Increased peripheral release of noradrenaline and uptake of adrenaline in essential hypertension?

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Summary

1. Twenty middle-aged men with untreated sustained essential hypertension for more than 5 years and 19 comparable normotensive controls were investigated. Both groups were derived from The Oslo Study, where they had served as control hypertensive and normotensive subjects.

2. Supine venous and arterial plasma catecholamines were increased in the hypertensive subjects compared with the normotensive subjects. The mean arterial–venous difference for adrenaline in the hypertensive (0.45 ± SE 0.08 nmol/l) was increased compared with the normotensive group (0.27 ± 0.03 nmol/l, P < 0.05). Similarly, the venous–arterial difference for noradrenaline was increased in the hypertensive (0.29 ± 0.13 nmol/l, P < 0.05) compared with the normotensive group (−0.07 ± 0.11 nmol/l).

3. The results are consistent with an increased release of adrenaline from the adrenal medulla and noradrenaline from the peripheral vascular beds (forearm) in essential hypertension. The increased arterial–venous difference for adrenaline in the hypertensive group also suggests an increased uptake of adrenaline in the peripheral vascular beds.

Key words: arterial–venous difference, catecholamine, co-transmitter, sympathetic nervous system.

Introduction

The hypothesis that essential hypertension may be related to an increased sympathetic tone has received much attention, and after the introduction of sensitive catecholamine assays several groups have reported increased plasma catecholamines in essential hypertension [1–5]. However, modest interest has been paid to the possibility of peripheral release and uptake of plasma catecholamines. This was the aim of the present study. We have measured venous and arterial plasma catecholamines in a group of well-characterized patients with long-standing untreated essential hypertension and in comparable normotensive subjects.

Patients and methods

The patients were 20 men with untreated essential hypertension who were randomly selected from The Oslo Study [6], where they had served as control hypertensive patients from 1973. In 1979 they had sustained hypertension for more than 5 years and averaged 176 ± 4/115 ± 2 mmHg (mean ± SE) in supine blood pressure. They averaged 51 ± 1 years of age (range 47–55), 81.5 ± 2.6 kg in weight, 176 ± 1.5 cm in height and 162 ± 12 mmol/day in urinary sodium excretion.

The control subjects were 19 men who had served in The Oslo Study [6] as control normotensive subjects since 1973 with blood pressure below 150/90 mmHg in the supine, sitting and standing positions. In 1979 they averaged 132 ± 3/83 ± 2 mmHg in supine blood pressure. They were selected to match the hypertensive group as closely as possible with respect to all important features, and they averaged 52 ± 1 years of age, 176.4 ± 1.3 cm in height and 159 ± 13 mmol/day in urinary sodium excretion. Body weight (76.4 ± 2.2 kg) was lower than in the hypertensive group, but the difference was moderate and, evaluated with a t-test, statistically insignificant (P > 0.10).

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Both the patients and controls were well conditioned to clinical examination and blood sampling and had a free sodium intake. All were ambulatory and fully employed, and none was addicted to alcohol or drugs. All had normal

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renal function and heart size and none of the hypertensive group had retinal changes more than Keith–Wagener grade II.

At the time of examination, between 08.15 and 09.15 hours, all the subjects had fasted overnight without intake of fluid, food, nicotine or caffeine. Each participant rested supine in a quiet room for 30 min. Then blood for catecholamine assay was drawn by puncture of the cubital vein and thereafter the femoral artery with a hypodermic 23 gauge needle. All the samples were immediately placed on ice, centrifuged and frozen at –70°C.

The catecholamines were measured with a radioenzymatic technique [7] with a lower detection limit of 0.03 nmol/l of plasma and no cross-reactivity between the two catecholamines. The coefficient of variation was 8 and 14% within-assay respectively for noradrenaline and adrenaline, 9 and 10% between two different technicians within-day and 9 and 13% between-days in 25 different plasma samples covering the complete concentration ranges in the present material. All determinations were performed by the same technician. The results are presented as means ± SE. Means were compared by Student’s t-test and results were considered statistically significant at \( P < 0.05 \).

Results

In the hypertensive patient venous and arterial noradrenaline and adrenaline were increased compared with the normotensive controls (Fig. 1). The following plasma concentrations (nmol/l) were observed in the two groups respectively: venous noradrenaline 3.25 ± 0.31 and 2.11 ± 0.15 (\( P < 0.005 \)); arterial noradrenaline 2.96 ± 0.26 and 2.18 ± 0.17 (\( P < 0.01 \)); venous adrenaline 0.38 ± 0.03 and 0.19 ± 0.22 (\( P < 0.001 \)); arterial adrenaline 0.82 ± 0.10 and 0.46 ± 0.04 (\( P < 0.005 \)). Arterial adrenaline concentration was higher than venous in both the hypertensive and the normotensive groups (\( P < 0.001 \)), and in the hypertensive patients venous noradrenaline was higher than arterial (\( P < 0.01 \)).

The arterial–venous difference for adrenaline was increased in the hypertensive group (0.45 ± 0.08) compared with the normotensive group (0.27 ± 0.03, \( P < 0.05 \)) (Fig. 1). Similarly, the venous–arterial difference for noradrenaline in the hypertensive group (0.29 ± 0.13) was increased compared with the normotensive group (–0.07 ± 0.11, \( P < 0.05 \)). When adding the arterial–venous difference for adrenaline and the venous–arterial difference for noradrenaline the discrimination between the hypertensive and the normotensive groups was even more pronounced, and the values averaged 0.74 ± 0.15 and 0.21 ± 0.09 in the two groups (\( P < 0.005 \)).

Discussion

The necessity of comparable patient and control groups was emphasized in a recent critical review of previous examinations concerning the role of the sympathetic nervous system in the pathogenesis of essential hypertension [5]. Our results are based on comparison of plasma catecholamines in a group of particularly well-characterized patients with those in comparable normotensive controls. All the participants had been regularly observed since 1973, and the hypertensive and normotensive groups were comparable with respect to all important features except for a moderately higher mean
weight in the hypertensive patients. The hypertensive patients had definitely elevated blood pressure for years, and all the subjects, both the hypertensive and normotensive, were well conditioned to clinical examination and blood sampling. In these aspects our study differed from most other similar studies.

The finding of increased venous noradrenaline and adrenaline support previous reports [1–5]; however, our study also showed increased arterial catecholamines in the hypertensive group. The increased arterial–venous and venous–arterial differences for plasma catecholamines in the hypertensive compared with the normotensive group are consistent with both increased adrenaline release from the adrenal medulla and increased noradrenaline release from the peripheral vascular sympathetic nerve endings. The increased arterial–venous difference for adrenaline also suggests an increased uptake of adrenaline by the peripheral vascular beds. This uptake may result in incorporation of adrenaline into transmitter stores in peripheral sympathetic terminals [8]. According to a recent hypothesis [9–12] there is a local release of adrenaline as a co-transmitter and subsequent activator of the prejunctional β-receptors. Thus an increased uptake of adrenaline into the peripheral transmitter stores of our hypertensive patients may permit an increased local release of adrenaline and an increased activation of the prejunctional β-receptors, leading to enhanced noradrenaline release, consistent with our findings.

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References