Hamberger & Lindqvist, 1966) or intraventricular phentolamine also prevented the hypotensive action of MDA. These results strongly suggest that intact central α -adrenergic neurones are involved in the hypotensive action of MDA, and that uptake of MDA into these neurones is a prerequisite for this action. β -Hydroxylation of MDA to α -methylnoradrenaline is also essential, since inhibition of central dopamine- β -hydroxylase by U-14,624 (Johnson *et al.*, 1970) also prevents the hypotensive action of MDA.

It is of interest that at higher doses (200 μ g *i.c.v.*) MDA induced characteristic dopaminergic behavioural effects (sniffing and gnawing) suggesting a measure of dopamine receptor stimulation. Although dopaminergic pathways are believed to be involved in the central regulation of blood pressure (Bolme, Fuxe & Lidbrink, 1972) haloperidol, which is known to inhibit dopamine-induced stereotype and gnawing behaviour (Janssen, Niemegeers & Schellekens, 1965) did not antagonize the hypertensive action of MDA.

These results are in agreement with the hypothesis of Henning & Rubenson (1971) that the hypotensive action of α -methyldopa is mediated via α -methylnoradrenaline acting at central α -adrenoceptors. The hypotensive action of α -methyldopa has also been found to be antagonized by central α -adrenoceptor blockade, adrenergic uptake or 6-hydroxydopamine treatment in animals (Finch & Haeusler, 1973; Kale & Satoskar, 1970) and by tricyclic antidepressant treatment in man (White, 1965).

Injection of α -adrenoceptor agonists into ventricles of the brain may cause either pressor or depressor responses, possibly reflecting the site of interaction of the drugs with the neurones in the brain (Gagnon & Melville, 1966; Heise & Kroneberg, 1973; Correa & Graeff, 1974; Sinha & Schmitt, 1974; Day & Roach, 1974). In our experiments α -methylnoradrenaline given intraventricularly in cats anaesthetized with chloralose caused pressor responses with no associated fall in blood pressure; similar results were observed when catecholamines were injected directly into the posterior hypothalamus (Philippu, Przuntek, Heyd & Burger, 1971). Electrical stimulation of different areas of the brain similarly causes pressor or depressor responses. Stimulation of the midbrain reticular formation, posterior hypothalamus or locus coeruleus (Haeusler & Finch, 1972; Finch & Haeusler, 1973; Przuntek & Philippu, 1973) causes

a rise in blood pressure. MDA reduced the pressor responses elicited by stimulation of the midbrain reticular formation, and also of the posterior hypothalamus (Finch, Hersom & Hicks, unpublished observations). It is a reasonable hypothesis that α -methyldopa and MDA may reduce these elicited pressor responses via α -methylnoradrenaline acting at central α -adrenoceptors, since Finch & Haeusler (1973) have shown the pretreatment with FLA-63, a dopamine- β -hydroxylase inhibitor abolished this inhibitory effect of α -methyldopa. Also clonidine partially inhibited the pressor response elicited by stimulation of the posterior hypothalamus (Haeusler & Finch, 1972; Haeusler, 1973). The mode of action of MDA and α -methyldopa in reducing centrally evoked pressor responses is still to be elucidated since Haeusler (1974) has reported that an increased sympathetic nerve activity after stimulation of the posterior hypothalamus could still be elicited, even when brain noradrenaline content had been depleted by reserpine and α -methylparatyrosine to 1-3% of normal. Therefore, non-noradrenergic neurones may be involved in this efferent pathway down to the preganglionic fibres.

Although the body of evidence is overwhelmingly in favour of a central locus of action for α -methyldopa and MDA, there is evidence supporting a peripheral false transmitter hypothesis. In the pithed rat, noradrenaline and α -methylnoradrenaline were found to be equipotent as pressor agents. However, MDA was considerably less potent than noradrenaline as a pressor agent and it is possible that this might reflect partially, a false transmitter action of MDA in the periphery. Finch (1971) could not show any impairment of the entire sympathetic outflow in the pithed rat by acute administration of α -methyldopa, but Finch & Haeusler (1973) found that α -methyldopa pretreatment reduced the vasoconstrictor responses to stimulation of the renal artery preparation, and that α -methylnoradrenaline had one eighth the potency of noradrenaline on this preparation. Recently Doxey & Scutt (1974) have shown that 4 pretreatments with α -methyldopa reduced the pressor responses to stimulation of the entire sympathetic outflow in the pithed rat, and reduced the positive chronotropic effects by stimulation of the cardiac nerves. Salmon & Ireson (1970) also claimed evidence for a short lasting peripheral impairment in the anaesthetized rat after α -methyldopa. Farmer (1965) also demonstrated impairment of the cat nictitating membrane after α -methyldopa.

In conclusion, MDA has been shown to exert a central control of the resting blood pressure in conscious animals. The results suggest that the hypotensive action of MDA involves intact central

α -adrenergic neurones and a central adrenergic uptake mechanism for the formation of α -methyl-noradrenaline.

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