Abstract—The purpose of this study was to evaluate the contribution of renal sodium handling by the proximal tubule as an independent determinant of blood pressure responsiveness to salt in hypertension. We measured blood pressure (BP), renal hemodynamics, and segmental renal sodium handling (with lithium used as a marker of proximal sodium reabsorption) in 38 hypertensive patients and 27 normotensive subjects (15 young and 12 age-matched) on a high and low sodium diet. In control subjects, changing the diet from a low to a high sodium content resulted in no change in BP and increases in glomerular filtration rate ($P<0.05$), renal plasma flow ($P<0.05$), and fractional excretion of lithium (FE$_{Li}$, $P<0.01$). In hypertensive patients, comparable variations of sodium intake induced an increase in BP with no change in renal hemodynamics and proximal sodium reabsorption. When analyzed by tertiles of their BP response to salt, salt-insensitive hypertensive patients of the first tertile disclosed a pattern of adaptation of proximal sodium reabsorption comparable to that of control subjects, whereas the most salt-sensitive patients of the third tertile had an inverse pattern with a high FE$_{Li}$ on low salt and a lower FE$_{Li}$ on high salt, suggesting an inappropriate modulation of proximal sodium reabsorption. The BP response to salt correlated positively with age ($r=0.34$, $P=0.036$) and negatively with the changes in FE$_{Li}$ ($r=-0.37$, $P=0.029$). In a multivariate analysis, the changes in FE$_{Li}$ were significantly and independently associated with the salt-induced changes in BP. These results suggest that proximal sodium reabsorption is an independent determinant of the BP response to salt in hypertension. (Hypertension. 2000;36:631-637.)

Key Words: hypertension, renal human blood pressure sodium

According to Guyton’s hypothesis, the pressure-natriuresis relation determined by the kidneys represents the mechanism involved in blood pressure that exhibits the biggest potential gain. Thus, it has been postulated that modifications of the pressure-natriuresis relation always participate in the genesis of hypertension regardless of the initial pathogenic factor. Kimura et al. have extended this approach and have proposed 3 major renal mechanisms leading to the development of hypertension: an increased preglomerular vascular resistance, a decrease in whole-kidney ultrafiltration, and an increase in tubular sodium reabsorption. They suggest that the first mechanism leads to a sodium-insensitive hypertension, whereas the latter two result in the development of salt-sensitive forms of hypertension.

With the lithium clearance technique used as a marker of sodium handling by the proximal segments of the nephron, an increased proximal reabsorption of sodium has been demonstrated in animal models of hypertension, in hypertensive patients, in normotensive subjects with 1 first-degree hypertensive relative and in patients with isolated office hypertension, that is, white-coat hypertension.

In our previous experimental and clinical studies, we found that the renal fractional excretion of lithium (FE$_{Li}$) varied in close relation with the fractional excretion of sodium (FE$_{Na}$) in normotensive rats and humans. Thus, on a high salt intake, the FE$_{Li}$ increased markedly, leading to a steep FE$_{Li}$/FE$_{Na}$ relation. In contrast, the FE$_{Li}$/FE$_{Na}$ relation was significantly flatter in hypertensives, suggesting that on a high sodium diet, hypertensive animals and humans were not adequately reducing their proximal sodium reabsorption to excrete the excess of salt. These observations had 2 limitations. First, these studies had a cross-sectional design. Thus, renal sodium handling was not measured in the same individuals on different salt intakes to evaluate whether this pattern was specific to some or to all hypertensive patients. In addition, because other important determinants of sodium excretion were not measured, such as renal hemodynamics and the activity of the renin-angiotensin system, one could not assess whether the renal tubular dysfunction was a primary event in hypertension or merely a consequence of renal hemodynamic alterations induced by hypertension.

The purpose of the present study was therefore to evaluate prospectively the changes in blood pressure, renal hemodynamics, hormonal profile, and segmental renal sodium handling in hypertensive patients and normotensive control subjects studied on high and low sodium diets. On the basis of our earlier findings, we expected hypertensive patients...
studied on a high salt intake to exhibit a lower FELi than normotensive subjects. We hypothesized that hypertensive patients able to increase their FEli on a high sodium diet and to reduce FEli during salt restriction have a salt-insensitive hypertension, whereas those with no salt-induced changes in FEli have a salt-sensitive hypertension.

Methods

Subjects

The study was conducted in 43 untreated hypertensive patients (18 women, 25 men) and 15 young male normotensives. Five hypertensive patients were excluded because they failed to lower their sodium excretion on a low salt diet, suggesting a poor compliance. Thus, 38 hypertensives completed the protocol. Hypertension was defined as a seated office diastolic blood pressure $>90$ mm Hg and/or a systolic pressure $>140$ mm Hg, with the use of a mercury sphygmomanometer, on 3 different occasions before beginning the study. Any antihypertensive therapy was stopped for 3 weeks before starting the protocol. No other therapy was allowed during the investigation. Specifically, female participants were not taking any hormones, and all were examined during the first part of their hormonal cycle. All participants gave their informed consent. The study protocol was approved by the institutional review committee.

Patients and control subjects were studied on a low sodium (LS) and high sodium intake (HS) protocol. The diet periods lasted for 1 week, and the sequence of the diets was randomized. The high salt diet was obtained by adding 6 g of NaCl to the regular diet. The low sodium diet was provided in the hospital to the young normotensive subjects, all meals being composed by a dietitian to reach a salt intake of 70 mmol Na/24 h. In hypertensive patients, salt restriction was obtained by providing careful dietary instructions (menu lists) to reach a daily salt intake of $\approx 70$ mmol Na/24 h. Because the normotensive control subjects were younger and had a lower salt excretion during salt depletion, a second age-matched control group (n = 12, 6 women/6 men) was enrolled. These subjects followed the same protocol as the hypertensive patients except for the renal clearances, which were not performed in this subgroup.

Procedures

On the seventh day of each dietary period, 12 hours of daytime (8 AM to 8 PM) ambulatory blood pressure was recorded, with measurements performed at 20-minute intervals (Profilomat, Disetronic). Participants were instructed not to smoke or to drink alcohol or any caffeine-containing beverages during that day. Simultaneously, 24-hour urine was collected to measure sodium, potassium, and endogenous trace lithium excretions. On the following day, the young normotensive subjects and the patients were investigated in the morning, after an overnight fast, to undergo clearance studies as reported previously. In brief, two intravenous catheters were inserted into antecubital veins, one for the infusion of insulin and p-aminohippurate (PAH) and a second into the contralateral forearm for drawing blood. After an oral water load of 8 mL/kg and a 2-hour period of equilibration, two 1-hour inulin and PAH clearances were obtained to measure glomerular filtration rate (GFR) and effective renal plasma flow (ERPF). Blood was also drawn to measure serum electrolytes including endogenous trace lithium, plasma renin activity (PRA), and plasma aldosterone levels.

Calculation of Renal Parameters

Clearances (C) were calculated with the formula $C_x = U_x \times V/P_x$, where $U_x$ and $P_x$ are urinary and plasma concentrations of the solute x, and V is the urine flow rate in mL/min. Fractional excretion (FE) was calculated as the clearance of x divided by the clearance of creatinine ($C_x/C_{\text{creat}}$) on the 24-hour urine collection. Fractional distal reabsorption of Na (FDRNa) was estimated as $\left[\frac{(FE_{\text{Li}} - FE_{\text{Na}})}{FE_{\text{Na}}/100}.\right]^{13}$

Analytic Methods

Urinary and plasma sodium as well as potassium were measured by flame photometry (IL-943, Instrumentation Laboratory) and creatinine was measured by the picric acid method (Cobas-Mira, Roche). Urinary and plasma concentrations of inulin and PAH were determined by photometry (Autoanalyzer II-Technicon, Bran & Luebbe). Endogenous trace lithium was measured by atomic absorption spectrophotometry.14 PRA15 and aldosterone16 were determined as previously described.

Statistical Analysis

Data are expressed as mean $\pm$ SEM. The statistical significance of differences between the 2 periods was evaluated by paired Student’s t test. A level of $P<0.05$ was considered statistically significant. The statistical significance of differences between the 3 study groups was evaluated by 1-way ANOVA test, followed by unpaired Student’s t tests if a level of $P<0.05$ was reached. In hypertensive patients, the blood pressure response to salt was regarded as a continuous variable. Therefore, data were analyzed in tertiles of changes in ambulatory blood pressure ($\Delta$ABPM) from one week to the other: $\Delta$ABPM = ABPMHS – ABPMLS. The statistical significance of differences between tertiles was evaluated with a 1-way ANOVA test, followed by unpaired Student’s t tests. A $x^2$ test was calculated to compare the ratio of men to women between tertiles. To evaluate relations between variables, Pearson’s correlation coefficients were calculated by means of linear regression analysis. Multiple regression analysis was performed to study the parameter that independently contributed to the blood pressure responsiveness to salt in hypertensive patients. A final model was created containing variables significantly correlated ($P<0.05$) to $\Delta$ABPM in univariate analysis and the changes in ERPF, which have been shown to contribute to the model (see Discussion). Because of the small number of patients included in the study, only 3 independent variables were included in the model as predictors of the blood pressure responsiveness to salt. This was done in the hypertensive group only and in all subjects together with normotension or hypertension.

Results

The clinical characteristics of the 3 groups are presented in Table 1. Hypertensive patients and their age-matched normotensive controls were significantly older than the young control group ($P<0.001$). In addition to baseline mean blood pressure, hypertensives also had a higher body weight than did normotensive controls. Serum electrolytes were comparable in all 3 groups.

Renal Response to Salt in Hypertensive Patients and Normotensive Control Subjects

Table 2 shows the blood pressure and the renal response to salt in the 3 groups studied. As mentioned earlier, sodium excretion was significantly lower in the young control subjects ($U_{\text{Na}V}: 14 \pm 2.4$ mmol/24 h) than in hypertensives ($U_{\text{Na}V}: 72 \pm 8.2$ mmol/24 h) and age-matched normotensives ($U_{\text{Na}V}: 64 \pm 14$ mmol/24 h) because of a stricter diet control. This is reflected also by lower FENa and FEli during salt depletion ($P<0.001$). Whereas in hypertensive patients, blood pressure decreased significantly on a low salt diet ($P<0.001$ low versus high salt diet), no salt-induced change in blood pressure was observed in either control group. A marked and significant increase in FEli was found in young normotensives when the diet was changed from a low to a high sodium content ($P<0.001$). In hypertensive patients and age-matched control subjects, although the change in FEli was comparable, an increase in FEli with salt loading was found only in...
normotensive subjects ($P<0.05$). The changes in fractional distal reabsorption of sodium (FDR$_{Na}$) were comparable in all 3 groups, although FDR$_{Na}$ tended to be slightly lower in patients on a high sodium diet, indicating some distal compensation necessary to maintain sodium balance.

Table 2 also depicts the changes in renal hemodynamics measured in hypertensives and young normotensive subjects. Changing the diet from a low to a high sodium content resulted in a marked increase in GFR and ERPF in control subjects, whereas in hypertensive patients, no significant change in renal hemodynamics was found.

**Renal Sodium Handling in Hypertension by Tertiles of Blood Pressure Response to Salt**

To avoid categorizing patients according to arbitrary criteria of salt sensitivity, hypertensive patients were analyzed by tertiles of their blood pressure response to changes from high to low sodium diet, based on daytime ambulatory blood pressure. The first tertile ($n=12$) corresponded to patients with the smallest changes in blood pressure and the third tertile ($n=13$) to those with the largest salt-induced changes in blood pressure. The baseline characteristics of the 3 tertiles including blood pressure were comparable except for age. Indeed, patients of the third tertile were slightly older (48 years versus 41 in the second tertile and 39 years in the first tertile, $P=NS$). The proportion of men to women was similar in each tertile ($\chi^2=0.67; df=2; P=NS$). The proportion of patients going from the low to the high sodium diet was also comparable in the 3 tertiles.

Table 3 presents the blood pressure and the renal and hormonal responses to salt in the tertiles. The diet-induced changes in sodium excretion ($U_{Na}\cdot V$) were comparable in the

**TABLE 1. Baseline Characteristics of the Groups**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertensives</th>
<th>Young Normotensives</th>
<th>Age-Matched Normotensives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>38</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>142±2.0</td>
<td>126±2.7‡</td>
<td>116±2.6‡</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>95±1.1</td>
<td>72±1.6‡</td>
<td>76±1.8‡</td>
</tr>
<tr>
<td>Age, yr (range)</td>
<td>43 (21-61)</td>
<td>23 (20-37)‡</td>
<td>40 (28-64)§</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4±0.7</td>
<td>22.1±0.5†</td>
<td>22.6±0.8*</td>
</tr>
<tr>
<td>Positive family history of hypertension</td>
<td>23</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Serum Na, mmol/L</td>
<td>142±0.4</td>
<td>141±0.4</td>
<td>142±0.4</td>
</tr>
<tr>
<td>Serum K, mmol/L</td>
<td>4.2±0.1</td>
<td>4.1±0.1</td>
<td>4.4±0.1</td>
</tr>
<tr>
<td>Serum Li, mmol/L</td>
<td>0.22±0.02</td>
<td>0.14±0.02</td>
<td>0.21±0.02</td>
</tr>
</tbody>
</table>

BP indicates blood pressure at inclusion visit; BMI, body mass index.

Values are mean±SEM.

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$ vs hypertensives.

**TABLE 2. Systemic and Renal Responses to Salt in Hypertensive Patients and Normotensive Control Subjects**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LS</th>
<th>HS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>104±1.6</td>
<td>109±1.5§</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76±1.3</td>
<td>76±1.4</td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>74.4±2.4</td>
<td>75.4±2.4§</td>
</tr>
<tr>
<td><strong>Electrolyte excretion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$U_{Na}\cdot V$, mmol/24 h</td>
<td>72±8</td>
<td>255±17§</td>
</tr>
<tr>
<td>FE$_{Na}$, %</td>
<td>0.30±0.06</td>
<td>1.00±0.10§</td>
</tr>
<tr>
<td>FE$_{K}$, %</td>
<td>11.9±0.6</td>
<td>11.7±0.6</td>
</tr>
<tr>
<td>FE$_{Li}$, %</td>
<td>20.7±1.5</td>
<td>20.5±1.7</td>
</tr>
<tr>
<td>FDR$_{Na}$, %</td>
<td>98.3±0.2</td>
<td>93.5±0.7§</td>
</tr>
<tr>
<td><strong>Renal hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>109±3</td>
<td>113±4</td>
</tr>
<tr>
<td>ERPF, mL/min</td>
<td>512±25</td>
<td>522±22</td>
</tr>
</tbody>
</table>

LS indicates low-salt diet; HS, high-salt diet; a, office blood pressure; and b, creatinine clearance.

Values are mean±SEM.

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$ vs hypertensives on the same salt diet; § $P<0.05$, ¶ $P<0.01$, ‡ $P<0.001$ vs LS.
between FE Li and FE Na, indicating an inappropriate response of whereas salt-sensitive patients have an inverse relation be-
mediate pattern. This suggests that salt-insensitive hyperten-
sion patients of the second tertile showed an inter-
porate in the tertiles when calculated on a high sodium diet. On a low salt diet, however, FDRNa was higher
segments was comparable in the tertiles when calculated on a high sodium intake. Because of the small number
patients in each tertile, these differences did not reach statistical significance. The response of PRA and plasma
aldosterone levels to the change in sodium diet did not differ among the tertiles.

Univariate and Multivariate Analysis in Hypertensive Tertiles

Univariate correlation coefficients between the salt-induced changes in ambulatory blood pressure and various clinical parameters are shown in Table 4. The blood pressure response to salt correlated positively with age \( (r = 0.34, P = 0.036) \) and negatively with the changes in FE Li \( (r = -0.37, P = 0.029) \) (Figure 2). No significant correlation was found between the salt sensitivity of blood pressure and ERPF or the changes in ERPF \( (r = -0.06) \) (Figure 2). However, the salt-induced changes in FE Li were weakly correlated with the changes in renal plasma flow \( (P = 0.040) \).

The results of the multivariate analysis are also presented in Table 4. On the basis of our hypothesis and the known effect of age and renal hemodynamics on the salt sensitivity of blood pressure, 3 independent variables were considered as correlates of the salt-induced change in blood pressure, that is, age, the change in ERPF, and the change in FE Li. No collinearity was found between these variables. A slight correlation was observed between the change in ERPF and the change in FE Li \( (P < 0.05) \). According to this analysis, the 3 variables were significantly and independently associated with the changes in ambulatory blood pressure. With this model, 31% of the variance of the pressure response to salt could be predicted (adjusted \( R^2 = 0.31 \)). When combining hypertensive and normotensive subjects in the multivariate analysis, these 3 variables remained significant correlates of
the blood pressure response to salt, although in this case age became a more dominant factor.

**Discussion**

Our results show that renal sodium handling by the proximal tubule as measured by the FE_{Li} is an independent determinant of the blood pressure response to salt in hypertensive patients. The data support our hypothesis that patients whose blood pressure is insensitive to salt have a normal pattern of adaptation of proximal and distal sodium reabsorption to changing salt intake, whereas those whose blood pressure depends markedly on sodium intake have an inverse pattern characterized by an inadequate proximal sodium retention on low salt and an inability to excrete the excess of salt on a high sodium diet. Age and the renal hemodynamic response to salt are 2 additional determinants of the blood pressure response to salt in hypertension. The contribution of proximal sodium reabsorption appears to be independent of the salt-induced variations in renal hemodynamics.

An increased proximal reabsorption of sodium in hypertension has been postulated by several investigators using different methods and protocols to assess renal sodium handling. However, these observations have been the matter of some considerable debate because decreases as well as increases or no difference in lithium clearance have been found in hypertensive patients or subjects predisposed to hypertension. We have suggested previously that the entire FE_{Li}/FE_{Na} relation differs in hypertension when compared with normotensive subjects. Albeit a different protocol was used in which each patient received randomly a high and low salt diet for 1 week, the present study largely confirms

**TABLE 4. Univariate and Multivariate Analysis of Factors Affecting Blood Pressure Responsiveness to Salt in Hypertensive Patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pearson Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.341</td>
<td>0.036</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.015</td>
<td>0.113</td>
</tr>
<tr>
<td>Fasting blood sugar</td>
<td>0.123</td>
<td>0.474</td>
</tr>
<tr>
<td>ΔFE_{Na}</td>
<td>−0.057</td>
<td>0.736</td>
</tr>
<tr>
<td>ΔFE_{Li}</td>
<td>−0.365</td>
<td>0.029</td>
</tr>
<tr>
<td>ΔFDR_{Na}</td>
<td>0.115</td>
<td>0.497</td>
</tr>
<tr>
<td>ΔGFDR</td>
<td>0.015</td>
<td>0.933</td>
</tr>
<tr>
<td>ΔERPF</td>
<td>−0.160</td>
<td>0.358</td>
</tr>
<tr>
<td>ΔWeight</td>
<td>−0.195</td>
<td>0.239</td>
</tr>
<tr>
<td>ΔPRA</td>
<td>0.081</td>
<td>0.628</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.358</td>
<td>0.022</td>
</tr>
<tr>
<td>ΔFE_{Li}</td>
<td>−0.531</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔERPF</td>
<td>−0.336</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Adjusted $R^2$=0.309.

**Figure 1.** Changes in mean arterial pressure (MAP), FE_{Na} and FE_{Li}, and ERPF in hypertensive patients according to tertiles of blood pressure response to salt (high salt, low salt). Values are mean±SEM; *P<0.05, ***P<0.001 vs first tertile.

**Figure 2.** Relation between changes in mean arterial pressure (MAP) and changes in FE_{Li} (top) and changes in ERPF (bottom) in hypertensive patients.
our initial observation, hypertensive patients as a group being again characterized by virtually no change in $\text{FE}_{\text{Li}}$ when varying salt intake whereas in normotensive control subjects, a steeper $\text{FE}_{\text{Li}}/\text{FE}_{\text{Na}}$ relation was found. In the present study, renal hemodynamics were also measured under the various experimental conditions of salt intake. In accordance with several earlier observations, a discrepant response in ERPF and GFR was observed in hypertensive patients and normotensive control subjects. Thus, high sodium intake induced an increased flow and GFR in normotensive control subjects, whereas ERPF and GFR did not change in hypertensive patients during high salt intake. This would seem to confirm the hypothesis that hypertensive patients have an increased preglomerular vascular tone.

The main finding of the present study is the observation that the pattern of changes in $\text{FE}_{\text{Li}}$ in response to variations in salt intake is an important and independent correlate of the salt sensitivity of blood pressure in hypertension. Methodologically, the concept of salt sensitivity has been criticized mainly for its lack of reproducibility and for its arbitrary definition, which does not take into account that salt sensitivity is a continuous variable. We have therefore chosen to analyze patients according to tertiles of their blood pressure responses to salt. In addition, ambulatory blood pressure recording was used to improve the precision and reproducibility of blood pressure measurements. With this approach, we found that the salt-induced changes in $\text{FE}_{\text{Li}}$ were comparable in sodium-insensitive patients (first tertile) and normotensive control subjects. However, in salt-sensitive patients of the third tertile, $\text{FE}_{\text{Li}}$ was higher on low salt and lower on high salt, suggesting an inappropriate modulation of proximal tubular sodium handling. Interestingly, salt sensitivity appeared to be due essentially to a fall in blood pressure occurring on low salt, blood pressure being comparable to the other tertiles on the high salt diet. Despite the decrease in blood pressure, the $\text{FE}_{\text{Li}}$ was not reduced in salt-sensitive patients. These observations tend to confirm the hypothesis that proximal reabsorption of sodium could be a determinant predicting salt sensitivity. An increased proximal reabsorption of sodium has also been found in hypertensive patients bearing the 1-Trp $\alpha$-adducin variant, who are particularly salt sensitive. Other investigators have reported that proximal sodium reabsorption determines the blood pressure response to salt in normotensive subjects and is a predictive factor for the development of hypertension.

A difference in the renal hemodynamic response to salt also appears to determine how sodium intake affects blood pressure. In accordance with previous findings, the changes in ERPF were indeed an independent determinant of the blood pressure response to salt in hypertensives in our multivariate analysis. In this respect, several investigators have found that sodium induces renal vasoconstriction in salt-sensitive patients and renal vasodilation in salt-resistant subjects. A similar pattern was observed in our hypertensive population, although the differences did not reach statistical significance. It is generally assumed that the impaired sodium handling found in hypertensive patients is related to the incapacity of the kidney to increase its blood flow in response to a high sodium intake. In agreement with this idea, a weak correlation was found between the changes in $\text{FE}_{\text{Li}}$ and the variations in ERPF, as one would expect from the tubuloglomerular feedback mechanism. However, $\text{FE}_{\text{Li}}$ correlated very well with the salt-induced changes in blood pressure, and this was not the case for the changes in ERPF. Moreover, in our multivariate analysis, $\text{FE}_{\text{Li}}$ appears to be a more robust independent factor predicting the change in blood pressure than is ERPF. Thus, our data suggest that proximal sodium reabsorption could be a determinant of salt sensitivity independent of the renal hemodynamic response. Yet, the mechanism leading to the impaired sodium handling remains to be determined, and one cannot exclude a priori that the same pathogenic pathway accounts for the renal hemodynamic and the tubular responses.

The renin-angiotensin system is still another important factor modulating the blood pressure response to salt. Thus, an inadequate or lacking response of the renin-angiotensin system leading to an insufficient renal vasodilation on a high sodium intake appears to contribute to the salt sensitivity of blood pressure. In our patients, comparable values of PRA and aldosterone were found in each tertile. In contrast to the observation of van Paassen et al., this finding would suggest that the altered proximal reabsorption of sodium is independent of the response of the renin-angiotensin system. Clearly, additional specific studies should be conducted to clarify the role of the various hormonal responses to changes in sodium intake.

In conclusion, the results of this study demonstrate that impaired sodium handling by the renal proximal tubule is an independent determinant of the blood pressure responsiveness to salt in hypertension. Age and the renal hemodynamic response are also important factors, but the disturbed renal tubular sodium reabsorption is independent of age or the capacity of the kidney to increase its blood flow on a high salt diet. Thus, the salt sensitivity of blood pressure is probably the result of a primary defect in tubular sodium reabsorption associated with an increase in preglomerular vascular resistance and in some patients with a reduction in whole kidney ultrafiltration, depending on age and the presence or absence of renal disease.

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Proximal Sodium Reabsorption: An Independent Determinant of Blood Pressure Response to Salt

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