Plasma Norepinephrine and Dietary Sodium Intake in Normal Subjects and Patients with Essential Hypertension

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SUMMARY To evaluate the relationship between sodium intake and the activity of the sympathetic nervous system in patients with essential hypertension, plasma catecholamine levels were measured in 49 essential hypertensive patients and 38 age-matched normal subjects under regular-, high-, and low-sodium diets (mean 24-hour sodium excretions; 116 ± 8, 267 ± 29, 31 ± 7 mEq/day, respectively). The levels of plasma norepinephrine were significantly (p < 0.01) higher in hypertensive patients than in normal subjects. However, they were significantly reduced by high-sodium intake and increased by low-sodium intake in both patients and controls. The percent decrease and change in the absolute plasma norepinephrine levels from low- to high-sodium states were greater in normal subjects than in the hypertensive patients. The results are interpreted as indicating that an abnormal relationship exists between sodium intake and the activity of sympathetic nervous system in patients with essential hypertension. (Hypertension 5: 767-771, 1983)

KEY WORDS • essential hypertension • urinary sodium excretion • plasma norepinephrine

MANY studies have focused on the role of the sympathetic nervous system in the development and maintenance of essential hypertension,1 but results have been conflicting. Some investigators have reported that essential hypertension correlates with increased excreted urinary catecholamine2 3 and plasma catecholamine levels, especially norepinephrine (NE). Other workers have found no change or a decrease in the levels of these neurotransmitters.4 3 Similar inconsistencies appear in the relationship between sodium intake and plasma NE levels. An elevation of plasma NE on sodium restriction and a decrease on sodium loading,6 7 as well as increases on both sodium regimens,8 have been reported.

There are very little data on the influence of sodium on the blood pressure and plasma NE of normal subjects and patients with essential hypertension. In this study we measured the levels of plasma NE and epinephrine (E) in age-matched normal subjects and patients with essential hypertension on strict sodium diets to investigate the effects of sodium intake on the activity of the sympathetic nervous system.

Materials and Methods

We studied 49 patients with essential hypertension (28 men and 21 women; mean age ± SEM, 45 ± 3 years) and 38 normal subjects (24 men and 14 women; mean age 44 ± 3 years). The normal subjects were volunteers with no family history of hypertension (not laboratory personnel) who met the following criteria: casual morning blood pressure less than 140 mm Hg systolic and 90 mm Hg diastolic, and normal findings for physical examination, routine blood chemistry, blood count, urinalysis, creatinine clearance, electrocardiogram, and chest x-ray. Patients with essential hypertension had casual morning blood pressure between 160 and 200 mm Hg systolic and between 95 and 115 mm Hg diastolic. Secondary hypertension was excluded by the usual tests, and no patient had congestive heart failure, ischemic heart disease, arrhythmia, stroke, peripheral ischemic angiopathy, or relevant renal functional impairment (plasma creatinine > 1.3 mg/100 ml). All antihypertensive medications were discontinued at least 3 weeks before initiation of this study.

All subjects were admitted in our hospital and followed a low-, regular-, and high-sodium diet (mean 24-hour sodium excretions; 31 ± 7, 116 ± 8, 267 ± 29 mEq/day, respectively) for 15 days. Each diet was administered for 5 days in a random sequence. Twenty-four hour urinary sodium and potassium excretions on the fifth day of each regimen were determined. On
the sixth day, blood pressure and pulse rate were taken after the subjects had reclined for 1 hour (7:00–8:00 a.m.).

Supine venous blood samples were drawn 20 minutes after cannulation, and again after the subjects had been upright for 5 minutes. Blood samples were assayed for plasma NE and epinephrine (E). Catecholamines were analyzed by a trihydroxyindole method after high performance liquid chromatography separation. In this method, the limits of detection (signal-to-noise ratios = 2) for E and NE were considered to be in the range of 0.05 to 5 pmoles and were linearly related to the fluorescence intensities expressed as peak heights. Mean coefficients of intraassay variations for 119 unselected consecutive determinations in our laboratory were 1.9% for plasma E, and 1.3% for plasma NE; the coefficients of interassay variation for control plasma (n = 10) was 2.2% for E, and 2.7% for NE. The average recoveries of E and NE were 99.7% and 99.5%, respectively. The data were evaluated statistically by one-way analysis of variance (ANOVA) for comparisons between means and by paired or unpaired Student’s t test. The data are expressed as means ± SEM.

Results

Although there were no differences in mean age, sex, body weight, pulse rate, mean urinary potassium excretion, plasma potassium levels, plasma sodium levels, supine plasma E, and upright plasma E levels between the 49 essential hypertensive patients and the 38 normal subjects, the systolic and diastolic blood pressures of the hypertensives were significantly higher than those of normal subjects regardless of the three sodium regimens (table 1).

The plasma renin activity (PRA) in the hypertensives was identical to that in normal subjects. PRA and plasma aldosterone concentration (PAC) in both groups showed a typical hyperbolic relationship to urinary sodium excretion. However, the supine and upright plasma NE levels of both the normotensives and hypertensives were inversely correlated with urinary sodium excretion (fig. 1). Furthermore, plasma NE levels in the hypertensives were higher than those in the normotensives for all sodium regimens.

The change in absolute plasma NE from high- to low-sodium diets was significantly greater (p < 0.01) in normal subjects (0.64 ± 0.08 pmole/ml, mean ± SEM) than in the hypertensive patients (0.46 ± 0.05 pmole/ml).

### Table 1. Clinical Data on Normal and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Low sodium</th>
<th>Regular sodium</th>
<th>High sodium</th>
<th>Low sodium</th>
<th>Regular sodium</th>
<th>High sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>38</td>
<td>49</td>
<td></td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>44 ± 3</td>
<td>45 ± 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>55 ± 5</td>
<td>55 ± 4</td>
<td>56 ± 5</td>
<td>57 ± 7</td>
<td>57 ± 5</td>
<td>57 ± 7</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>115 ± 2</td>
<td>118 ± 2</td>
<td>119 ± 2</td>
<td>135 ± 3*</td>
<td>148 ± 4*</td>
<td>150 ± 5*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>72 ± 2</td>
<td>75 ± 2</td>
<td>73 ± 3</td>
<td>89 ± 4**</td>
<td>92.4 ± 4**</td>
<td>93 ± 3**</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>86 ± 2</td>
<td>89 ± 2</td>
<td>88 ± 3</td>
<td>104 ± 4**</td>
<td>111 ± 4**</td>
<td>112 ± 4**</td>
</tr>
<tr>
<td>PR</td>
<td>68 ± 2</td>
<td>69 ± 3</td>
<td>69 ± 2</td>
<td>75 ± 2*</td>
<td>73 ± 1</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>U_aV (mEq/day)</td>
<td>32 ± 5</td>
<td>118 ± 7</td>
<td>275 ± 24</td>
<td>30 ± 3</td>
<td>115 ± 8</td>
<td>260 ± 20</td>
</tr>
<tr>
<td>U_KV (mEq/day)</td>
<td>40 ± 2</td>
<td>35 ± 3</td>
<td>38 ± 4</td>
<td>39 ± 3</td>
<td>36 ± 3</td>
<td>37 ± 2</td>
</tr>
<tr>
<td>P-NE (supine)</td>
<td>1.27 ± 0.09</td>
<td>0.95 ± 0.11</td>
<td>0.63 ± 0.04$§§$†</td>
<td>2.14 ± 0.19*</td>
<td>1.87 ± 0.12*</td>
<td>1.68 ± 0.14*§</td>
</tr>
<tr>
<td>P-NE (upright)</td>
<td>2.09 ± 0.21</td>
<td>1.39 ± 0.11</td>
<td>0.89 ± 0.09$§§$†</td>
<td>3.39 ± 0.29*</td>
<td>2.47 ± 0.21*</td>
<td>2.36 ± 0.25*§</td>
</tr>
<tr>
<td>P-E (supine)</td>
<td>0.23 ± 0.02</td>
<td>0.19 ± 0.02</td>
<td>0.22 ± 0.02</td>
<td>0.24 ± 0.03</td>
<td>0.21 ± 0.03</td>
<td>0.23 ± 0.04</td>
</tr>
<tr>
<td>P-E (upright)</td>
<td>0.47 ± 0.08</td>
<td>0.30 ± 0.06</td>
<td>0.35 ± 0.04</td>
<td>0.59 ± 0.10</td>
<td>0.42 ± 0.06</td>
<td>0.30 ± 0.05$</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>3.5 ± 0.3</td>
<td>2.9 ± 0.4</td>
<td>1.6 ± 0.2§§$†</td>
<td>4.9 ± 0.8††</td>
<td>2.4 ± 0.3§§$†</td>
<td>1.7 ± 0.3§§$††</td>
</tr>
<tr>
<td>PAC (ng/dl)</td>
<td>11.0 ± 0.8</td>
<td>6.3 ± 0.6</td>
<td>4.6 ± 0.5§§$††</td>
<td>14.8 ± 1.2</td>
<td>6.9 ± 0.7§§$†</td>
<td>4.8 ± 0.9§§$†</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; U_aV = urinary sodium excretion; U_KV = urinary potassium excretion; P-NE = plasma norepinephrine; P-E = plasma epinephrine; values are expressed as means ± SEM.

* p < 0.01, ** p < 0.001, compared with normal subjects.
†p < 0.01, ††p < 0.001, compared with regular sodium.
§p < 0.01, §§§p < 0.001, compared with low sodium.
pmole/ml). In addition, the percent decrement of both the supine and upright plasma NE values from low- to high-sodium intake was significantly greater in the normotensives than the hypertensives (fig. 2). On the other hand, there were no significant differences in plasma NE levels in each sodium intake state or NE suppressibility during high-salt intake between salt-sensitive patients (n = 20) and salt-nonsensitive patients (n = 29), classified by the criteria described by Kawasaki et al.10

Comparison of mean blood pressure with supine plasma NE levels revealed a positive correlation (r = −0.58, p < 0.05) in hypertensive patients and a negative correlation (r = −0.60, p < 0.05) in normal subjects. A significant relationship between the changes in plasma NE values and the changes in systolic blood pressure from low- to high-sodium intake was seen in hypertensives (r = −0.90, p < 0.01), but not in normotensives (r = −0.18, NS).

**Discussion**

The etiology of essential hypertension remains unknown. It has been proposed that plasma catecholamines, especially plasma NE, are involved in the development of essential hypertension.11, 12 The influence of sodium intake on blood pressure is well established. Experimental and epidemiological studies have shown a close relation between sodium intake and the development of essential hypertension.13–15 The interrelationship of sodium intake, blood pressure, and catecholamines has been evaluated in normal subjects, and an elevation of blood pressure in normal subjects by high-sodium intake has been demonstrated.16 However, there has been very little investigation with respect to varying the sodium intake.

In this study we attempted to clarify the role of plasma catecholamines in patients with essential hypertension by investigating the relationships between sodium intake and plasma NE in them and normal subjects. For all three sodium regimens, plasma NE in the hypertensives was higher than in the normal subjects. Plasma NE decreased significantly with high-sodium intake and increased with low-sodium intake in both normotensives and hypertensives. The slopes of the plasma NE concentrations were similar between these two groups, but the percent change for the hypertensives was significantly less than that for the normotensives because their absolute levels during low-sodi-

**FIGURE 1.** Mean supine plasma levels of norepinephrine (NE) as a function of mean urinary sodium excretion over a period of 24 hours in normal subjects (NORMAL) and in patients with essential hypertension (HBP).

**FIGURE 2.** Percent decrease in the levels of plasma norepinephrine (NE) in patients with essential hypertension in the supine and upright position when their diet was changed from low to high sodium.
um intake were higher and the changes in absolute plasma NE levels from low- to high-sodium intake were less than in the normal subjects. Our findings that plasma NE was inversely correlated with sodium intake in normal subjects is in agreement with other reports. In experimental normotensive animals, a decrease in the levels of plasma NE with high-sodium intake or volume expansion and an increase with low-sodium intake have been reported. Thus, patients with essential hypertension may have both high plasma NE levels and impaired suppressibility of plasma NE during high-sodium intake, indicating hyperactivity of the sympathetic nervous system in these patients.

Furthermore, in hypertensive patients, the mean blood pressure was positively correlated with supine plasma NE levels (r = 0.58, p < 0.05); however, in normal subjects it was negatively correlated (r = -0.60, p < 0.05). A significant relationship was seen between the change in plasma NE and the change in systolic blood pressure from low- to high-sodium intake only in the patients with essential hypertension. This evidence also suggests that hyperactivity of the sympathetic nervous system is involved in essential hypertensive patients.

Campese et al. described that from low- (10 mEq/day) to high- (200 mEq/day) sodium intake, plasma NE decreased significantly (p < 0.05) in normal subjects and in salt- nonsensitive patients, but not in salt-sensitive patients. In other words, the change in plasma NE from low- to high-sodium intake in salt-sensitive hypertensive patients was smaller than in normal subjects. Their findings in salt-sensitive hypertensive patients are in agreement with our present results, namely, that the patients with essential hypertension have impaired suppressibility of plasma NE during high-sodium intake. However, we could not confirm the difference in plasma NE suppressibility during high-sodium intake between salt-sensitive and salt-nonsensitive patients, nor their findings that there were no differences in mean plasma NE levels during low- and regular-sodium intake between normal and hypertensive subjects. Weidmann et al. and many other investigators have shown that plasma NE during regular-sodium intake is higher in hypertensive patients than in normal subjects. This difference may be caused by such factors as the differences in the amounts of sodium and potassium intake. We found that plasma NE was higher for all three sodium regimens in hypertensive patients than in normal subjects, and that the patients had impaired suppressibility.

Goldstein reported that the method of measurement, sampling, age, amounts of sodium intake, and selection of normal control subjects are important factors in comparing plasma NE between normal subjects and patients with essential hypertension. The influence of age on plasma catecholamines has been documented, but because normotensives and hypertensives were age-matched in our study, the higher levels of plasma NE in the patients were considered not to be the results of an age difference. High-potassium and low-sodium intakes have been shown to increase the levels of plasma NE, whereas low-potassium and high-sodium intakes decrease these levels in mild essential hypertensive patients. Urinary potassium excretion may be more important than urinary sodium excretion because of the increased urinary NE with high potassium intake in Sprague-Dawley rats. However, in the present study, urinary potassium excretion levels were not significantly different between the normotensives and hypertensives on any of the three sodium regimens; therefore, the influence of potassium intake can be excluded. In addition, age and urinary sodium and potassium excretion with each of the diets were strictly matched between normal control subjects and hypertensive patients.

It is quite likely that the inverse correlation between plasma NE and urinary sodium excretion was caused mainly by changes in sodium intake. This likelihood is supported further by the observation that, with all three dietary regimens, plasma NE in the hypertensives was significantly greater than in the normal subjects, whereas the percent decrease and the change in absolute plasma NE levels from low- to high-sodium intake were greater in the normal subjects than the hypertensives. These findings suggest that the activity of the sympathetic nervous system is suppressed by increased sodium intake, and the suppression is much lower in hypertensive patients than in normal subjects.

Esler et al. demonstrated that in some patients with essential hypertension the half-time of the rapid component of NE disappearance from plasma was prolonged. They suggested that a defect in neuronal uptake of NE may result in a higher rate of NE spillover to plasma and higher plasma concentration in these patients. It is possible that the effect of changing salt balance might affect the neuronal uptake, and consequently cause the change in plasma NE levels. Further studies are needed to elucidate these possibilities.

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References
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