Effects of Sodium Salts on Pressor Reactivity in Salt-Sensitive Men

Arya M. Sharma, Sabine Schattenfroh, Hans-Michael Thiede, Wolfgang Oelkers, and Armin Distler

Blood pressure in patients with essential hypertension is raised by sodium chloride but not by nonchloride sodium salts. Although a high sodium chloride diet is known to augment the pressor response to norepinephrine and angiotensin II, the effect of nonchloride sodium salts on pressor responsiveness has not been studied so far. To examine whether sodium chloride and nonchloride sodium salts evoke different pressor responses to these agonists, we performed graded norepinephrine and angiotensin II infusions in salt-sensitive (n=7) and salt-resistant (n=8) normotensive subjects. The subjects were given a low salt diet (20 mmol/day) for 3 weeks, to which a supplement of 200 mmol sodium per day, provided as either sodium chloride or sodium citrate, or a placebo was added for 1 week each. We found that, although sodium chloride raised mean arterial blood pressure in the salt-sensitive subjects (p<0.005), sodium citrate did not. However, under both sodium salts pressor response to norepinephrine and angiotensin II was significantly greater than under placebo (p<0.02). Furthermore, with both sodium salts, pressor response in the salt-sensitive subjects was greater than in the salt-resistant subjects (p<0.01). This study thus demonstrates that, although blood pressure in salt-sensitive individuals is raised by sodium chloride only, both sodium chloride and sodium citrate evoke similar increases in pressor response to norepinephrine and angiotensin II. Since pressor response increased with both sodium salts but resting blood pressure increased only with sodium chloride, enhanced pressor responsiveness alone cannot account for the sodium chloride–induced rise in resting blood pressure. (Hypertension 1992;19:541–548)

Key Words • salt-sensitive hypertension • sodium chloride • catecholamines • vascular reactivity • renin-angiotensin-aldosterone system

An enhanced pressor response to endogenous vasoactive substances including norepinephrine and angiotensin II has been found in patients with essential hypertension1–12 and in genetically predisposed normotensive subjects,11,13,14 and this response has been assumed to play a major role in the pathogenesis of essential hypertension. A high dietary sodium chloride intake increases the pressor response to both norepinephrine15 and angiotensin II,16 and this could contribute to the salt-induced blood pressure rise in salt-sensitive individuals. Although the blood pressure–raising effect of salt has previously been thought to be mediated by the sodium ion alone, increasing evidence indicates that it depends on the administration of both sodium and chloride (see Reference 17 for review). Thus, in patients with essential hypertension, a blood pressure rise was induced by the administration of sodium chloride as a supplement to a low salt diet but not by comparable amounts of sodium provided as either the bicarbonate,18,19 citrate,20 or phosphate21 salt.

Whether this difference between the blood pressure effects of sodium chloride and nonchloride sodium salts is due to their evoking different pressor responses to norepinephrine and angiotensin II has not been studied previously. Therefore, we studied the effect of the dietary intake of sodium chloride or sodium citrate on the pressor response to these substances in salt-sensitive normotensive subjects with positive family histories of hypertension. We also compared the effects of both sodium salts on plasma levels and urinary excretion of catecholamines, plasma levels of renin activity, angiotensin II and aldosterone, and the response of renal plasma flow to angiotensin II infusions in these individuals. Salt-resistant normotensive individuals with negative family histories of hypertension served as control subjects. We selected genetically predisposed normotensive subjects for our study because these subjects offer the unique opportunity of studying pathogenic mechanisms believed to be related to hypertension without the confounding presence of overt hypertension and its sequelae.

Methods

The protocol of the study was approved by the Ethics Committee of our hospital. All participants gave their consent in writing.
Assessment of Salt Sensitivity

Salt sensitivity was assessed, as described previously, in a total of 34 subjects before the commencement of the study. In brief, subjects were given a standardized diet containing 20 mmol sodium chloride, 60 mmol potassium, and 20 mmol calcium per day for 14 days, adding either placebo or a supplement of 200 mmol NaCl/day for 1 week each. Total urinary electrolyte excretion served as a measure for the accuracy of urine collection. Subjects with at least one parent under treatment for hypertension were regarded as having a positive family history of hypertension.

Study Protocol

Ten salt-sensitive subjects with positive family histories and 10 salt-resistant subjects with negative family histories of hypertension agreed to participate in the study. In addition to the low salt diet described above, subjects were given, as a daily supplement, 40 capsules containing either sodium chloride or sodium citrate (5 mmol sodium per capsule) or a placebo for 7 days each. The sequence of the three regimens (placebo, sodium chloride, and sodium citrate) was randomized according to a Latin square design. The resultant daily intake of 220 mmol during the high sodium periods exceeds the average sodium intake in West European societies by roughly 25%, but is still well within the normal range. Compliance was assessed throughout the study by measuring daily 24-hour urinary sodium, chloride, and potassium excretion. Creatinine excretion served as a measure for the accuracy of urine collection. Subjects were considered compliant when sodium and chloride excretion was below 35 mmol/24 hr during the last 3 days of the low sodium chloride period, above 180 mmol/24 hr during the last 3 days of the high salt period, and when sodium excretion was higher than 180 mmol/24 hr and chloride excretion was lower than 35 mmol/24 hr during the last 3 days of the sodium citrate period.

On the sixth day of each period, after 30 minutes of rest and insertion of a venous Teflon cannula, blood pressure was measured as described above. Then, after 3 hours at supine rest, a venous blood sample was drawn from an antecubital vein for determination of sodium, chloride, potassium, calcium, renin activity, angiotensin II, aldosterone, and catecholamines. In addition, an arterial blood sample was drawn from the radial artery for assessment of the acid base and blood gas status, the results of which have been reported previously. Pressure response to intravenous norepinephrine infusion was then assessed by obtaining dose–response curves for norepinephrine (Arterenol, Hoechst, FRG) as described previously. Norepinephrine was infused in doses of 0.05, 0.1, and 0.2 μg/kg/min. Each dose was infused for 10 minutes. Blood pressure recorded every minute reached a new plateau after 3–5 minutes at each dose, and the means of the last five readings were used to calculate the representative blood pressure response to each dose.

On the seventh day of each period the effect of graded intravenous infusions of angiotensin II (Hypertensin, CIBA-GEIGY) on blood pressure, renal plasma flow, and aldosterone secretion was determined. Renal plasma flow was measured as the clearance of para-aminohippurate (PAH) (Nephrotest, BAG, Lich, FRG) as described by Schnurr et al and corrected for 1.73 m² body surface area. Angiotensin II was infused in doses of 2, 4, and 8 ng/kg/min. The 60-minute infusion of each dose was followed by drawing blood samples for measurement of aldosterone and PAH. Blood pressure was measured at 5-minute intervals during the infusion periods, and the means of the last six readings were used to calculate the pressor response to each angiotensin II dose.

Laboratory Procedures

Plasma and urinary electrolytes were measured by standard laboratory techniques. Plasma renin activity, angiotensin II, and aldosterone were assayed as described previously. Plasma and urinary catecholamines were measured by reversed-phase, high-performance liquid chromatography (HPLC) with electrochemical detection (BCJM 1, ERC, Alteglofsheim, FRG) and by applying a slight modification of the method of Frayn and Maycock. In brief, after the addition of the internal standard (3,4-dihydroxy-benzylamine, Sigma, Munich, FRG) the heparinized plasma or urine sample was adjusted to pH 6.5 and passed over a weak cation exchange column (Biorex 70 100 mesh, Bio Rad, Munich, FRG). After washing with water, the catecholamines were eluted with 3 M NaCl. Eluate pH was adjusted to 8.5 in the presence of sodium metabisulphite (antioxidant). The amines were then further extracted by binding to acid-washed aluminum oxide. After washing and elution with 0.1 M perchloric acid, an aliquot was injected into the HPLC system, where the amines were separated by passing through a steel column (120×4 mm) packed with spherisorb ODS II (3 μm) (Knauer, Berlin, FRG). The mobile phase consisted of a sodium citrate
buffer (pH 4.5) containing 10% methanol and octanesulfonic acid (100 mg/l). The flow rate was set at 0.3 ml/min. The detection potential at the glassy carbon electrode versus the Ag/AgCl reference electrode was set at 800 mV. All samples were measured in duplicate. Recovery ranged between 60% and 70% for all amines.

**Statistics**

Statistical analysis was performed using the SPSS/PC+ software package (SPSS Inc., Chicago, Ill.). The salt sensitivity of an individual subject was tested by using the independent t test to detect significant differences between the 30 blood pressure readings taken during the high salt diet and those during the low salt diet. Subsequently, the means of the 30 blood pressure readings as well as all other variables under the different regimens were compared within each group by the two-tailed t test for paired samples, the significance level being reduced to p<0.016 to compensate for multiple comparisons (placebo versus sodium chloride, placebo versus sodium citrate, and sodium chloride versus sodium citrate). Otherwise, statistical significance was defined as p<0.05. The response to angiotensin and norepinephrine infusion between the two groups was compared by two-way analysis of variance (ANOVA) for repeated measures over time under each regimen. Otherwise, the two-tailed t test for independent samples was used for comparisons between the salt-sensitive and salt-resistant groups. Results are presented as mean±SEM.

**Results**

Two salt-resistant and three salt-sensitive subjects were excluded from analysis because of poor compliance as assessed by urinary sodium and chloride excretion. There was no difference in age (25.0±0.4 versus 25.6±0.8 years) or body mass index (21.4±0.8 versus 22.8±0.9 kg/m²) between the remaining salt-sensitive and salt-resistant subjects.

Physical, plasma, and urinary variables were shown in Table 1. There was no significant difference in urinary excretion of sodium and chloride between the two groups under the different regimens. A rise in diastolic and mean arterial pressure was induced in the salt-resistant group. Body weight was not significantly affected in either group.

In the salt-sensitive group, the pressor response to graded norepinephrine infusion was higher at all doses with both high sodium regimens than with the low salt diet (p<0.01, ANOVA) (Figure 1). In contrast, pressor response to norepinephrine was not significantly affected by sodium intake in the salt-resistant group. Although the pressor response to norepinephrine under the low salt regimen was similar in the two groups, the pressor response to the highest norepinephrine dose under both high sodium regimens was significantly greater in the salt-sensitive than in the salt-resistant subjects (p<0.05, ANOVA). Plasma levels and urinary excretion of norepinephrine, epinephrine, and dopamine are shown in Table 2. Plasma norepinephrine levels were lower with both sodium chloride and citrate.
than with placebo, although the difference was significant only in the salt-sensitive group (p<0.01). There were no significant treatment effects on plasma epinephrine and dopamine. Urinary excretion of plasma epinephrine was not significantly affected by either regimen.

Under both high sodium chloride and sodium citrate, the salt-sensitive subjects showed a greater overall pressor response to angiotensin II than under placebo (Figure 2) (p<0.01, ANOVA). With both sodium salts, pressor response to the lowest angiotensin II dose was also augmented in the salt-resistant group (p<0.05, ANOVA). Although the two groups did not differ in their pressor response to angiotensin II under the low salt regimen, under both sodium salts pressor response was significantly higher in the salt-sensitive subjects than in the salt-resistant group (p<0.05, ANOVA). Under the low salt regimen, there was a comparable decrease in renal plasma flow (PAH clearance) during angiotensin II infusion in both groups (Figure 2). However, the angiotensin II–induced reduction in renal plasma flow was augmented under both sodium salts in the salt-sensitive subjects (p<0.05, ANOVA), but was not significantly changed in the salt-resistant individuals. The plasma aldosterone concentration after angiotensin II infusion was lower under the high sodium regimens in both groups (p<0.01, ANOVA) (Figure 3). Although the two groups did not differ in their adrenal angiotensin II responsiveness under the low salt regimen, the plasma aldosterone concentration in response to the angiotensin II infusion tended to be lower in the salt-resistant than in the salt-sensitive individuals during both high sodium regimens. Plasma renin activity, angiotensin II, and aldosterone levels were significantly lower under both the sodium chloride and the sodium citrate regimens compared with placebo in both groups (p<0.01; Figure 4).

Discussion

The current study demonstrates that in salt-sensitive normotensive individuals, pressor response to exogenous norepinephrine and angiotensin II increases under a high dietary intake of sodium administered as either sodium chloride or sodium citrate. Thus, the enhanced pressor response to norepinephrine and angiotensin II known to be induced by a high salt intake clearly depends on sodium but not on chloride balance. As opposed to sodium chloride, however, sodium citrate failed to raise resting blood pressure. The different effects of the two salts on resting blood pressure can, therefore, not be accounted for by differences in their effects on the pressor response to norepinephrine or angiotensin II. Moreover, our data do not support the assumption that the sodium chloride–induced rise in resting blood pressure is directly linked to the concomitant rise in pressor response to norepinephrine or angiotensin II.

Previous studies have demonstrated that pressor response to exogenous norepinephrine is inversely correlated to plasma levels of norepinephrine, and this has been attributed to a decreased availability of adrenergic receptors with increasing sympathetic activity and vice versa. In the current study, plasma norepinephrine was significantly reduced under both high sodium regimens in the salt-sensitive subjects. One reason for the increased pressor response to norepinephrine in these subjects could therefore be a functional upregulation of vascular α-adrenergic receptors or postreceptor mechanisms after a reduction in sympathetic outflow. Such an adaptation thus need not necessarily have a net effect on resting blood pressure. This assumption is supported by

**Figure 1.** Line plot shows change in mean arterial pressure (MABP) during graded norepinephrine (NA) infusion in salt-resistant (n=8) and salt-sensitive (n=7) normotensive subjects during administration of placebo, sodium chloride, and sodium citrate as a supplement to a low salt diet (mean±SEM).

**Table 2.** Plasma Levels and 24-Hour Urinary Excretion of Catecholamines in Salt-Resistant and Salt-Sensitive Normotensive Subjects During the Administration of Placebo, Sodium Chloride, and Sodium Citrate as a Supplement to a Low Salt Diet

<table>
<thead>
<tr>
<th>Variables</th>
<th>Salt-resistant (n=8)</th>
<th>Salt-sensitive (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Sodium chloride</td>
</tr>
<tr>
<td></td>
<td>242±21</td>
<td>206±15</td>
</tr>
<tr>
<td></td>
<td>30±4.1</td>
<td>26.2±9.1</td>
</tr>
<tr>
<td></td>
<td>22.1±4.4</td>
<td>16.7±1.7</td>
</tr>
<tr>
<td>Urinary catecholamine excretion</td>
<td>40.7±3.3</td>
<td>33.7±5.1</td>
</tr>
<tr>
<td></td>
<td>4.2±0.3</td>
<td>5.6±1.0</td>
</tr>
<tr>
<td></td>
<td>241±21</td>
<td>248±25</td>
</tr>
<tr>
<td>Values are mean±SEM.</td>
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*p<0.01 vs. placebo.
the finding that, although pressor response was increased under sodium citrate in the salt-sensitive group, resting blood pressure did not change significantly. In contrast, in the salt-resistant group, sodium intake did not significantly influence either pressor response to norepinephrine or plasma norepinephrine levels. As with the interrelation between the pressor response to norepinephrine and plasma levels of norepinephrine, the pressor response to angiotensin II has also been shown to correlate inversely with plasma levels of angiotensin II and renin activity. In our present study, both sodium salts lowered plasma angiotensin II levels and renin activity while enhancing pressor response to angiotensin II in both groups. During both high sodium regimens, however, pressor response was higher and plasma levels of angiotensin II and renin activity tended to be lower in the salt-sensitive than in the salt-resistant subjects. The augmented angiotensin II-induced reduction in renal plasma flow under both sodium salts observed in the salt-sensitive group is compatible with an increased sensitivity of the renal vasculature to angiotensin II in these individuals. Since blood pressure in the salt-sensitive group was raised only by sodium chloride but not by sodium citrate, our data show that the sodium-induced augmentation of vascular responsiveness to angiotensin II does not necessarily result in a net increase of resting blood pressure. Although upregulation of receptor sensitivity to norepinephrine and angiotensin II as a consequence of lower circulating levels of these agonists under a high salt diet may be one mechanism leading to the greater pressor response observed in the salt-sensitive subjects, sodium-induced effects on other factors known to influence pressor response, such as increased cytosolic calcium or altered baroreceptor reflex function, must likewise be considered.

In our present study, both sodium salts had a similar suppressive effect on the angiotensin II-induced release of aldosterone. Salt depletion is known to sensitize the
adrenal cortex to angiotensin II, but whether this effect is mediated by changes in chloride balance has not been studied previously. Our data now show that chloride depletion per se does not enhance the sensitivity of the adrenal cortex to angiotensin II infusion. Therefore, sodium but not chloride depletion seems to account for the sensitization of the adrenal cortex to angiotensin II observed during salt restriction. Plasma aldosterone levels during angiotensin II infusion in our study were slightly but not significantly lower in the salt-resistant than in the salt-sensitive group under both high sodium diet regimens. Though a high salt diet has been shown to lower plasma levels of norepinephrine and angiotensin II, the effect of a nonchloride sodium salt on plasma catecholamines and angiotensin II levels has not been studied in humans previously. Our finding that both sodium salts have comparable suppressive effects on plasma levels of norepinephrine, renin activity, angiotensin II, and aldosterone suggests that sympathetic nervous system and the renin-angiotensin-aldosterone system are primarily modulated by sodium and not chloride intake. This is in agreement with data showing that both sodium chloride and nonchloride sodium salts suppress plasma renin activity and aldosterone levels in hypertensive subjects as well as in the doxycorticosterone-acetate and one-kidney, one clip rat models of hypertension. However, there are conflicting data from studies performed in the Sprague-Dawley rat and in normal individuals suggesting that chloride rather than sodium regulates renin secretion. Thus, in normal Sprague-Dawley rats, renin activity was suppressed by sodium chloride added to a low salt diet but not by various nonchloride sodium salts providing equal amounts of sodium. Similarly, normal individuals on a low sodium diet showed suppression of plasma renin activity after acute intravenous infusion of saline but not after sodium bicarbonate. Although the difference between our findings and the effect of the nonchloride sodium salt on renin activity in the latter study may be due to renin activity being influenced differently by acute sodium bicarbonate loading than with chronic administration of a nonchloride sodium salt, we cannot provide a ready explanation for the discrepancy between our findings and those obtained from studies in the Sprague-Dawley rat.

It has been suggested that failure to appropriately suppress sympathetic activity with a high salt diet may contribute to salt sensitivity in patients with essential hypertension. This, however, does not appear to hold true for salt-sensitive normotensive subjects, since in our salt-sensitive subjects plasma norepinephrine levels decreased with high salt intake. Thus, failure of plasma norepinephrine to decrease with high salt intake in patients with salt-sensitive hypertension may reflect a phenomenon secondary to established hypertension such as a resetting of baroreceptor reflexes or sympathetic outflow rather than a primary defect.

In this current study, as in a previous study in normotensive individuals performed by Skrabal et al., the pressor response to norepinephrine under a high salt diet was greater in salt-sensitive than in salt-resistant subjects. In addition, we found that systemic and renal vascular response to angiotensin II in the salt-sensitive subjects was likewise enhanced under the high sodium diet (the sodium content of which, however, was still within the normal range). Enhanced pressor response to norepinephrine and angiotensin II has been found in the majority of studies performed in patients with essential hypertension, but some authors have failed to confirm this. Differences in the study protocol and in the assessment of reactivity to the agent infused as well as other factors including age, salt intake, and race may account for these inconsistent findings. Thus, in a recent study that failed to find a greater pressor response to norepinephrine in patients with essential hypertension than in normotensive control subjects, hospitalization before the examination decreased diastolic pressure to less than 90 mm Hg on the day of the study in most patients previously classified as hypertensive in an outpatient setting. In another recent negative study, different total doses of norepinephrine were administered to the two study groups, and the pressor response was expressed as percent change in blood pressure per nanomole increase in plasma norepinephrine, an approach very different from the analysis using dose-response curves applied in our and most other studies. Since, as our study indicates, enhanced pressor responsiveness to vasoactive...
substances may be present in subgroups of normotensive subjects who are salt sensitive, have a family history of hypertension, or both, an inappropriate choice of normotensive control groups may further explain why some investigators have failed to find hyperreactivity to pressor agents in hypertensive subjects compared with normotensive control subjects.

Structural alterations leading to a thickening of the walls of resistance arterioles have been proposed to account for the hyperreactivity to pressor agents observed in hypertensive subjects. The observation in this and other studies of an enhanced pressor response to norepinephrine and angiotensin II in normotensive individuals predisposed to the development of hypertension clearly indicates that enhanced reactivity to these substances may be present before the development of overt hypertension and, therefore, does not result from changes secondary to established hypertension. However, structural changes cannot completely be ruled out as a cause of hyperreactivity since there is some indirect evidence suggesting that such changes may already be present in normotensive offspring of patients with essential hypertension. Other mechanisms, including an increased $alpha_2/alpha_2$-adrenergic receptor ratio, a sodium-induced rise in cytosolic calcium, or altered baroreceptor reflex function, that could all be operative even in the absence of structural changes appear to be more likely to account for the increased reactivity observed in our salt-sensitive subjects.

In a series of studies by Williams and Hollenberg, a subset of patients with salt-sensitive hypertension designated "non-modulators" has been described. These patients are characterized by their failure to increase aldosterone response to angiotensin II during salt restriction and failure to increase renal blood flow response to angiotensin II when on a high salt diet. These individuals were reported to account for 55-65% of patients with salt-sensitive hypertension. In contrast, in our salt-sensitive normotensive subjects both adrenal responsiveness and renal blood flow response to angiotensin II were significantly affected by salt intake, and these individuals must therefore be regarded as "modulators." One may therefore speculate that, although salt sensitivity in established hypertension may be associated with "non-modulation," this does not apply to young salt-sensitive normotensive subjects. Weinberger and Fineberg have recently reported that salt-sensitive normotensive subjects experience an increase in blood pressure as they grow older, and it would be of interest to follow up these individuals to observe whether they become non-modulators as they grow older and overt hypertension develops.

Several mechanisms have been suggested to account for the different blood pressure effects of sodium chloride and non-chloride sodium salts. As pointed out in a recent review by Boegehold and Kotchen, the anion supplied along with sodium may determine its effect on plasma volume by influencing its distribution among intracellular and extracellular compartments, thus accounting for different blood pressure effects despite a similar sodium balance. As noted in the present study, sodium bicarbonate and citrate are known to reduce urinary calcium excretion, which may likewise affect the blood pressure response to sodium intake. The alkalizing effect of sodium citrate or bicarbonate may also contribute to their failure to raise blood pressure in salt-sensitive individuals.

In summary, the present study demonstrates that, although blood pressure in salt-sensitive individuals is raised by sodium chloride only, both sodium chloride and sodium citrate evoke similar increases in the pressor response to norepinephrine and angiotensin II. This increase in pressor response depends on sodium but not on chloride balance. Since pressor response increases with both sodium salts but resting blood pressure increases with sodium chloride only, enhanced pressor responsiveness alone obviously does not account for the salt-induced rise in resting blood pressure. Importantly, under a high (though normal) sodium diet, the pressor response to both norepinephrine and angiotensin II was higher in salt-sensitive than in salt-resistant subjects. The pathophysiological significance of this finding for the possible later development of hypertension in these genetically predisposed individuals remains to be determined.

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