Relation of Plasma Renin to End Organ Damage and to Protection of K⁺ Feeding in Stroke-Prone Hypertensive Rats

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With the technical assistance of Antoinette Rookard

We studied the effects of regular diet (0.35% NaCl/1.1% potassium), high sodium diet (4% NaCl/0.75% potassium), or high sodium and high potassium diet (4% NaCl/2.11% potassium) on blood pressure, plasma renin activity, renal and cerebrovascular lesions, and incidence of stroke and mortality in male stroke-prone spontaneously hypertensive rats (SHRSP). In the first 4 weeks, the rise in blood pressure was higher in high NaCl than in high NaCl/high potassium or regular diet groups. However, by 8 and 12 weeks, the blood pressure in all three groups was similar. After 4 weeks of diet, plasma renin activity was similar in the three groups (3.4±0.8, 4.1±0.9, and 5.2±1.6 ng/ml/hr, in high NaCl, high NaCl/high potassium, and regular diet groups, respectively) and were not related to sodium excretion. After 8 weeks, plasma renin activity was significantly increased only in the high NaCl group (13.7±3.7 ng/ml/hr), and by 12 weeks plasma renin activity was significantly higher in the high NaCl group (25.3±3.6 ng/ml/hr) than in the high NaCl/high potassium (11.1±2.9 ng/ml/hr) or in the regular diet (7.8±4.6 ng/ml/hr) groups. Moderate to severe renal vascular lesions were first detected in the high NaCl group by 8 weeks of diet. At 12 weeks, renal vascular damage index (RVDI), estimated histologically, was significantly higher in the high NaCl group (RVDI = 79±14) than in the high NaCl/high potassium (RVDI = 40±11) and regular diet (RVDI = 7.8±4.6) groups. At this time, incidence of stroke was 81% in high NaCl, 24.5% in high NaCl/high potassium, and 7.7% in regular diet groups. The data demonstrate that: 1) the increase in mortality, stroke, and renal and cerebrovascular lesions in SHRSP fed a high sodium diet is associated with a paradoxical rise in plasma renin activity; 2) the protective effect of high potassium in SHRSP fed a high potassium diet is related to a lower blood pressure at 2-4 weeks and a lower plasma renin activity, but not a lower blood pressure at 8-12 weeks; 3) this rise in plasma renin activity demonstrates that a high potassium diet suppresses or delays a primary or secondary paradoxical rise in plasma renin activity and thus, angiotensin II in the rats fed a high sodium diet. This action together with possible direct effects of potassium in the vasculature contributes to the protective effect on end organ damage and stroke in SHRSP. (Hypertension 1990;15:318-326)

Sodium chloride toxicity and a protective effect of potassium has been a subject of investigation since the last century.¹ The pioneering studies of Meneely et al² showed that dietary potassium supplementation protects rats from premature mortality due to high sodium chloride intake. Potassium feeding was effective in increasing survival, but it lowered blood pressure only in the groups with the highest sodium intakes.

More recently, studies by Tobian and his associates³-⁵ demonstrated impressive effects of dietary potassium administration in stroke-prone spontaneo
ously hypertensive rats (SHRSP) to protect against the development of stroke, to prolong survival, and to prevent structural lesions in small arterial vessels. They reported that the beneficial effects were demonstrable in the absence of any significant reduction in arterial blood pressure. Their data may have relevance to humans as high dietary potassium intake has been found to be associated with a low incidence of stroke in a 12-year prospective study in an adult population. In this study, an inverse correlation was found between 24-hour potassium intake and blood pressure. Furthermore, high potassium intake was protective independent of effects on blood pressure.

The mechanisms underlying the protective role of potassium supplementation in SHRSP are still unclear. Potassium might interfere with a number of mechanisms that have been implicated in the adverse effects of high sodium intake in SHRSP. Such mechanisms include changes in extracellular fluid volume, activation of central or autonomic nervous system, enhanced vascular reactivity to pressor agents, direct effect on smooth muscle, renal hemodynamic changes, and changes in the renin-angiotensin system.

Previous research from our laboratory has defined the effects of dietary potassium deprivation and administration on plasma renin activity (PRA) in both animals and human subjects. We also detected a positive correlation between PRA and the development of stroke and heart attack in humans. Furthermore, the activity of the renin system has been implicated in vascular injury, including stroke, in a variety of clinical and experimental situations.

The present study was designed to investigate further the role of dietary sodium and potassium and the renin-angiotensin-aldosterone system in the pathogenesis of stroke in SHRSP.

Methods

SHRSP were obtained from the colony at the University of Iowa (Iowa City, Iowa). Male, 6-week-old rats were group housed under controlled conditions of light and temperature, with water and food intake ad libitum. Animals were divided randomly into three groups according to diet. The first group was fed a Japanese-style diet (Ziegler Bros., Inc., Gardners, Pennsylvania) containing 4% NaCl and 0.75% KCl (high NaCl group, n=36). The second group received an identical diet containing 4% NaCl with a K-Citrate supplement (final potassium content, 2.11%) (high NaCl/high potassium group, n=37). A third group received a regular rat chow (Formulab Chow, 5008) containing 0.35% NaCl and 1.1% KCl (regular diet group, n=33). Rats were maintained on their assigned diets and studied over a period of 12 weeks. Rats were examined daily for clinical signs of stroke and survival throughout the study. Clinical assessment of stroke was based on the presence of evident and stable hemiplegia, akinesis, lethargy, and hyporesponsiveness according to the symptomatological classification described by Volpe et al. Renin and Stroke in SHRSP.
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**Blood Pressure and Body Weight**

Figure 1 (upper panel) shows the blood pressure values measured biweekly from 0 to 12 weeks in all rats studied in the three different diet groups. Blood pressure increased in all groups throughout the 12-week study. However, rats fed high sodium had significantly higher blood pressure at 2 and 4 weeks compared with rats fed high sodium/high potassium and those fed regular chow (week 2, $t=4.01, p<0.001$ and $t=2.81, p<0.05$; week 4, $t=2.99, p<0.05$ and $t=3.12, p<0.01$ against high sodium/high potassium and regular chow, respectively). High potassium diet led to a lesser rise in blood pressure in the first 4 weeks of the study. At 6, 8, 10, and 12 weeks, no blood pressure differences were observed among the groups.

The analysis of growth determined by biweekly measurements of body weight is shown in Figure 1 (lower panel). No difference in body weight among the groups was observed during the first 4 weeks. At weeks 6, 8, 10, and 12, rats fed a normal chow continued to grow and had significantly higher body weight when compared with rats fed a high sodium or a high sodium/high potassium diet.

**Plasma Renin Activity and Urinary Sodium and Potassium Excretion**

PRA did not change significantly throughout the study in SHRSP maintained on a regular diet (Figure

**Statistical Analysis**

Statistical analysis was performed with analysis of variance. Adjustments for multiple comparisons were made by using the method of Bonferroni. Correlation coefficients were calculated by parametric and nonparametric methods. With death or stroke as end points, separate survival analyses were performed with the life-table method. Mantel-Cox and Breslow statistics were used for testing the equality of survival curves. Stepwise regression analysis (Cox models) using PRA values, blood pressure, and diet as covariants was performed. Results are expressed as mean±SEM.
TABLE 1. Effects of the Three Dietary Regimens on Other Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>U_{\text{NaV}} (mg/24 hr)</td>
<td>Regular diet</td>
<td>n.a.</td>
<td>n.a.</td>
<td>22.4±8</td>
<td>32.3±4</td>
</tr>
<tr>
<td></td>
<td>High NaCl</td>
<td>n.a.</td>
<td>40.6±12</td>
<td>107±21*</td>
<td>107±25*</td>
</tr>
<tr>
<td></td>
<td>High NaCl/High K</td>
<td>n.a.</td>
<td>25.4±8</td>
<td>107±25*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regular diet</td>
<td>66±19</td>
<td>142±33*</td>
<td>183±39*</td>
<td>71±4</td>
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<tr>
<td>ANF (fmol/ml)</td>
<td>High NaCl</td>
<td>176±42*</td>
<td>113±37*</td>
<td>86±16</td>
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<tr>
<td></td>
<td>High NaCl/High K</td>
<td>144±62*</td>
<td>106±17*</td>
<td>85±8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regular diet</td>
<td>n.a.</td>
<td>4.3±3</td>
<td>7.5±3</td>
<td></td>
</tr>
<tr>
<td>PA (ng/dl)</td>
<td>High NaCl</td>
<td>1.1±1</td>
<td>18.5±8†</td>
<td>22±12*†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High NaCl/High K</td>
<td>2.2±1</td>
<td>17.6±13</td>
<td>23±10†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regular diet</td>
<td>45±2</td>
<td>45.2±2</td>
<td>40.3±1</td>
<td>44.5±0.4</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>High NaCl</td>
<td>45.8±1</td>
<td>41.6±1</td>
<td>42.6±2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High NaCl/High K</td>
<td>44.4±1</td>
<td>42.2±1</td>
<td>41.7±1</td>
<td></td>
</tr>
</tbody>
</table>

U_{\text{NaV}}, total urinary protein excretion; ANF, plasma atrial natriuretic factor; PA, plasma aldosterone; Hct, peripheral hematocrit. n=27 rats given regular diet; n=38 rats given high NaCl diet; and n=37 rats given high NaCl/high potassium diet.

*p<0.05 vs. 0 or 4 weeks.
†p<0.05 vs. regular diet.

2). After 4 weeks of diet, PRA did not differ among the groups: 5.2±1.6, 4.1±0.9, and 3.4±0.8 ng/ml/hr in regular chow, high NaCl and high NaCl/high potassium groups, respectively, although there was a significantly higher sodium excretion (U_{\text{Na}}V) in both high NaCl groups. After 8 weeks, PRA was markedly elevated in the high NaCl group as compared with the 4-week measurement and compared with rats on regular chow or on high NaCl/high potassium (13.7±3.9 vs. 13±2.1 ng/ml/hr). The lack of significant differences among groups at 8 weeks was partly due to the large range of PRA values in the high NaCl group. After 12 weeks, the difference in PRA between the high NaCl group and the other two groups was greater and statistically significant (25.3±3.6 in high NaCl vs. 11.1±2.9 in high NaCl/high potassium and 7.8±1.8 ng/ml/hr in regular chow). PRA was not significantly elevated in the potassium-supplemented group as compared with the regular diet group. At this time, a marked rise in PRA occurred in six rats, whereas the remaining eight showed relatively low renin values (see also Figure 4). The rise in PRA in these two groups occurred despite the high sodium intake, which would normally be expected to suppress PRA (Figure 2).

As expected, urinary potassium excretion was highest in the high NaCl/high potassium group. It did not differ among the regular diet and the high NaCl groups (Figure 2).

Effect of the Diets on Other Parameters

At 12 weeks, total urinary protein excretion was significantly higher in both high NaCl groups compared with the regular diet group. In the rats receiving the potassium supplement, urinary protein loss was comparable on average to that in the high NaCl group. Analysis of the individual rats showed, however, that protein loss was remarkable only in the rats with considerable renal lesions and elevated PRA.

![Cumulative proportion of stroke-exempt rats](https://hyper.ahajournals.org/)

**Figure 3.** Line graph showing cumulative proportion of stroke-exempt (upper panel) and cumulative proportion of surviving stroke-prone spontaneously hypertensive rats (lower panel) estimated on population exposed at beginning of each week in three dietary groups. Mantel-Cox test computed to evaluate equality of curves defined by group, and generalized Wilcoxon statistics showed no significant differences between regular diet group and high NaCl/high potassium group. Same tests showed significant differences between high NaCl group and both high NaCl/high potassium (both p values <0.01) and regular diet (both p<0.01) groups.
TABLE 2. Stepwise Multiple Regression Analysis Using Diet, Plasma Renin Activity, and Absolute Changes in Blood Pressure as Covariates

<table>
<thead>
<tr>
<th>A. Step no. 0</th>
<th>Log likelihood</th>
<th>$\chi^2$</th>
<th>$p$ value</th>
</tr>
</thead>
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<tr>
<td>Diet</td>
<td>-82.4</td>
<td>5.44</td>
<td>0.0197</td>
</tr>
<tr>
<td>PRA</td>
<td>-79.3</td>
<td>11.72</td>
<td>0.0006</td>
</tr>
<tr>
<td>$\Delta BP_2$</td>
<td>-83.87</td>
<td>2.55</td>
<td>0.1106</td>
</tr>
<tr>
<td>$\Delta BP_4$</td>
<td>-83.65</td>
<td>3.01</td>
<td>0.0830</td>
</tr>
<tr>
<td>$\Delta BP_E$</td>
<td>-85.15</td>
<td>0.00</td>
<td>0.9857</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Step no. Variable entered</th>
<th>Log likelihood</th>
<th>Improvement $\chi^2$</th>
<th>Global $\chi^2$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>...</td>
<td>-85.1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1</td>
<td>PRA</td>
<td>-79.29</td>
<td>11.72</td>
<td>12.852</td>
</tr>
<tr>
<td>2</td>
<td>$\Delta BP_2$</td>
<td>-76.54</td>
<td>5.499</td>
<td>19.005</td>
</tr>
</tbody>
</table>

PRA, plasma renin activity; $\Delta BP_2$, $\Delta BP_4$, $\Delta BP_E$, absolute change in blood pressure at 2 weeks, 4 weeks, and end of study, respectively.

Thus, significant correlations were found between PRA and 24-hour urinary protein excretion ($r=0.558$, $n=38$, $p<0.05$) and between the RVDI and 24-hour urinary protein excretion ($r=0.542$, $n=36$, $p<0.05$) at 12 weeks.

Plasma ANF was elevated after 4 weeks in all three groups compared with baseline values (Table 1). This increase was sustained at 8 weeks, but at 12 weeks ANF in all three groups had returned to values not different from those obtained at the beginning of the study.

After 4 weeks of diet, plasma aldosterone (Table 1) was not significantly different between the two groups fed high NaCl. However, between 4 and 8 weeks, plasma aldosterone increased markedly in both groups receiving high NaCl intake, so that at both 8 and 12 weeks of diet, plasma aldosterone was higher in both high NaCl groups compared with the normal salt group. A direct effect of potassium to stimulate aldosterone biosynthesis is reflected in the lack of difference in plasma aldosterone levels between high NaCl and high NaCl/high potassium groups at weeks 8 and 12 despite the lower PRA in the high potassium group.

Peripheral hematocrits (Table 1) did not change significantly during the dietary manipulations and did not differ among the groups.

Analysis of Stroke Incidence and Survival

A life table and survival function analysis of the study population is shown in Figure 3. The upper panel shows the cumulative proportion of exposed SHRSP exempt from stroke at the beginning of each interval. At 12 weeks, 92.3% of the rats on the regular diet group, 75.5% in the high NaCl/high potassium group, and only 18.9% in the high NaCl group ($p<0.0001$ vs. both other groups) were exempt from stroke. The lower panel of Figure 3 depicts the cumulative proportion of surviving SHRSP at the beginning of each interval. After 12 weeks, survival was 95% in the rats on the regular diet, 74.7% in the high NaCl/high potassium group, and 49.5% in the high NaCl group ($p<0.05$ vs. both other groups). The incidence of stroke and survival was not statistically

TABLE 3. Distribution of Renal Lesions in the Three Dietary Groups of Stroke-Prone Spontaneously Hypertensive Rats During the Course of the Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of rats</th>
<th>Kidney disease score*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 (%)</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular diet</td>
<td>(n=6)</td>
<td>100</td>
</tr>
<tr>
<td>High NaCl</td>
<td>(n=8)</td>
<td>100</td>
</tr>
<tr>
<td>High NaCl/High K</td>
<td>(n=9)</td>
<td>100</td>
</tr>
<tr>
<td>After 8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular diet</td>
<td>(n=6)</td>
<td>100</td>
</tr>
<tr>
<td>High NaCl</td>
<td>(n=9)</td>
<td>55.6</td>
</tr>
<tr>
<td>High NaCl/High K</td>
<td>(n=10)</td>
<td>70.0</td>
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<tr>
<td>After 12 weeks</td>
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<td></td>
</tr>
<tr>
<td>Regular diet</td>
<td>(n=13)</td>
<td>76.9</td>
</tr>
<tr>
<td>High NaCl</td>
<td>(n=12)</td>
<td>0</td>
</tr>
<tr>
<td>High NaCl/High K</td>
<td>(n=15)</td>
<td>26.7</td>
</tr>
</tbody>
</table>

*0, no lesions; ±, occasional, early necrosis of small arteries and arterioles; 1+, necrosis of arteries and arterioles with focal secondary tubular necrosis and regeneration; 2+, moderate arterial necrosis with regenerative changes of cortical and medullary parenchyma; 3+, extensive necrosis of arteries and arterioles with focal infarcts and diffuse tubular regenerative changes.
different between the regular diet group and the high NaCl/high potassium group.

**Relation Between Diet, Plasma Renin Activity, Blood Pressure, and Stroke**

To analyze the influence of the different diets on PRA, blood pressure, and the incidence of stroke, and the interrelation among these parameters, a multiple stepwise regression was performed using dietary group, PRA at sacrifice, and the absolute change in blood pressure after 2 weeks (ΔBP2), 4 weeks (ΔBP4), and end of study (ΔBPEx) as covariates (Cox proportional hazards regression model).

The results are summarized in Table 2. At step 0, PRA and diet significantly affected the stroke event rate. However, after stepwise regression only PRA and the absolute change in blood pressure after 4 weeks contributed significantly to the stroke event rate.

**Renal Lesions**

Table 3 shows the distribution of the renal lesions in the kidney in the three dietary groups. At 4 weeks, no detectable lesions were observed in any rats. At 8 weeks, none of the SHRSP on a regular diet showed evidence of kidney lesions, whereas in both groups fed high NaCl a few rats showed moderate to marked vascular lesions (4 of 10 in the high NaCl group, 3 of 10 in the high NaCl/high potassium group). At 12 weeks, only 7.7% of the SHRSP on a regular diet showed renal damage. In contrast, 75% of the high NaCl group and 46.6% of the high NaCl/high potassium group showed a renal score ranging between 2+ and 3+. The RVDI obtained in the high NaCl group (79±14) was higher than that estimated in the high NaCl/high potassium group (40±11, p<0.05) or in the regular diet group (7.8±4.6, p<0.01). The values obtained in the regular diet group did not differ significantly from those of the high NaCl/high potassium rats.

Renal lesions were mostly limited to the inner cortex. Focal involvement of the outer cortex and the medulla occurred only with the most advanced degree of kidney damage.

Figure 4 illustrates that in all groups, PRA values elevated above 10 ng/ml/hr were invariably associated with considerable vascular disease (RVDI>12), whereas PRA values less than 10 ng/ml/hr were associated with little or no renal vascular damage. Consequently, PRA and RVDI were significantly correlated (Kendall's τ=0.591, df=36, p<0.0001).

Close inspection of Figure 4 also shows that potassium supplement completely prevented development of renal vascular disease and increased PRA in eight of 14 rats. The remaining six developed renal pathological lesions not unlike those observed in the high NaCl rats. In contrast, only one of 11 high NaCl rats did not show increased PRA and renal vascular disease.

A highly significant correlation was also found between the RVDI and the ischemic stroke score (r=0.818, p<0.001).

**Discussion**

One of the most striking findings of the current study is the paradoxical rise in renin that occurred during high sodium intake in SHRSP. Such an increase in PRA, which was associated with an extremely high incidence of stroke and increased mortality, was not observed in SHRSP on normal sodium intake, in which only one nonfatal stroke was observed. The rise in renin was significantly attenuated in the high salt SHRSP that were supplemented with potassium, in which the incidence of stroke and mortality was not significantly different from the group on regular diet. These results extend previous findings showing that high salt intake accelerates the development of malignant hypertension in SHRSP and that dietary potassium supplementation leads to a protection against stroke.

The unusual behavior of the renin-angiotensin system in SHRSP raises two important issues: 1) the possible role of high circulating levels of renin and angiotensin II in the genesis of the vascular lesions and 2) the mechanisms leading to the alteration of normal sodium/renin relation.

Previous studies have shown a progressive increase in plasma renin in the late stages of hypertension in SHRSP maintained on a normal sodium intake. In some of those studies, high levels of renin and hence angiotensin II were associated with a higher incidence of cerebrovascular lesions and stroke, although on average the rise in plasma renin was not shown to occur before the development of vascular complications. Therefore, it was concluded that high renin levels did not have a pathogenic role but were an indicator of underlying renal angionecrosis.
On the other hand, recent observations support an involvement of the renin-angiotensin system in the accelerated development of vascular lesions in this form of malignant hypertension. Malignant hypertension and stroke rapidly develop in stroke-resistant SHR after receiving a transplanted kidney from SHRSP, suggesting that the kidney of SHRSP possesses properties that increase the risk of stroke. Also, studies in salt-loaded SHRSP given converting enzyme inhibitors show a decrease in mortality and kidney lesions, suggesting that the renin-angiotensin system is involved in the development of the disease. In our study, PRA was not suppressed after 4 weeks of diet despite a fourfold to sixfold increase in the distal delivery of sodium. At this time, renal vascular lesions were not evident, which suggests that SHRSP cannot normally suppress renin release in response to high sodium intake. In addition, after 12 weeks of diet, proteinuria was comparable in the high NaCl group and in the high NaCl/high potassium group, suggesting that an alteration in renal function is not solely responsible for the different morbidity and mortality observed in the two groups.

On the basis of these observations, it might be speculated that renal damage expresses its pathogenic effect in part through elevated production of renin. Such a hypothesis is further supported by the effects of converting enzyme inhibitors in SHRSP. They prevent the development of hypertension, cerebrovascular lesions and stroke, and kidney lesions. Protection from renal lesions by converting enzyme inhibitors has also been reported to be independent of a decrease in blood pressure. Obviously the antihypertensive effect of converting enzyme inhibitors in this model could also account in part for the protective effect, as other antihypertensive drugs can prevent the development of hypertension in SHRSP. On the other hand, Tobian and coworkers showed that both incidence of stroke and mortality rate are reduced by potassium supplement despite the lack of any hypotensive effect.

In contrast, our data demonstrate that the rate of rise in blood pressure at 2 and 4 weeks may be an important contributing factor to the incidence of end organ damage and survival. During the first 4 weeks, blood pressure levels in rats fed a high potassium diet were not different from those fed a regular diet and were significantly lower than in the rats fed a high sodium diet without potassium supplementation. An analysis of the data reported by Stier et al in SHRSP treated by converting enzyme inhibitors also demonstrates that blood pressure was lower during the first 4 weeks of salt loading and converting enzyme inhibitor administration (Figure 2).

In the present study, the protective effects of potassium were associated with a lower PRA. This observation reinforces the hypothesis that enhanced activity of the renin-angiotensin system might accelerate the development of vascular lesions and stroke in SHRSP.

The reason for the altered relation between sodium excretion and renin during high sodium intake in SHRSP is not clear. It seems unlikely that contraction in plasma volume, as a result of excessive natriuresis, is the cause as the hematocrits were not significantly different, and ANF levels were not different among the groups. Furthermore, the observations of Dietz et al also suggest no changes in plasma volume in SHRSP fed a high NaCl/high potassium diet. It should be noted that in Dahl salt-sensitive rats, chronic high salt intake was shown to cause a reduction in renal blood flow and glomerular filtration rate that might in turn lead to stimulation of renin release. Nagaoka et al suggested that the hyperreninemia may be a consequence of uncontrolled renin release due to renal arteriolar and tubular damage. Our observation that PRA was not suppressed at 4 weeks, when renal vascular and parenchymal lesions were not detectable, suggest an additional mechanism, an inability to suppress PRA, that may be genetic in origin. Whatever the mechanism, the lack of renin suppression during high sodium diet is likely to be harmful in animals with accelerating hypertension.

The protective effect of potassium on the salt-induced increase in renal and cerebrovascular lesions previously described by Tobian et al in SHRSP is confirmed by the present study. Our results suggest that this effect is an "all or nothing" event as some of the rats seem to be completely protected while others develop malignant hypertension. The mechanisms by which potassium supplement attenuates the renin rise are unclear. Potassium may directly reduce renin secretion as demonstrated previously. Potassium can also indirectly decrease renin release by reducing the sympathetic tone as has been shown in SHRSP. In addition, potassium may indirectly reduce renin release by increasing the glomerular filtration rate and reducing proximal tubular sodium and suppressing renin release via the macula densa signal. Finally, potassium might prevent the increase in renin secretion by attenuating the renal and vascular or endothelial damage in SHRSP. However, these effects might be at least partially explained by a potassium-induced reduction in renin, thereby limiting the removal of the negative effects of renin and angiotensin II on the vascular wall.

In conclusion, the present study shows that high sodium intake in SHRSP results in a paradoxical and inappropriate rise in PRA that is attenuated by high potassium intake. The changes in PRA correlate with the incidence of renal vascular lesions and strokes, so that vascular protection might be related to the reduced PRA. The protective effect of potassium might also be related to the lower blood pressures during the early phase of the K+ treatment. Third, a direct effect of potassium on the vasculature might explain the amelioration of end organ damage and the lower PRA. Thus, although our data suggest an important role for renin, it is also possible that the protective effect of K+ is independent of renin and...
that increases in renin are the consequence rather than the cause of injury.

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References


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**KEY WORDS** • malignant hypertension • atrial natriuretic factor • aldosterone • angiotensin II • blood pressure
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