Transient enhancement of sympathetic nervous system activity by long-term restriction of sodium intake

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ABSTRACT To further investigate the relationship between salt intake and sympathetic nervous system activity, the short- and long-term effects of a low-salt diet (40 meq/day) were assessed in 10 normal subjects. Measurements of hemodynamic, hormonal, and other parameters were obtained on the day preceding institution of the low-salt diet (day 0) and on days 4, 7, 30, and 60 of the diet. Urinary sodium excretion was 178 ± 10 meq/24 hr on day 0 and 31 ± 4, 38 ± 4, 45 ± 6, and 47 ± 7 meq/24 hr on days 4, 7, 30, and 60, respectively (all p < .001 compared with day 0). Blood pressure, urinary potassium, serum electrolytes, and cardiac function (as assessed by echocardiography) were not modified by the 2 month low-salt diet. Plasma renin activity and plasma aldosterone were significantly elevated above control values throughout the entire period of the low-salt diet. In contrast, plasma norepinephrine concentration increased significantly only on days 4 and 7 (from 253 ± 20 pg/ml on day 0 to 495 ± 32 pg/ml, p < .001, and 347 ± 22 pg/ml, p < .05, respectively), returning to baseline at days 30 (280 ± 18 pg/ml) and 60 (262 ± 18 pg/ml). Changes in plasma epinephrine paralleled those observed for norepinephrine. Similarly, resting heart rate and the blood pressure response to isometric exercise were significantly increased only on days 4 and 7 of the low-salt diet. These results suggest that sympathetic nervous system activity is enhanced only transiently during a sustained reduction in sodium intake.

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IT HAS LONG been hypothesized that the level of sodium intake affects sympathetic nervous system activity both in normal and in hypertensive subjects. There have been several reports that circulating catecholamines increase during dietary sodium restriction and decrease upon sodium loading, although some conflicting data exist. There have been contradictory reports on the influence of sodium intake on vascular reactivity and total peripheral resistance. Sullivan et al. reported an increase in total peripheral resistance during sodium depletion in borderline hypertensive subjects, whereas Takeshita et al. observed an increase in forearm vascular resistance during salt loading in subjects with hypertension. Other authors have reported that salt loading induces vasodilatation in normotensives and vasoconstriction in hypertensive subjects. Finally, it has been reported that high sodium intake increases the vascular sensitivity to norepinephrine while it decreases the basal plasma concentration of norepinephrine, but others have found no change in renal vascular reactivity to norepinephrine during acute sodium depletion.

These discrepancies could be ascribed to differences in the experimental protocols used in the studies, such as differences in animal species used or clinical characteristics of the population studied (e.g., with respect to age, blood pressure) and differences in the duration and degree of the changes in salt intake.

The purpose of the present study was to assess the time course of the humoral and hemodynamic responses to a moderate reduction in sodium intake, particularly as related to sympathetic nervous system activity, in a homogeneous group of normal human subjects.

Methods

Twelve normal volunteer subjects from 23 to 39 years old (mean ± SEM = 35 ± 3.5 years) were enrolled in the study. As a group they had no history of serious illness and no family history of hypertension. Informed written consent was obtained from each and they took no drugs for the duration of the study. To achieve an equilibrium on a standardized diet for baseline measurements, the subjects were admitted to our metabolic...
ward and were maintained on a daily diet containing 200 meq sodium, 70 meq potassium, 60 g protein, 50 g fat, 280 g carbohydrate, and 400 mg calcium, for 1 week after their entry into the study. Each subject consulted with the research dietician before the study and personal food preferences were allowed as much as possible. After 7 days on this diet (day 0), the following baseline measurements were obtained: body weight, supine and upright heart rate and blood pressure, 24 hr urinary sodium and potassium excretion, 2 hr supine plasma renin activity, aldosterone, epinephrine and norepinephrine levels, peripheral venous hematocrit, creatinine clearance, and serum sodium and potassium. Resting M mode echocardiographic and blood pressure and heart rate responses to isometric exercise were determined after the humoral measurements. Blood samples for catecholamine measurement were drawn with the subject in the supine position on a comfortable bed at least 30 min after the insertion of a 20-gauge butterfly needle into a forearm vein. The room was kept quiet, darkened, and warm for the entire study. Subjects avoided caffeine, smoking, and strenuous physical exercise for the 24 hr preceding the sampling.

Subsequently, the subjects were prescribed a diet containing identical quantities of potassium, protein, fat, carbohydrate, and calcium, but only 40 meq of sodium, and were followed in the outpatient clinic for 60 days. The diet was reinforced periodically by reconsulting the dietician. Measurements of the above-mentioned parameters were repeated on days 4, 7, 30, and 60 of the diet. In addition, 24 hr urinary electrolytes were measured on day 1.

Plasma concentrations of norepinephrine and epinephrine were measured by a radioenzymatic method. Plasma renin activity and aldosterone levels were measured by radioimmunoassay and sodium and potassium concentrations in serum and urine were determined by flame photometry. Adequacy of 24 hr urine collection was evaluated by measurement of urinary creatinine. Blood pressure was measured by mercury sphygmomanometer according to the recommendations of the American Heart Association.

The isometric muscular exercise consisted of sustained handgrip in the supine position on a hydraulic adjustable dynamometer. After the subjects had become familiar with the technique, maximum voluntary contraction of the dominant hand was assessed 15 min before the start of the actual experiment. After a 15 min period of supine rest, blood pressure and heart rate measurements were obtained each minute for 5 min in the non-dominant arm and averaged to obtain the baseline value. The subjects then performed 75% maximum contraction handgrip for 1 min. Blood pressure and heart rate were measured during the last 15 sec of the effort. Percent changes in mean blood pressure and heart rate in response to handgrip were used for statistical comparisons.

M mode echocardiography was performed with the patient in left lateral position after 30 min of supine rest with use of an Irex system 2 echocardiograph with a 2.25 MHz, 15 mm diameter transducer. All tracings for left ventricular dimensions were recorded at the level of the tips of the mitral valve. The dimensions measured in each tracing, using the leading-edge technique and following the recommendations of the American Society of Echocardiography, were ventricular septal thickness, left ventricular posterior wall thickness, and left ventricular diameter, with each dimension measured at both end-diastole and end-systole. The readings were performed by two observers in a double-blind fashion. Three beats were measured routinely; as many as 5 were measured if the recording was not easy to read. (Agreement between the two observers and reproducibility of the readings by the same observer were within 1 mm.) Heart rate values were obtained from a simultaneously recorded electrocardiogram. Echocardiographically measured volumes in end-diastole and end-systole were derived with the cube formula. Echocardiographic left ventricular mass index was calculated as the difference between total left ventricular end-diastolic volume (including muscle shell) and the inner left ventricular volume multiplied by effector 1.05 (the specific weight for heart muscle) and divided by body surface area. Stroke volume was defined as the difference between end-diastolic and end-systolic volume, and cardiac output by multiplying stroke volume by heart rate. Mean blood pressure was obtained by adding one-third of the pulse pressure to diastolic blood pressure. Total peripheral resistance (dyne x sec x cm-5) was calculated by dividing mean blood pressure by cardiac output and multiplying by 80. The mean velocity of circumferential fiber shortening (sec-1) was calculated as the percent change in left ventricular dimension divided by the left ventricular ejection time.

Statistical analysis was performed by one-way analysis of variance (ANOVA). Differences were considered statistically significant at a level of p < .05. Data are expressed as mean ± SEM.

Results

Two of the 12 enrolled subjects were excluded during the course of the study because their 24 hr urine creatinine and sodium excretion indicated inaccuracy in urine collection and/or noncompliance with the low-sodium diet. Therefore, data from only 10 subjects were considered in further analysis.

Urinary sodium excretion was 178 ± 10 meq/24 hr on the last day of the normal sodium diet (day 0) and fell to 122 ± 20 meq/24 hr after 1 day on the low-sodium diet. Three more days were then allowed to achieve equilibrium on the new sodium regimen before the first humoral and hemodynamic measurements were obtained. Urinary sodium fell to 31 ± 4 meq/24 hr on day 4, to 38 ± 4 meq/24 hr on day 7, to 45 ± 6 meq/24 hr on day 30, and to 47 ± 7 meq/24 hr on day 60 (p < .001 for all as compared with the control value) (figure 1). There were no significant differences among the urinary sodium values obtained on days 4, 7, 30, and 60 of the low-sodium diet.

Table 1 shows the effects of the low-sodium diet on the different humoral and hemodynamic parameters. Blood pressure was not significantly altered. Both supine and upright heart rate increased modestly but significantly on days 4 and 7, returning to baseline thereafter. Supine plasma renin activity and aldosterone concentrations were significantly increased by day 4 of low sodium intake and remained significantly above baseline at days 7, 30, and 60. Body weight decreased significantly by day 7, whereas no significant change was detectable in urinary potassium excretion, creatinine clearance, or hematocrit.

Figure 1 illustrates the changes in plasma epinephrine and norepinephrine as related to the concurrent values for urinary sodium excretion. Plasma concen-
The reliability of the catecholamine pattern found during the low-salt diet is supported by data obtained from four normal subjects given a 200 meq sodium diet identical to our control diet for 2 months. In these subjects, plasma norepinephrine and epinephrine concentrations measured on days 0, 4, 7, 30, and 60 were, respectively, 272 ± 20, 252 ± 21, 295 ± 26, 249 ± 18, and 279 ± 28 pg/ml for norepinephrine (all NS compared with 0 control) and 61 ± 17, 67 ± 15, 57 ± 8, 66 ± 10, and 54 ± 10 pg/ml for epinephrine (all NS compared with 0 control). No significant change from control in urinary sodium excretion could be detected during the 2 months of the diet in these subjects.

Table 2 summarizes the hemodynamic response to the low-salt diet as assessed by echocardiography and responses to isometric exercise. No significant change in any of the resting cardiovascular parameters was detected by echocardiography. In contrast, the percentage of increase in mean blood pressure induced by isometric exercise was significantly greater on days 4 and 7 compared with that under control conditions. This effect of sodium restriction was no longer apparent on days 30 and 60 of the diet. The heart rate response to exercise was not significantly affected by the low-salt diet.

**Discussion**

The evaluation of sympathetic nervous system activity has long been difficult and controversial. However, with the introduction of sensitive radioenzymatic assays for measurement of circulating catecholamines,

### TABLE 1

**Time course of effects of the low-salt diet (40 meq/day) on different hemodynamic and humoral parameters (n = 10)**

<table>
<thead>
<tr>
<th>Days on diet</th>
<th>0</th>
<th>4</th>
<th>7</th>
<th>30</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>128 ± 7</td>
<td>125 ± 4</td>
<td>124 ± 4</td>
<td>120 ± 4</td>
<td>120 ± 6</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>76 ± 5</td>
<td>78 ± 4</td>
<td>75 ± 3</td>
<td>76 ± 5</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>Upright BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>136 ± 4</td>
<td>126 ± 3</td>
<td>129 ± 5</td>
<td>122 ± 5</td>
<td>124 ± 5</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>82 ± 5</td>
<td>79 ± 4</td>
<td>79 ± 5</td>
<td>81 ± 6</td>
<td>81 ± 5</td>
</tr>
<tr>
<td>Supine HR (beats/min)</td>
<td>59 ± 2</td>
<td>65 ± 2^*</td>
<td>65 ± 2^*</td>
<td>57 ± 3</td>
<td>55 ± 2</td>
</tr>
<tr>
<td>Upright HR (beats/min)</td>
<td>72 ± 4</td>
<td>88 ± 7^*</td>
<td>80 ± 3^*</td>
<td>78 ± 5</td>
<td>72 ± 4</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>1.42 ± 0.2</td>
<td>4.42 ± 0.7^*</td>
<td>2.95 ± 0.5^*</td>
<td>2.86 ± 0.6^*</td>
<td>2.62 ± 0.6^A</td>
</tr>
<tr>
<td>PAC (pg/ml)</td>
<td>130 ± 9</td>
<td>260 ± 35^*</td>
<td>174 ± 16^*</td>
<td>191 ± 16^A</td>
<td>167 ± 10^A</td>
</tr>
<tr>
<td>UKV (meq/24 hr)</td>
<td>50 ± 3</td>
<td>45 ± 4</td>
<td>41 ± 5</td>
<td>55 ± 7</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>42 ± 0.8</td>
<td>43 ± 0.8</td>
<td>43 ± 0.8</td>
<td>44 ± 0.9</td>
<td>44 ± 0.3</td>
</tr>
<tr>
<td>Cr Cl (ml/min)</td>
<td>131 ± 10</td>
<td>124 ± 14</td>
<td>116 ± 13</td>
<td>130 ± 12</td>
<td>134 ± 13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 ± 3</td>
<td>72 ± 3</td>
<td>71 ± 3^*</td>
<td>71 ± 2^A</td>
<td>70 ± 2^A</td>
</tr>
</tbody>
</table>

BP = blood pressure; HR = heart rate; PRA = plasma renin activity; PAC = plasma aldosterone; UKV = urinary potassium excretion; Hct = hematocrit; Cr Cl = creatinine clearance.

^\*p < .05.
a number of recent studies have indicated that such measurements can provide a reliable index of sympathetic activity under certain conditions, particularly when factors such as body posture, age, smoking, caffeine consumption, stress, exercise, medications, salt intake, and blood pressure are taken into account. Much care was thus devoted in the present study to control of the blood sampling procedure, and only normal subjects falling into a restricted age range were studied. In addition, hemodynamic parameters that, at least in part, reflect neural sympathetic discharge were also monitored to further validate plasma catecholamine levels as a measure of sympathetic nervous system activity.

In keeping with most previous observations, our results show that plasma catecholamine levels increase when sodium intake is decreased. However, in the present study, the increase in plasma catecholamines was detectable only in the early period of the low-salt diet. Measurements obtained after 30 and 60 days of a continuous low-salt diet showed that both plasma epinephrine and norepinephrine concentrations were no longer different from those obtained during the control period.

Consistent with the trend observed in plasma catecholamine levels are two additional findings of our study. First, the small but significant increases in heart rate (mostly in the upright position) paralleled those observed in plasma catecholamine levels, since they were restricted to the observations made on days 4 and 7. Similarly, the blood pressure response to isometric exercise was significantly enhanced only in the early period of the low-salt diet.

Taken together, these findings indicate that, in normotensive subjects, a sustained and protracted reduction in salt intake enhances sympathetic activity only transiently. A few earlier observations are consistent with our findings. For example, Carroll et al. reported that long-term sodium depletion in dogs did not alter plasma catecholamine concentration despite a fourfold increase in plasma renin activity. Fujita et al. reported that in salt-sensitive hypertensive patients switched from a low- to a high-salt diet, plasma nor-epinephrine decreased initially but then increased toward control values. These findings are compatible with the hypothesis that the catecholamine response to a change in sodium intake is transient.

Although we found that a transient increase in plasma catecholamines was associated with increases in heart rate and blood pressure responses to exercise, we failed to detect a significant effect of the low-salt diet on resting cardiac output or peripheral resistance, as evaluated by echocardiography. This contrasts in part with some earlier findings. However, in most studies showing changes in local or systemic vascular resistance or contractility during a low-salt diet, the responses to far more drastic sodium restriction were evaluated principally in patients with borderline or es-

### TABLE 2

<table>
<thead>
<tr>
<th>Days on diet</th>
<th>0</th>
<th>4</th>
<th>7</th>
<th>30</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVVID (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastole</td>
<td>5.0±0.2</td>
<td>5.0±0.2</td>
<td>5.0±0.2</td>
<td>5.1±0.1</td>
<td>5.1±0.2</td>
</tr>
<tr>
<td>Systole</td>
<td>3.4±0.2</td>
<td>3.5±0.2</td>
<td>3.5±0.2</td>
<td>3.6±0.2</td>
<td>3.6±0.2</td>
</tr>
<tr>
<td>LVV (cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastole</td>
<td>126±10</td>
<td>127±11</td>
<td>127±10</td>
<td>130±12</td>
<td>130±12</td>
</tr>
<tr>
<td>Systole</td>
<td>49±6</td>
<td>50±6</td>
<td>51±6</td>
<td>50±7</td>
<td>52±8</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>96±4</td>
<td>96±5</td>
<td>97±5</td>
<td>98±5</td>
<td>98±5</td>
</tr>
<tr>
<td>VCF (sec⁻¹)</td>
<td>1.1±0.05</td>
<td>1.08±0.05</td>
<td>1.08±0.05</td>
<td>1.03±0.04</td>
<td>1.05±0.05</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.6±0.7</td>
<td>6.4±0.6</td>
<td>6.6±0.3</td>
<td>6.3±0.3</td>
<td>6.3±0.3</td>
</tr>
<tr>
<td>TPR (dynes × sec × cm⁻³)</td>
<td>1240±208</td>
<td>1255±198</td>
<td>1200±78</td>
<td>1198±55</td>
<td>1241±85</td>
</tr>
<tr>
<td>%Δ MBP</td>
<td>+22.3±4</td>
<td>+41±5</td>
<td>+40.5</td>
<td>+28±4</td>
<td>+23±3</td>
</tr>
<tr>
<td>%Δ HR</td>
<td>+42±10</td>
<td>+43±7</td>
<td>+52±8</td>
<td>+50±9</td>
<td>+40±7</td>
</tr>
</tbody>
</table>

LVID = left ventricular internal diameter; LVV = left ventricular volume; LVMI = left ventricular mass index; VCF = mean velocity of circumferential fiber shortening; CO = cardiac output; TPR = total peripheral resistance; HR = heart rate; MBP = mean blood pressure.

*Δ < .05.
tablished hypertension who might have different hemodynamic responses than the normal subjects studied herein.

Another important finding of our study is that, unlike the parameters reflecting sympathetic function, both plasma renin activity and plasma aldosterone remained elevated for the duration of the low-salt diet. This is not surprising, given the known complexity of the control of renin secretion by the kidney. Thus, although the transient stimulation of sympathetic activity may have contributed to the initial rise in plasma renin, other mechanisms (such as stimulation via the macula densa) appear able to sustain the stimulation of the renin-angiotensin system despite waning of the sympathetic response. It must be pointed out that, since hormonal measurements were made only in the supine position, we may have underestimated the degree of stimulation of the renin-angiotensin system (as well as of the sympathetic nervous system) during long-term sodium depletion. It thus remains possible that some degree of sympathetic activation might persist in the upright posture, although our data on exercise responses are evidence against this. Whatever the case, the present findings demonstrate a dissociation between the long-term responses of the renin-angiotensin and sympathetic nervous systems.

The mechanisms responsible for the initial stimulation of sympathetic function induced by sodium restriction and for the waning of this response over the long term are not elucidated by the present study. It is, of course, possible that angiotensin II itself plays a role in stimulating the sympathetic nervous system, since several mechanisms have been proposed whereby this could occur.33-37 If so, it is difficult to understand why the sympathetic response would fade despite maintained activation of the renin-angiotensin system; however, there is evidence that long-term angiotensin infusion appears to only transiently increase arterial epinephrine levels.38 Other mechanisms are possible, such as initial changes in blood volume followed by redistribution of volume, but further work is needed to clarify this point.

In conclusion, our findings indicate that the duration of the change in salt intake has to be taken into account in evaluating the sympathetic nervous system responses to a reduction in sodium intake. They also support the hypothesis that long-term blood pressure homeostasis in normal subjects is accomplished mainly through the kidney and its control mechanisms, as indicated by the more sustained response of the renin-angiotensin system, whereas the autonomic nervous control of the circulation principally contributes to the short-term control of blood pressure homeostasis during long-term changes in sodium intake.

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