Increased Plasma Norepinephrine in Young Patients with Essential Hypertension under Three Sodium Intakes

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SUMMARY Increased sympathetic nerve activity may play an important role in the pathogenesis of essential hypertension. It is well known that both dietary sodium intake and age influence the plasma norepinephrine (NE) concentration. The present study was undertaken to evaluate the effects of age on sympathetic nerve activity in patients with essential hypertension and normal control subjects under low-, regular-, and high-sodium regimens (mean 24-hour sodium excretions: 30 ± 4, 116 ± 7, 280 ± 15 mEq, respectively). Plasma NE and epinephrine (E) were analyzed by trihydroxyindole methods after high-performance liquid chromatography separation. Subjects were categorized by age into young (<40 yrs), middle-aged (40-60 years), and old (>60 years) subgroups. Mean plasma NE in hypertensive patients was significantly higher (p < 0.01) than in normal subjects on each of the sodium regimens. In normal control subjects, there was a significant positive correlation between age and plasma NE with all three sodium intakes. However, no correlation was seen in hypertensive patients on any of the sodium regimens, because in the young subgroup of hypertensive patients the mean plasma NE was significantly higher than that of normal control subjects. These results suggest that the increased sympathetic nerve activity plays an important role in the pathogenesis of essential hypertension, especially in young patients. (Hypertension 6: 315-321, 1984)

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

MANY studies have focused on the involvement of the sympathetic nervous system in the pathogenesis and development of essential hypertension. However, the findings remain controversial. Some investigators have reported increased levels of plasma norepinephrine (NE) and increased excretion of urinary NE in patients with essential hypertension. Others workers have reported no change or decrease in these factors. Reports on the relationship between age and plasma NE are also inconsistent. Some investigators have shown an elevation of plasma NE with aging in normal subjects, and/or patients with essential hypertension. It is also well known that the amount of sodium intake influences plasma NE levels. There are several studies on the relationship between age and plasma NE in normal subjects and patients with essential hypertension under various sodium intakes.

In this study, we evaluated the influence of age on plasma NE and epinephrine (E) in both normal subjects and patients with essential hypertension under low-, regular-, and high-sodium intake.

Materials and Methods

Subjects

Forty-four patients with essential hypertension (19 men and 25 women) and 30 normal control subjects (11 men and 19 women) were included in this study. The normal subjects consisted of volunteers with no family history of hypertension; they were not hospital or laboratory personnel. These subjects fulfilled the following criteria: their casual morning blood pressure was less than 140 mm Hg systolic and 90 mm Hg diastolic, and they had normal findings upon physical examination, including routine blood chemistry, blood count, urinalysis, creatinine clearance, electrocardiogram, and chest x-ray.

Patients with essential hypertension had a casual morning blood pressure ranging from 160 to 200 mm Hg systolic and from 95 to 115 mm Hg diastolic, and they had normal findings upon physical examination, including routine blood chemistry, blood count, urinalysis, creatinine clearance, electrocardiogram, and chest x-ray.

Patients with essential hypertension had a casual morning blood pressure ranging from 160 to 200 mm Hg systolic and from 95 to 115 mm Hg diastolic on at least three occasions. Secondary hypertension was excluded by the usual tests, and no patients had congestive heart failure, ischemic coronary artery disease,
arrhythmia, stroke, peripheral ischemic angiopathy, or relevant renal functional impairment. Plasma creatinine levels were all less than 1.3 mg/100 ml, and creatinine clearance rates were higher than 80 ml/min in all subjects with any of the sodium regimens. All medications were discontinued at least 3 weeks prior to the initiation of this study.

All subjects were separated according to age: young (≤40 years), middle (40–60 years), and old (>60 years). Hypertensive patients included eight patients in the young subgroup, 20 in the middle-aged subgroup, and 16 in the old subgroup. Normal control subjects included 10 subjects in each age group.

**Conditions of Blood Sampling**

All subjects were admitted to our hospital and kept on a low sodium diet (mean urinary sodium excretion \(U_N\), 30 ± 4 mEq/day), regular sodium diet (mean \(U_N\), 116 ± 7 mEq/day), and high sodium diet (mean \(U_N\), 280 ± 15 mEq/day) for 15 days. Each diet was administered for 5 days in a random sequence. Twenty-four-hour urinary sodium and potassium excretions on the 5th day of each regimen were determined. On the morning of Day 6, the blood pressure and pulse rate were measured after the subjects had been recumbent for 1 hour (7:00–8:00 am). Venous blood samples were drawn 20 minutes after cannulation and again after the subjects had been upright for 5 minutes. These samples were analyzed for plasma NE and E, plasma renin activity, and plasma aldosterone concentration.

**Assay Methods**

Catecholamines were analyzed by trihydroxyindole methods after high performance liquid chromatography separation.\(^{18}\) In these methods, the limits of de-

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

<table>
<thead>
<tr>
<th></th>
<th>Low-sodium diet</th>
<th>Regular-sodium diet</th>
<th>High-sodium diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young</td>
<td>Middle</td>
<td>Old</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>32 ± 4</td>
<td>54 ± 3</td>
<td>65 ± 4</td>
</tr>
<tr>
<td><strong>SBP (mm Hg)</strong></td>
<td>134 ± 13</td>
<td>141 ± 2</td>
<td>150 ± 2</td>
</tr>
<tr>
<td><strong>DBP (mm Hg)</strong></td>
<td>88 ± 2</td>
<td>93 ± 2</td>
<td>97 ± 2</td>
</tr>
<tr>
<td><strong>MAP (mm Hg)</strong></td>
<td>112 ± 1</td>
<td>115 ± 4</td>
<td>118 ± 4</td>
</tr>
<tr>
<td><strong>PR (bpm)</strong></td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>PAC (ng/dl)</strong></td>
<td>10 ± 1</td>
<td>10 ± 2</td>
<td>9 ± 1</td>
</tr>
<tr>
<td><strong>PRA (ng/ml/hr)</strong></td>
<td>3.0 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td><strong>U_N (mEq/day)</strong></td>
<td>28 ± 4</td>
<td>29 ± 3</td>
<td>20 ± 3</td>
</tr>
<tr>
<td><strong>U_V (mEq/day)</strong></td>
<td>120 ± 1</td>
<td>125 ± 5</td>
<td>130 ± 5</td>
</tr>
<tr>
<td><strong>PAC (ng/dl)</strong></td>
<td>17 ± 2</td>
<td>16 ± 1</td>
<td>16 ± 1</td>
</tr>
</tbody>
</table>

\(SBP = \) systolic blood pressure; \(DBP = \) diastolic blood pressure; \(MAP = \) mean blood pressure; \(PR = \) pulse rate; \(U_N = \) urinary sodium excretion; \(U_V = \) urinary potassium excretion; \(PRA = \) plasma renin activity; \(PAC = \) plasma aldosterone concentration. Values are expressed as means ± SEM.

\(^*\)p < 0.01, \(^**\)p < 0.001, compared with normal controls.

\(^\dagger\)p < 0.01, \(^\ddagger\)p < 0.001, compared with low-sodium diet.

\(^\$$p < 0.01, \(^\ddagger\$$p < 0.001, compared with regular-sodium diet.
tection (signal-to-noise ratios = 2) were considered to be 0.02 pmol for E and 0.04 pmol for NE. The amounts of E and NE in the range of 0.05 to 5 pmol were linearly related to the fluorescence intensities expressed as the peak height. Mean coefficients of intraassay variation 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) were 2.2% for E and 2.7% for NE. The average recoveries of E and NE were 99.7% and 99.5%, respectively. Plasma renin activity and plasma aldosterone concentration in both normotensive and hypertensive individuals were increased by the low-sodium regimen in all age subgroups. There were no differences in plasma renin activity and plasma aldosterone concentration between hypertensive and normal individuals with respect to the sodium regimen.

The systolic and diastolic blood pressure levels of the patients were significantly higher than those of normal subjects in each age subgroup on each sodium regimen. There were no significant differences between normal and hypertensive subjects in body weight, pulse rate, mean urinary Na+ and K+ excretion, and plasma Na+ and K+ levels on each sodium regimen (Table 1). Plasma renin activity and plasma aldosterone concentration in both normotensive and hypertensive subjects were measured by the radioimmunoassay (RIA) method.

**Data Analysis**

Values were expressed as means ± SEM. 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.

**Results**

The mean age of each subgroup of essential hypertensive patients (young group: 34 ± 3 years, middle group: 55 ± 4 years, old group: 67 ± 4 years) did not differ from those of the normal control subjects (32 ± 4 years, 54 ± 3 years, 65 ± 4 years, respectively).

The mean supine and upright plasma NE levels of the hypertensive patients were significantly higher (p < 0.01) than those of the normotensive subjects; the difference was greater in the young and middle-aged subgroups than the older subgroup (Figure 1). When supine and upright plasma NE levels were plotted as a function of age, normotensive individuals showed positive age-NE correlations in all three sodium regimens; the hypertensive patients showed no correlations in any of the three sodium regimens, however (Figure 2). Mean supine and upright plasma E in each age group and individual plasma E levels of both normotensive and hypertensive individuals were not related to age in any of three sodium regimens (Figures 3 and 4).

![Figure 1](http://hyper.ahajournals.org/)
Supine Plasma Norepinephrine

Low Sodium Diet

Normal Diet

High Sodium Diet

Upright Plasma Norepinephrine

Low Sodium Diet

Normal Diet

High Sodium Diet

Discussion

It is well known that enhanced sympathetic nerve activity may play an important role in the pathogenesis and maintenance of essential hypertension. However, the pathogenesis of essential hypertension is very complicated. It has been proposed that the plasma NE level is an index of sympathetic nerve activity. Plasma NE level is influenced by sodium intake and age. There are many reports comparing plasma NE between hypertensive and normotensive individuals, but the results have not always been conclusive. Some investigators reported that the plasma NE level of
The plasma norepinephrine (NE) levels of hypertensive patients (EHT) and normotensive control subjects (NT) in the supine and upright posture as a function of the age subgroups.

In this study, we demonstrated a significant positive correlation between age and plasma NE levels only in normal control subjects, and not in patients with essential hypertension. Plasma NE in hypertensive patients, especially the young subgroup, was significantly higher ($p < 0.01$) than in normal control subjects. These results suggest that enhanced sympathetic nerve activity plays an important role in the pathogenesis and maintenance of essential hypertension, and that this is more obvious in younger patients.

Recently, Goldstein et al. examined the relationship between age and plasma NE levels in subjects in the supine position; since these subjects were outpatients, their sodium intake was unknown. These investigators also found a significant positive correlation between age and plasma NE only in normal control subjects, and not in hypertensive patients. In their earlier report, however, they noted a positive correlation between age and plasma NE levels in both normal subjects and hypertensive patients. This discrepancy may be caused by differences in the amounts of sodium or potassium intake between outpatients and admitted patients. With regards to sodium intake, we found that plasma NE levels did not correlate with age in hypertensive patients, because young and middle-aged hypertensive patients had significantly higher plasma NE levels than older patients.

Since only a small fraction of the NE released by the sympathetic nervous system enters the circulation, the extent to which plasma NE concentration reflects sympathetic nerve firing rates is open to question. However, plasma NE concentration has been used as a biochemical index of sympathetic activity, since NE is a sympathetic nervous system transmitter. It is also known that the concentration of plasma NE is significantly correlated with the NE release from sympathetic nerves. Thus, it is possible to use plasma NE levels as an index of sympathetic nerve activity.
FIGURE 4. Epinephrine levels of hypertensive patients (○) and normotensive individuals (★) as a function of age in the supine and upright position under three sodium intakes. There are no correlations between age and plasma epinephrine levels in both normotensive and hypertensive subjects.
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