Sodium Restriction Lowers High Blood Pressure Through a Decreased Response of the Renin System – Direct Evidence Using Saralasin

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Twenty-nine patients with essential hypertension were studied while on their normal diets, on the 5th day of a high sodium diet (around 350 mmol/day) and on the 5th day of a low sodium diet (10 mmol/day). The fall in mean arterial pressure on changing from the high sodium to the low sodium diet was 9.0 ± 1.6 mmHg and the rise in the plasma renin activity in the same period was 2.52 ± 0.41 ng/ml/h, these two variables being significantly correlated ($r = -0.45$; $P < 0.02$). An infusion of saralasin was given on the 5th day of the low sodium diet. A highly significant negative correlation was found between the fall in blood pressure on sodium restriction and the change in blood pressure with saralasin ($r = -0.52$; $P < 0.005$); this correlation was still significant when corrected for the severity of the hypertension ($r = -0.41$; $P = 0.03$) while it became non-significant if controlled for plasma renin activity on the low sodium diet ($r = -033$; NS). These results provide direct evidence that the fall in blood pressure which is seen on reducing sodium intake in many patients with essential hypertension is, at least in part, directly mediated by the reactivity of the renin angiotensin system.

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Introduction

Although sodium restriction reduces blood pressure in many patients with essential hypertension [1-3], the mechanism through which it acts is not clear [4-6]. In essential hypertension there is a wide range of blood pressure responses during short-term sodium restriction [7,8]. Several authors have suggested that the fall in blood pressure with sodium restriction is related to the blunting of the renin response that occurs in many patients with essential hypertension [7-12].

We therefore conducted a study looking at the changes in blood pressure with alteration in sodium intake and looking directly at the importance of the renin system on the low sodium diet by infusing 1-Sar-8-ala-angiotensin II (saralasin), a competitive inhibitor of angiotensin II.

Patients and methods

Twenty-nine patients with essential hypertension, referred to the Blood Pressure Unit by local family doctors, were studied. Patients with renal failure (plasma creatinine > 120 μmol/l), ischaemic heart disease, or cerebrovascular disease, or who were taking oral contraceptives or any other drug were excluded from the study. Subjects either had not previously received blood pressure lowering treatment or, if they had, it was stopped 3 months prior to the study. Patients were members of a larger sample which had been previously investigated as reported elsewhere [9]; they were consecutively seen in the Blood Pressure Unit and recruited for the present study when saralasin became available. All subjects were followed 3 months in

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the Blood Pressure Unit on no treatment. At the end of this run-in period, subjects were admitted to the study if their supine diastolic blood pressures were greater than 90 mmHg and less than 130 mmHg. There were 13 males and 16 females; 22 were white and seven black. The mean age of the group was 45.9 ± 2.1 years (mean ± s.e.m.; range 21-70 years) and mean supine arterial pressure was 130.3 ± 2.5 mmHg. Informed consent was obtained from each subject. Patients were studied for three consecutive dietary periods: on their normal diets (approximately 150 mmol sodium/day), then on a high sodium intake (around 350 mmol/day) for 5 days, followed by a low sodium intake of 10 mmol/day for 5 days. High sodium diet was achieved by supplementing the normal diet with 20 Slow sodium tablets (CIBA 10 mmol/tablet). Low sodium diet was provided by the metabolic ward kitchen. Potassium intake was not altered for either diet. Throughout the study all subjects were allowed to go about their normal activities; they were not admitted to hospital but were discouraged from vigorous exercise. During the study all patients were seen in the Blood Pressure Unit at the same time of the day, by the same nurse in the same room. Blood pressure was measured between 10 a.m. and 12 noon in the same arm by nurses using semi-automatic ultrasound sphygmomanometers (Arteriosonde) [13] with attached recorder, on the final day of the normal diet and on the 5th day of high and low sodium diets. The measurements were therefore free from any observer bias. Supine and standing blood pressures were taken as the mean value of five readings obtained at 1-2 min intervals with the patients in the corresponding positions; supine blood pressure was measured before standing blood pressure. Pulse rate was measured with a Cambridge 3048 pulse monitor. Body weight was recorded at each visit. During the study, 24 h urine collections were obtained during the last 2 days of each dietary period.

Saralasin (1-Sar-8-ala-angiotensin II), a competitive inhibitor of angiotensin II, was infused on the 5th day of the low sodium diet by using an incremental infusion of 0.05 μg/kg/min for 20 min, 0.25 μg/kg/min for 20 min and finally 1.25 μg/kg/min for 20 min. Patients were infused sitting upright in a chair which could, if necessary, be tipped back, with a 1 h control period before and after infusion. Blood pressure was measured every 1-3 min with an Arteriosonde. Blood was taken in fasting conditions, without stasis, after the patient had been sitting upright for 10 min between 10 a.m. and 12 noon, for electrolytes, urea, creatinine and plasma renin activity on the last day of the normal, high and low sodium diets. On the 5th day of the low sodium diet, plasma renin activity was measured by radio-immunoassay [14] before saralasin infusion. Mean arterial pressure was calculated as diastolic pressure plus one-third of pulse pressure. The blood pressure response to saralasin was calculated as the change in mean arterial pressure between the 20 min before infusion and the last 10 min at the highest rate of infusion. As plasma renin activity levels are known to be distributed abnormally in the population, log transformation of the values was used. Student's two-tailed paired t-tests, simple and partial correlation analyses were carried out using the University of London computer and the North Western Universities' Statistical Package for the Social Sciences.

Results

On their normal diets, the mean supine arterial pressure in the 29 patients was 130.3 ± 2.5 mmHg, the mean urinary sodium excretion was 155.8 ± 10.2 mmol/24 h and mean plasma renin activity was 0.95 ± 0.14 ng/ml/h. On the 5th day of the high sodium diet there was no significant change in the mean supine arterial pressure (129.9 ± 2.4 mmHg), urinary sodium excretion rose to a mean of 287.2 ± 16.0 mmol/24 h and plasma renin activity fell to 0.50 ± 0.09 ng/ml/h. Measurements on the 5th day of the low sodium diet showed that the mean supine arterial pressure fell to 120.9 + 2.0 mmHg, mean urinary sodium excretion was 18.5 ± 1.7 mmol/24 h and mean plasma renin activity rose significantly to 3.03 ± 0.41 ng/ml/h ($P < 0.001$). The mean fall in blood pressure from high to low sodium diet was 9.0 ± 1.6 mmHg ($P < 0.001$). A significant negative correlation was found between the fall in blood pressure on low sodium diet and the rise in plasma renin activity ($r = -0.45$; $P < 0.02$; Fig. 1). Full details of systolic and diastolic blood pressure changes and other variables that were measured are shown in Table 1.

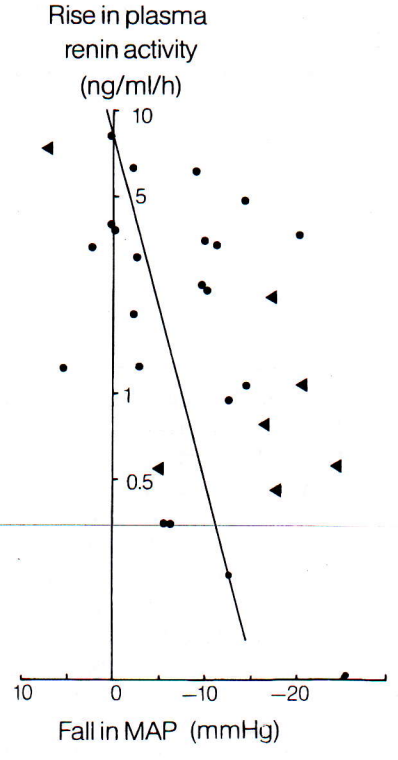

Fig. 1. Relationship between fall in mean arterial pressure (MAP) on changing from the high sodium to the low sodium diet and renin changes in 29 patients with essential hypertension ($r = -0.45$; $P < 0.02$). ● = white; ▲ = black.

Table 1. Effects of alteration of sodium intake in 29 patients with essential hypertension

	Normal diet	High sodium diet	Low sodium diet
Supine systolic blood pressure (mmHg)	169.4 ± 3.6	170.0 ± 3.3	154.5 ± 2.7**
Supine diastolic blood pressure (mmHg)	110.8 ± 2.5	109.9 ± 2.4	104.2 ± 2.1**
Standing systolic blood pressure (mmHg)	169.3 ± 3.4	169.8 ± 3.3	152.4 ± 2.9**
Standing diastolic blood pressure (mmHg)	119.1 ± 2.7	118.3 ± 2.5	112.1 ± 2.1**
Supine pulse (beats/min)	76.9 ± 2.2	78.1 ± 2.2	82.1 ± 2.4*
Standing pulse (beats/min)	85.8 ± 2.3	85.7 ± 2.5	94.1 ± 2.7*
Weight (kg)	70.0 ± 2.5	70.4 ± 2.5	68.3 ± 2.4**
Plasma renin activity (ng/ml/h)	0.95 ± 0.14	0.50 ± 0.09‡	3.03 ± 0.41**
Urinary sodium (mmol/24 h)	155.8 ± 10.2	287.2 ± 16.0‡‡	18.7 ± 1.7**
Urinary potassium (mmol/24 h)	64.8 ± 3.5	64.4 ± 3.6	49.4 ± 1.9**

Results given as mean ± s.e.m.
*$P < 0.05$; **$P < 0.001$, for differences between effects of low sodium diet and both high sodium diet and normal diet.
‡$P < 0.005$; ‡‡$P < 0.001$, for differences between effects of high sodium diet and normal diet.

Before saralasin infusion, on the last day of the low sodium diet, mean sitting arterial pressure was 120.1 ± 2.0 mmHg and during the last 10 min of maximal infusion rate the value fell to 116.8 ± 2.9 mmHg ($P < 0.05$); individual changes ranged from −26.7 to +11.7 mmHg (Fig. 2). The change in blood pressure with saralasin on the low sodium diet showed a highly significant correlation with the fall in blood pressure on going from high to low sodium diet (r = −0.52; $P < 0.005$), thus indicating that the greater the fall in blood pressure on sodium restriction, the less the fall in blood pressure with saralasin (Fig. 3). There was also a highly significant correlation between the blood pressure fall with saralasin and the plasma renin activity on the low sodium diet (r = 0.71; $P < 0.001$; Fig. 4), as well as for the rise in plasma renin activity on going from high to low sodium diet (r = 0.72; $P < 0.001$). The severity of hypertension (mean blood pressure on normal diet) was also related to the blood pressure sensitivity to sodium restriction (r = 0.43; $P < 0.02$), to the blood pressure changes with saralasin (r = −0.41; $P < 0.05$) and to changes in plasma renin activity on going from high to low sodium diet (r = −0.44; $P < 0.02$). To rule out any spurious correlation, because of the close interrelationships among these

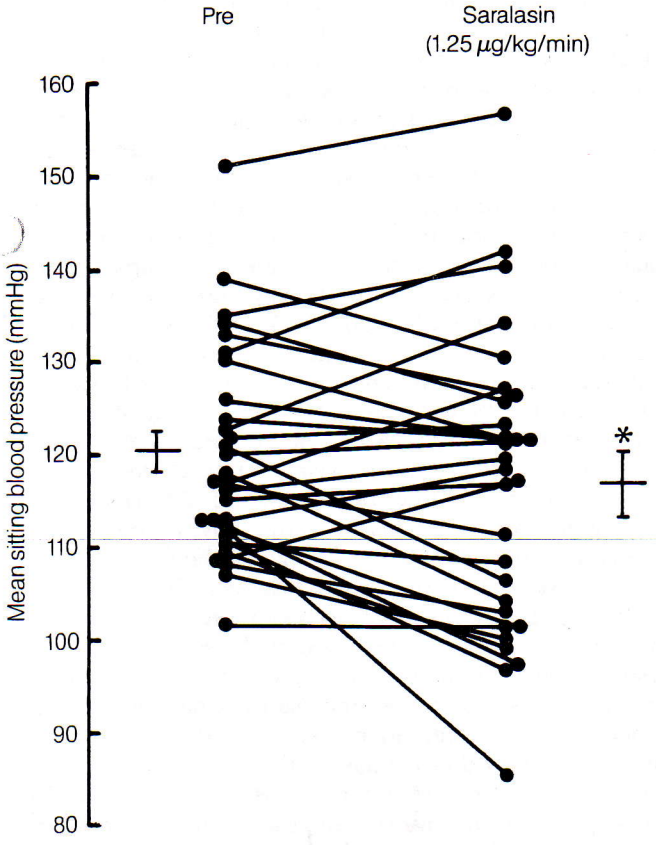

Fig. 2. Blood pressure response to saralasin infusion (5th day of 10 mmol Na^+ diet) in 29 patients with essential hypertension (mean ± s.e.m.; *$P < 0.05$).

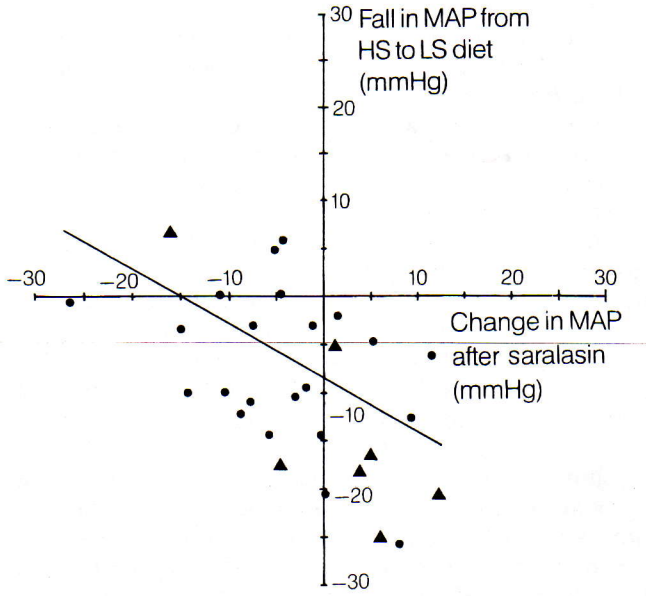

Fig. 3. Relationship between fall in mean arterial pressure (MAP) on changing from the high sodium (HS) to the low sodium (LS) diet and blood pressure response to saralasin (1.25 μg/kg/min) infused on the 5th day of the low sodium diet in 29 hypertensives (r = −0.52; $P < 0.005$). ● = white; ▲ = black.

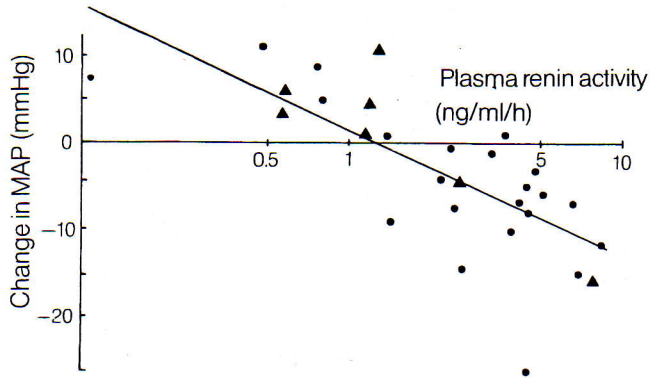

Fig. 4. Relationship between change in mean arterial pressure (MAP) after saralasin infusion and levels of plasma renin activity on the 5th day of the low sodium diet in 29 patients with essential hypertension ($r = 0.71$; $P < 0.001$). ● = white; ▲ = black.

variables, a partial correlation analysis was carried out. This analysis showed that the relationship between sodium sensitivity (considered as blood pressure fall on sodium restriction) and blood pressure change during saralasin infusion was still significant when controlled for the severity of hypertension ($r = -0.41$; $P = 0.03$) while it was no longer significant if corrected for the rise in plasma renin activity from the high to the low sodium diet ($r = -0.35$; NS).

Discussion

Sodium restriction reduces blood pressure in many patients with essential hypertension [1-3] and appears to be more effective the higher the blood pressure [11]; nevertheless, the mechanism whereby it lowers blood pressure is not clear. Alteration in sodium intake causes little change in blood pressure in normotensive subjects [11]. Several authors have pointed out that the blood pressure response to a reduction of sodium intake could be partly explained by a decreased responsiveness of the renin-angiotensin system [7-12,15]. Some studies have shown that patients with the greatest fall in blood pressure with sodium restriction have the least rise in plasma renin activity [9]. This inverse relationship might suggest that in essential hypertension a blunted response of the renin-angiotensin system to sodium restriction leads to a greater fall in blood pressure in these patients. Epidemiological evidence has shown that on a normal sodium diet, the higher the blood pressure, the lower the plasma renin activity [16].

Chinn *et al.* [17] demonstrated that circulating angiotensin II, both in normal subjects and in patients with essential hypertension, is within the range that is known to modulate arterial pressure directly. Posternack *et al.* [18] demonstrated that angiotensin II plays an active role in sustaining normal blood pressure under conditions of considerable sodium depletion. MacGregor *et al.* [19] also provided evidence, using a converting enzyme inhibitor (Captopril), that the renin angiotensin system maintains blood pressure in normotensive subjects on a normal sodium intake. The importance of the compensatory rise of plasma renin activity and angiotensin II in the maintenance of blood pressure in normotensive subjects was also demonstrated by a greater fall in blood pressure with captopril in these normotensive subjects on a low sodium diet [20]. Pressor sensitivity to angiotensin II is known to decrease with reduction in sodium intake and to vary between patients, thus complicating the relationship found between measurements of the activity of the renin-angiotensin system and the blood pressure fall with sodium restriction [21].

Saralasin is a competitive inhibitor of angiotensin II but it has agonist activity, when angiotensin II levels are low [22,23]. Using an incremental infusion rate up to a maximum of 1.25 μg/kg/min and infusing patients while sitting upright may minimize this agonist activity. As short-term infusion, saralasin blocks only the immediate effects of circulating angiotensin II. Therefore, saralasin will underestimate the participation of the renin system in the maintenance of blood pressure. Nevertheless, it accurately reflects the relative importance of the renin system in sustaining blood pressure when comparing different individuals and will allow for differences in sensitivity to angiotensin II between patients. In our study, the fall in blood pressure with saralasin was closely correlated with the plasma renin activity before the infusion, as reported by others [24,25], but more important is its inverse relation to the fall in blood pressure with sodium restriction. The study therefore provides direct evidence that the fall in blood pressure which is seen on reducing sodium intake in patients with essential hypertension is, at least in part, directly mediated by the reactivity of the renin system and the degree of rise of angiotensin II. This decreased responsiveness of the renin system in many patients with essential hypertension may account for the greater decrease in blood pressure on reduction of sodium intake seen in hypertensive patients compared to normotensive subjects [9]. It may also explain the differences observed by some [7,8] in the sensitivity of hypertensive patients to sodium restriction. Patients with essential hypertension tend to have a level of plasma renin activity below that observed in age-matched normotensive subjects [26], although there appears to be a continuous distribution of plasma renin activity without any division into distinct populations [27,28]. Hypertensive patients with a low plasma renin activity are resistant to elevation of plasma renin activity by the usual stimuli [29,30]. Severity of hypertension has been closely related to blood pressure sensitivity to sodium restriction [9,12], but this is likely to be mediated by the lowered responsiveness of the renin-angiotensin system as blood pressure rises [16]. Other mechanisms have also been proposed as involved in blood pressure sensitivity to alteration of sodium intake. The activation of the sympathetic nervous system may possibly limit the fall in blood pressure during sodium restriction, in view of an increase in plasma noradrenaline found by some investigators [31-34] in normotensive subjects, although there do not appear to be any reports in hypertensive subjects. Changes in the level of a circulating sodium

transport inhibitor [35] might also partly account for differences in sensitivity to sodium restriction. Our study, while not excluding these or other possible factors, does demonstrate the direct importance of the response of the renin-angiotensin system to sodium restriction in determining the observed blood pressure fall.

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