Interaction of dopamine, methyldopa and reserpine in the sympato-adrenal system in essential hypertension


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Summary

1. The interactions of dopamine, reserpine and methyldopa on blood pressure of normal subjects and of those with essential hypertension were examined.

2. When biosynthesis of noradrenaline from dopamine was blocked by reserpine, dopamine induced a prominent depressor effect in essential hypertension.

3. The long-term treatment with methyldopa induced a marked potentiation of the pressor action of dopamine in hypertension, although no significant pressor response was found in normal subjects.

4. It is suggested that methylnoradrenaline may accumulate in peripheral nerve endings of patients with essential hypertension in comparison with normal subjects, and this accumulated methylnoradrenaline potentiates the pressor response to dopamine in essential hypertension.

Key words: catecholamine, hypertension, methylnoradrenaline, sympathetic nervous system.

Methods

Twelve normotensive subjects aged 27–63 (average 41) years and twenty-one hypertensive patients aged 17–56 (average 36) years were studied. The hypertensive group consisted of five cases of borderline hypertension, ten of moderate hypertension and six of severe hypertension. Anti-hypertensive drugs had been discontinued at least 2 weeks before the study and an intake of sodium ad libitum (approximately 250 mmol/day or above) was allowed. After an overnight fast, dopamine, diluted with 5% glucose solution, was infused intravenously at a rate of 2, 3, 4, 5, 6 or 7 μg min⁻¹ kg⁻¹.

Diuretic and natriuretic effects of dopamine were calculated from urine collected during 60 min of dopamine infusion.

Results

Effect of dopamine on blood pressure in normal and hypertensive subjects

In healthy subjects, dopamine elevated systolic blood pressure at high doses and it reduced diastolic blood pressure at low doses.

In twenty-one hypertensive patients, pre-infusion blood pressures were 163 mmHg (SEM 4.8) systolic and 97 mmHg (SEM 4.4) diastolic. Infusions of dopamine reduced blood pressure; the maximum reduction was obtained at a rate of 3 μg min⁻¹ kg⁻¹, with which the mean pressures were reduced to 145 mmHg (SEM 3.9) systolic and 87 mmHg (SEM 3.9) diastolic. At high dosage, blood pressure returned to about the pre-infusion level. In one-third of the hypertensive group the blood pressure remained lowered at higher rates of infusion.
Urinary volume increased from 1.8 (SEM 1.0) to 5.7 (SEM 1.5) ml/min and urinary sodium output from 250 (SEM 9.8) to 534 (SEM 15.4) mmol/min in normal subjects. In hypertensive patients, urinary volume increased from 1.0 (SEM 1.0) to 4.8 (SEM 1.4) ml/min and urinary sodium output from 175 (SEM 9.3) to 537 (SEM 16.0) mmol/min. There was no significant difference in diuretic and anti-diuretic effects between the two groups.

Influence of acutely administered reserpine on the vasodepressor effect of dopamine

Reserpine (1 mg) was injected intramuscularly 1 h before the infusion of dopamine in six hypertensive patients. In five of these, a control study without reserpine pretreatment was carried out. A marked fall of blood pressure was observed after dopamine infusion in patients pretreated with reserpine. Mean blood pressure fell from 127 (SEM 7.7) to 105 (SEM 7.3) mmHg during infusion of dopamine at a rate of 4 μg min⁻¹ kg⁻¹ and the low pressure lasted for several hours after the infusion had been discontinued. In a control study without acute administration of reserpine, blood pressure fell from 128 (SEM 9.9) to 122 (SEM 5.1) mmHg during infusion at a rate of 4 μg min⁻¹ kg⁻¹. There was no significant change in urine volume or urinary sodium output between patients with and without reserpine pretreatment.

Influence of methyldopa on the cardiovascular effects of dopamine

Five normotensive volunteer subjects and seven hypertensive patients were given methyldopa in daily doses of 0.75–1.5 g for 1–4 weeks. In control subjects, long-term treatment with methyldopa did not change the vascular effect of dopamine. However, a marked potentiation of the vasopressor effect of dopamine was induced by methyldopa in hypertensive patients. Blood pressure increased from 160/100 mmHg to 171/94 mmHg at 2 μg min⁻¹ kg⁻¹, to 185/93 mmHg at 3 μg min⁻¹ kg⁻¹, to 207/95 mmHg at 4 μg min⁻¹ kg⁻¹, to 194/72 mmHg at 5 μg min⁻¹ kg⁻¹, to 212/83 mmHg at 6 μg min⁻¹ kg⁻¹ and to 215/85 mmHg at 7 μg min⁻¹ kg⁻¹. Thus a dose-dependent increase of systolic blood pressure was found; diastolic blood pressure was moderately reduced at all doses.

Instead of methyldopa, L-dopa was administered for 2 weeks in three hypertensive patients. After this treatment dopamine infusion was depressor, rather than pressor at low doses. Blood pressure returned to pre-infusion levels at high doses.

Influence of chronically or acutely administered reserpine on the enhanced vasopressor effect of dopamine induced by methyldopa

Three hypertensive patients received methyldopa and reserpine orally for 2 weeks, and then dopamine was infused. The prominent pressor effect of dopamine observed after treatment with methyldopa was abolished, and an opposite, depressor response was observed. Mean blood pressure was lowered from 116 mmHg to 100–106 mmHg at low doses. In three cases with acute intramuscular administration of reserpine (1 h before dopamine infusion), however, the enhanced vasopressor effect was not altered. Mean blood pressure rose from 119 mmHg to 130 mmHg at 5 μg min⁻¹ kg⁻¹ and to 133 mmHg at a rate of 7 μg min⁻¹ kg⁻¹.

Discussion

It is reported that the vasodepressor effect of dopamine is due to renal and mesenteric vasodilatation mediated by the action of dopamine on dopamine receptors (McNay, McDonald, & Goldberg, 1965; Eble, 1964). Dopamine is also known to release noradrenaline from sympathetic nerve endings (Tai, Langer & Trendelenburg, 1967; Neuvonen & Westermann, 1973). In the present study, a mild reduction of blood pressure was observed in hypertensive subjects by dopamine infusion, whereas a mild pressor response was found in normal subjects. Thus dopamine seems to have dual effects on the blood pressure, pressor and depressor. The present study indicates that the latter, pressor, effect is slightly dominant in normotensive subjects and the former, depressor, effect is dominant in hypertensive subjects.

The vasodepressor effect of dopamine was markedly potentiated by reserpine in hypertensive patients. Reserpine blocks the uptake of dopamine and noradrenaline into the storage vesicles in the sympathetic nerves, the storage of pressor amines being lowered (Giachetti, Hollenbeck & Shore, 1974). It is likely that this is the reason the pressor component is weakened and the depressor reaction is exaggerated in patients pretreated with reserpine.
In hypertensive patients treated with methyldopa, dopamine infusion elicited a marked elevation of blood pressure, whereas methyldopa administration in normal control subjects caused no change in the response to dopamine infusion. This suggests that the effect of methyldopa in peripheral noradrenergic nerves in essential hypertension is different from that in normal subjects. We suggest that methylnoradrenaline accumulates in the nerve endings in essential hypertension, in comparison with normal subjects, and that the accumulated methylnoradrenaline potentiates the direct and indirect pressor action of dopamine in hypertensive patients. On the other hand, oral administration of L-dopa did not change the blood pressure response to dopamine. This result suggests that noradrenaline biosynthesized from L-dopa did not raise the store level.

The long-term administration of reserpine suppressed the pressor response of dopamine induced by methyldopa in essential hypertension. This result suggests that long-term treatment of reserpine depletes methylnoradrenaline in nerve endings and this inhibits the pressor effect of dopamine. But the acute reserpine treatment did not cause this inhibition of pressor reaction to dopamine. This may be explained as follows: methylnoradrenaline, which had accumulated in the vesicles, was released acutely from the granules. The inactivation of methylnoradrenaline by monoamine oxidase in the nerve terminal cytosol is slower than that of noradrenaline and sufficient methylnoradrenaline remains to elicit a pressor response when released by dopamine within 1 h after reserpine injection. The present data support the view that the metabolism of catecholamines is altered in essential hypertension, in comparison with normotensive subjects.

References