Adrenergic Activity and Peripheral Hemodynamics in Relation to Sodium Sensitivity in Patients with Essential Hypertension

MARIANNE I. KOOLEN AND PETER VAN BRUMMELEN

SUMMARY In 25 outpatients with essential hypertension, sodium sensitivity, defined as the difference in mean arterial pressure (AMAP) between 2 weeks of high-sodium (300 mmol per day) and 2 weeks of low-sodium (LS) intake (50-100 mmol per day), was studied in relation to the plasma norepinephrine (NE) level, NE release, and pressor response to intravenous NE. In addition, forearm blood flow (FBF) was measured by plethysmography. There were two control periods of regular sodium intake, one of 4 weeks' duration at the beginning of the study and one of 2 weeks' duration at the end. The AMAP ranged from +18 to -8 mm Hg. The eight patients in whom AMAP was greater than 10 mm Hg were regarded as salt-sensitive. When compared with salt-insensitive subjects, salt-sensitive patients had higher plasma NE levels in the control period (p < 0.05) and after 2 weeks of HS intake (p < 0.01). Sodium sensitivity was directly related to the change in plasma NE between the HS and LS periods (p < 0.001). The NE release decreased in salt-insensitive subjects whereas it increased in salt-sensitive patients between the LS and HS periods. Changes in NE release were directly related to sodium sensitivity (p < 0.05). The pressor response to NE was not significantly influenced by changes in sodium intake. The FBF fell in salt-sensitive patients and increased in salt-insensitive subjects between the LS and HS periods. Sodium sensitivity was directly related to the change in forearm vascular resistance (p < 0.01). Our data indicate that changes in adrenergic activity and in vascular resistance contribute significantly to sodium sensitivity. (Hypertension 6: 820-825, 1984)

KEY WORDS * adrenergic mechanisms • essential hypertension • forearm vascular resistance * norepinephrine release • plasma norepinephrine • sodium sensitivity

On the basis of their blood pressure (BP) response to changes in dietary sodium intake, patients with essential hypertension can be arbitrarily divided into salt-sensitive and salt-insensitive groups.1°3 There is evidence that, apart from the renin-angiotensin-aldosterone system, the adrenergic nervous system could play a role in these differences in sodium sensitivity.1°3 This is not surprising, since it has been reported that neurogenic mechanisms contribute to the hypertensive effect of sodium loading in experimental models like the DOCA-salt rat,2 Dahl's genetically salt-sensitive strain,3 and the stroke-prone spontaneously hypertensive rat (SHR).4 Moreover, in patients with borderline essential hypertension,1 the adrenergic nervous system could be involved in the BP increasing effect of a high-salt (HS) intake. Recently, it was found that during a HS intake, salt-sensitive patients do not suppress the plasma NE concentration (PNE) as effectively as salt-insensitive patients.23 Therefore, persistent adrenergic activity could contribute to the increase in BP under this condition. However, because PNE is determined by both release and clearance, estimates of adrenergic nerve activity based on PNE should be interpreted with caution, and measurement of NE kinetics could provide a better index.23

In the present study, the contribution of adrenergic mechanisms to salt sensitivity in patients with essential hypertension was investigated by measuring PNE, NE release (NER), the pressor response to exogenous NE, as well as forearm blood flow (FBF) at two levels of sodium intake.

Methods

Patients

Twenty-five Caucasians with essential hypertension, 15 men and 10 women with a mean age of 41.3 years (range 22-61 years), participated in this study after giving informed consent. Diastolic blood pressure was between 90 and 115 mm Hg on at least three

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occasions when measured in the outpatient clinic during routine visits, with the patient sitting. The diagnosis of essential hypertension was established in all cases after appropriate clinical, biochemical, and radiological investigations had excluded secondary causes of elevated arterial pressure.

Study Protocol

Before the study began, all antihypertensive medication was gradually withdrawn. After a control period of 4 weeks during which time the patients continued on their regular diet, two 2-week study periods were started, one with a low-sodium (LS) intake (3-6 g NaCl per day) and the other with a HS intake (18 g NaCl per day). The sequence of the LS and HS periods was randomly assigned. The study was concluded with another period of 2 weeks with a regular sodium intake. Potassium intake was kept constant during the study. The special diets were prescribed on an individual basis by a dietician. The HS intake was achieved by adding Slow Sodium tablets (600 mg NaCl per tablet) to the diet.

During the whole study, the patients were seen at weekly intervals in the outpatient clinic; all visits took place in the morning during which the body weight was measured, and BP and heart rate were taken after the patient had rested supine for 5 minutes. Blood for determination of PNE was collected from the patient while seated, via an indwelling catheter that had been inserted 30 minutes earlier into an antecubital vein.

The 24-hour urine sample of the previous day was used to determine the excretion of sodium, potassium, and creatinine. At the end of the LS and HS study periods, FBF, NER, and the BP response to exogenous NE were measured immediately after the routine procedures.

FBF was measured by way of venous occlusion and Silastic strain gauge plethysmography with a Hokanson EC-3 plethysmograph (Hokanson Corporation, Issaquah, Washington). The tracings were recorded on a polygraph (Siemens Mingograf 803, Siemens-Elema AB, Solna, Sweden), and blood flow was calculated from six consecutive recordings. The studies were done in a quiet room maintained at a constant temperature of 20° C and with the patient in the supine position. The arm in which the FBF was measured was elevated to above the level of the heart and was comfortably supported. Forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure (MAP) by FBF, and expressed as arbitrary units.

NER was measured according to the method of Fitzgerald et al. After the introduction of a second catheter into the opposite brachial vein, the patient rested supine for 30 minutes. Then basal BP and heart rate were measured. This was followed by the infusion of a freshly prepared solution of 5% L-NE in dextrose at a rate of 0.06 μg/kg/min for 60 minutes. Blood for PNE estimation was drawn 10 minutes before (basal value) and 30, 45, and 60 minutes after starting the infusion.

The NE clearance was calculated as the quotient of the NE infusion rate and the difference between steady-state and basal PNE. Steady-state PNE was the mean of the values obtained after 30, 45, and 60 minutes of infusion. The NER was calculated by multiplying the NE clearance by basal PNE. During the NE infusion, the BP was measured every 10 minutes. The difference between the steady-state BP during NE infusion (mean value of BP after 30, 40, 50 and 60 minutes) and the basal BP was taken as the pressor response to NE. All BP measurements were done in triplicate by one observer with a mercury sphygmomanometer, and the mean of these three values was used for analysis. Diastolic BP was read upon the disappearance of the Korotkoff sounds (Phase V). The MAP was calculated by adding one-third of the pulse pressure to the diastolic BP. The PNE was determined by the radioenzymatic method according to Henry et al. Urinary sodium, potassium, and creatinine were measured by routine chemical methods. The symbol A was used to indicate the difference for the various variables between the period of HS and LS.

Statistics

After a significant influence of the dietary sequence had been excluded by analysis of variance (ANOVA) for crossover design, the data were analyzed irrespective of the dietary sequence that had been followed. Statistical analysis further included simple linear regression analysis and Student’s t test for paired and unpaired observations. Mean values ± SEM are given; values of p < 0.05 were regarded as significant.

Results

Blood Pressure, Heart Rate, Body Weight, Urinary Sodium, and Potassium Excretion

Data on clinical variables and urinary sodium and potassium excretion are given in Table 1. The aimed levels of sodium intake were reached. Urinary potassium excretion was not different for all study periods. Urinary sodium and potassium excretion after the first week of LS and HS intake were comparable to those of the corresponding second week. Heart rate did not differ significantly among the study periods. Body weight at the end of the LS period was significantly less when compared with the other periods. At the end of the LS period, both systolic and diastolic BP were significantly lower than at the end of the HS period, whereas only diastolic BP was significantly different from the values in the first control period.

Large interindividual differences were found in the MAP changes between the end of the HS and LS periods (range + 18 to —8 mm Hg; Figure 1). For each patient, this change in MAP was taken as a measure of sodium sensitivity and is referred to as AMAP. The data were analyzed in two ways, by calculating the correlation coefficients for sodium sensitivity and the other variables studied, and also by dividing the patients into salt-sensitive and nonsalt-insensitive groups according to the criteria of other authors. In eight of the 25 patients, AMAP was > 10 mm Hg, and these
TABLE 1. Clinical Data at the End of the Four Periods of Different Sodium Intake

<table>
<thead>
<tr>
<th></th>
<th>First control period (C,)</th>
<th>Low-sodium period (LS)</th>
<th>High-sodium period (HS)</th>
<th>Second control period (C2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP supine (mm Hg)</td>
<td>145.5±3.0</td>
<td>142.0±2.4t</td>
<td>148.2±3.4</td>
<td>145.2±3.3</td>
</tr>
<tr>
<td>Diastolic BP supine (mm Hg)</td>
<td>97.1 ± 1.6</td>
<td>91.4±1.5t</td>
<td>96.0±2.1</td>
<td>95.6±1.8</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>78.4 ±1.6</td>
<td>78.0±1.6</td>
<td>76.2±1.9</td>
<td>79.2±1.7</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>77.4±2.7</td>
<td>76.3±2.7</td>
<td>77.8±2.7</td>
<td>77.3±2.7</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 hr)</td>
<td>135.9±11.6</td>
<td>62.2±6.2*4:</td>
<td>270.0±4.9</td>
<td>1399 ±11.5</td>
</tr>
<tr>
<td>Urinary potassium (mmol/24 hr)</td>
<td>72.8±4.6</td>
<td>70.2±4.2</td>
<td>72.6±5.2</td>
<td>74.7±4.5</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*p < 0.001, statistical significance of differences between LS and C,. 
*tp < 0.05, statistical significance between LS and HS periods. 
*XP < 0.001, statistical significance between LS and HS periods.

patients were regarded salt-sensitive. They were older than the salt-insensitive patients (45.6 ± 3.5 vs 39.2 ± 2.6 years), but the difference was not statistically significant. There were no differences in family history of hypertension or in sex distribution for the two groups. Urinary sodium excretion was not significantly different for salt-sensitive patients compared with salt-insensitive patients, either at the end of the LS period (71.0 ± 9.5 vs 58.1 ± 8.0 mmol/24 hr) or at the end of the HS period (278.2 ± 26.4 vs 267.5 ± 20.2 mmol/24 hr). It was found that AMAP correlated with control MAP (r = 0.50, p < 0.01) and more closely with MAP at the end of the HS period (r = 0.75, p < 0.001). A weak correlation was present between AMAP and age (r = 0.42, p < 0.05). The AMAP was not correlated with changes in bodyweight (r = 0.28, NS) or changes in urinary sodium excretion (r = 0.10, NS).

Plasma Norepinephrine, Norepinephrine Release, and the Pressor Response to Exogenous Norepinephrine

Mean values for PNE in the various study periods are given in Table 2. Both after 1 week and 2 weeks of LS, PNE was significantly higher when compared with the control period (p < 0.01) and also when compared with PNE at the end of the first week of HS (p < 0.01). PNE during HS was not significantly different from PNE in the control period, but an increase was observed between the first and the second week of HS (p < 0.05). In the control period, salt-sensitive patients had higher PNE values when compared with salt-insensitive patients (p < 0.05), and only in the former was an increase in PNE observed during the second week of salt loading (Figure 2) (p < 0.05). The NER and pressor response to exogenous NE were only measured at the end of the LS and HS periods (Table 2). The NER for all patients was not significantly different between the HS and LS periods, but it was increased in the HS period compared with the LS period in salt-sensitive patients (4.3 ± 1.7 vs 2.5 ± 0.8 /ig/min) while it was decreased in salt-insensitive patients (1.7 ± 0.3 vs 3.3 ± 0.7 /ng/min). The small
TABLE 2. Plasma Norepinephrine (PNE), Norepinephrine Clearance (NEC), Endogenous Norepinephrine Release (NER), and Pressor Response to Norepinephrine (PRNE)

<table>
<thead>
<tr>
<th></th>
<th>First-control period (C.)</th>
<th>Low-sodium period (LS)</th>
<th>High-sodium period (HS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Week 1</td>
<td>Week 2</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>326 ±20</td>
<td>446 ±48*</td>
<td>452 ±37*</td>
</tr>
<tr>
<td>NEC (liter/min)</td>
<td></td>
<td>5.6±0.4</td>
<td>2.8±0.5</td>
</tr>
<tr>
<td>NER (ug/min)</td>
<td></td>
<td>2.8±0.5</td>
<td>12.8±1.6</td>
</tr>
</tbody>
</table>

Mean values ± SEM are given.
* p < 0.01 vs control period (C.).
tp < 0.01 vs first week of LS.
%p < 0.01 vs second week of LS.
§p < 0.05 vs first week of HS.

A significant inverse correlation between basal PNE and the pressor response to exogenous NE was only found during the HS period (r = -0.47; p < 0.05).

TABLE 3. Correlation Coefficients Relating the Difference in Blood Pressure Between the High-Sodium (HS) and Low-Sodium (LS) Periods (AMAP) with Plasma Norepinephrine (PNE), with Changes in Plasma Norepinephrine, and with Changes in Norepinephrine Release (ANER)

<table>
<thead>
<tr>
<th></th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control period</td>
<td>0.46*</td>
</tr>
<tr>
<td>PNE</td>
<td>0.43*</td>
</tr>
<tr>
<td>1st week of LS</td>
<td>0.56t</td>
</tr>
<tr>
<td>2nd week of HS</td>
<td>0.56t</td>
</tr>
<tr>
<td>Changes in PNE</td>
<td></td>
</tr>
<tr>
<td>2nd vs 1st week of HS</td>
<td>0.51t</td>
</tr>
<tr>
<td>2nd week of HS vs 2nd week of LS</td>
<td>0.60t</td>
</tr>
<tr>
<td>ANER</td>
<td>0.46*</td>
</tr>
</tbody>
</table>

*p < 0.05.
ip < 0.01.
%p < 0.001.

FIGURE 2. PNE levels for salt-sensitive (——*) and nonsalt-sensitive (o—o) patients for the control period, 1st and 2nd week of a low-sodium intake (50-100 mmol/day), and 1st and 2nd week of a high-sodium intake (300 mmol/day). *p < 0.05; **p < 0.01; compared to nonsalt-sensitive patients.

FIGURE 3. Correlation between change in plasma norepinephrine concentration between the 2nd week of high-sodium intake and the 2nd week of low-sodium intake and the difference in mean arterial pressure between the period of high- and low-sodium intake.
Division of the patients according to their sodium sensitivity revealed that salt-sensitive patients had higher PNE levels, both in the first control period and during the second week of HS intake (Figure 2), whereas urinary sodium and potassium excretions were similar for both groups in all study periods. These differences in PNE levels agree with the observations of Campese et al.\(^3\) that under these circumstances salt-sensitive patients have PNE levels inappropriately high for their level of sodium intake. In the present study, an initial suppression of PNE levels during the HS intake was found in all patients, followed by an escape in the salt-sensitive group. This pattern is reminiscent of that of Fujita’s salt-sensitive patients\(^7\) and also of the changes in NE excretion observed in rats that developed severe hypertension during sodium loading.\(^8\) Furthermore, the present study shows that the higher PNE levels in salt-sensitive patients during HS intake resulted from an increase in NE release. This observation is compatible with the inappropriately high central sympathetic discharge found in animals that were developing hypertension during a HS intake.\(^8\)

The relevance of these changes in adrenergic activity to the BP response is further supported by the direct relationship found between sodium sensitivity and the change in NE release in the present study.

Apart from increased adrenergic activity, an enhanced pressor response to NE could also contribute to the BP-increasing effect of sodium loading. However, the findings from the present study do not support this possibility, since the pressor response to NE was not influenced by the level of sodium intake, and the individual changes in pressor response between the HS and LS periods were not related to sodium sensitivity. Although a direct relationship between NE pressor response and the level of sodium intake has been reported for normotensive subjects,\(^20\) it should be noted that the presence of such a relationship in hypertensives is controversial.\(^21,22\) Because of the inverse relation found between PNE and NE pressor response in this and another study,\(^23\) and between PNE and the levels of sodium intake,\(^15,18\) it is conceivable that changes in pressor response by dietary sodium manipulations are only observed if suppression of PNE during HS intake is undisturbed.

This study also shows a different effect of HS intake on peripheral hemodynamics in salt-sensitive and salt-insensitive patients, since an increase in FVR during HS intake was only seen in the salt-sensitive patients. Increases in vascular resistance during sodium loading have been reported in animals\(^5,6\) and in borderline hypertensive patients,\(^7\) and recently these changes have been related to sodium sensitivity.\(^23\) A role for neurogenic factors has been suggested.\(^5,7\) However, we were unable to demonstrate a direct relationship between sodium-induced changes in FVR and changes in PNE or NE release. Other factors, such as a sodium transport inhibitor,\(^25\) or an inappropriately high activity of the renin-angiotensin-aldosterone system,\(^1,2\) could have contributed to the observed increases in peripheral resistance.

**Discussion**

The present study confirms the reported interindividual differences in BP response to changes in dietary sodium intake in patients with essential hypertension\(^1,3,14\) and provides further evidence that the adrenergic nervous system is involved in the BP-raising effect of a HS intake.\(^2,3\)

When compared with the period of normal sodium intake, PNE levels were significantly increased during the LS diet, a change similar to that observed in other studies in normotensive subjects\(^15-18\) and hypertensive patients.\(^18\) During the HS intake, however, PNE levels were not significantly different from control values.

**Forearm Blood Flow and Forearm Vascular Resistance**

For all patients, FBF and FVR were not significantly different between the HS and LS periods, but it was found that FBF was decreased in the HS period compared with the LS period in salt-sensitive patients, while it was slightly increased in salt-insensitive patients (Figure 4). The FVR in salt-sensitive patients was increased during HS compared with LS, while it was decreased in salt-insensitive patients (Figure 4). The change in FVR for salt-sensitive patients ( + 8.9 ± 4.5 U) differed significantly (p = 0.009) from that in salt-insensitive patients (—5.8 ± 2.8 U). The AMAP correlated inversely with AFAF (r = —0.46, p < 0.05) and directly with AFBR (r = 0.52, p < 0.01). Regression analysis of AFVR on ANER (r = 0.29) and AFVR on APNE between the HS and LS period (r = 0.34) showed a weak positive correlation that was not significant.
Acknowledgments

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