Potassium Supplementation Attenuates Experimental Hypertensive Renal Injury

Demetrios Ellis,2 Barbara Banner, Janine E. Janosky, and Peter U. Feig

ABSTRACT

The long-term roles of dietary sodium and potassium on the renal end-organ damage of hypertension were investigated in Wistar-Kyoto (WKY) and in spontaneously hypertensive (SHR) rats. Eight rats from each strain were maintained since 1 month of age on one of four dietary combinations of either low (0.4%) or high (6.0%) NaCl and low (0.51%) or high (7.6%) KCl providing sodium/potassium molar ratios of 1:1, 1:1.5, 15:1, and 15:15, respectively. Urinary sodium/potassium excre-tion ratios confirmed the proportion of salts consumed. Systolic blood pressures (SBP) were similar at 5 months of age and at the completion of the study at 9.5 months; SBP was significantly higher in SHR than in WKY rats and was not attenuated by dietary potassium supplementation of a magnitude that raised plasma potassium concentrations. Albumin excretion rate (AER) was also higher in SHR than in WKY rats ($P < 0.0001$). In SHR, AER rose further with high sodium intake ($P < 0.035$) but, contrary to SBP, was ameliorated by an equimolar addition of potassium ($P = 0.01$). Morphologic lesions were generally absent in WKY rats and were more common in SHR as a group ($P < 0.001$). In all four SHR groups, the graded histopathologic injury correlated well with measured AER but a major improvement in hypertensive renal lesions occurred largely in the KCl-supplemented, salt-loaded SHR group. These results show a disassociation between the effects of dietary monovalent cations on the level of SBP and their effect on renal injury. Sodium aggra-vates renal injury and potassium protects against this renal effect of sodium independent of SBP effect. A high dietary sodium/potassium ratio appears to promote renal end-organ damage by mechanisms un-related to SBP.

Key Words: Hypertension, potassium, glomerular protection, experimental

Epidemiologic data support the hypothesis that sodium (Na) and potassium (K) have opposing roles on arterial blood pressure in humans (1–6). However, it is difficult to isolate the effect of dietary Na from that of K. This is because of the inverse relation between Na and K content in the diet and the effect of Na intake on urinary K excretion (6) and because of the polygenic nature of essential hypertension, the multiple environmental risk factors contributing to its development, and the variations in the sensitivity to Na. The inverse relationship between dietary K intake and blood pressure has also been demonstrated with some conflicting results due to variations in the level of initial blood pressure, the racial composition of the subjects, the baseline intakes of Na and K, and the duration of clinical trials (7–18). Animal models of hypertension have provided more convincing evidence supporting the role of dietary K supplementation in attenuating Na-dependent hypertension (19–26). Of note is that recent evidence suggests that, irrespective of effects on blood pressure, brain end-organ damage of hypertension can be reduced by K (27–30) even if aggravated by Na-induced hypertension (31,32). This study investigates whether dietary K protects against blood pressure-induced renal injury. We used a salt-independent model of genetic hypertension, the spontaneously hypertensive rat (SHR), and its syngeneic normoten-sive control strain, the Wistar-Kyoto (WKY) rat (33) in order to be able to observe end-organ effects of diet in the virtual absence of blood pressure effects. The potential influence of long-term variations in dietary Na and K on albuminuria, a marker of glo-merular injury, and renal histopathology were ex-aired.

METHODS

Animals

One-month-old male rats, 32 SHR and 32 WKY, were purchased from Harlan-Sprague Dawley (Indi-
anapolis, IN) and were placed as pairs of WKY/SHR in cages with free access to food and water. Systolic blood pressure (SBP) was measured at 1 (prediet), 5, and 9.5 months of age by the tail-cuff method (Narco Biosystems, Houston, TX) in warmed unanesthetized animals accustomed to the procedure, and the mean of three measurements at each occasion was used for analysis. Rats were weighed on a dual beam balance. At 9.5 months, animals were killed after phenobarbital anesthesia, blood was drawn from the abdominal aorta into heparinized tubes, and the left kidneys were removed, decapsulated, and placed in Formalin.

**Diet**

Diet (Ralston Purina, St. Louis, MO) were prepared from a purified mixture containing 19% protein (wt/wt; standard amount) and either low (0.4%) or high (6.0%) NaCl and low (0.51%) or high (7.6%) KCl. The diets differed only in the amount of Na and K and the Na/K molar ratio: diet I, low Na, low K; molar ratio 1:1; diet II, low Na, high K; molar ratio 1:15; diet III, high Na, low K, molar ratio 15:1; diet IV, high Na, high K; molar ratio 15:15 or 1:1 (Table 1). At 9.5 months of age, before being killed, animals were placed for 24 h in metabolic cages, constructed to separate urine from stool and thus limit contamination of the urine collected for biochemical studies (Nalgene Inc., Rochester, NY). Urine was collected for 24 h and was frozen for analysis (see below). The intake of cations was estimated from the output, assuming steady-state electrolyte balance. This assumption is valid for sodium where extrarenal loss is negligible, but less so for potassium, where stool content may contribute to losses. Therefore, caloric and protein intakes in these rats were estimated from Na intake and the known fixed proportions and even distribution of calories, protein, and Na in the diet.

**Analytical Studies**

Urine collections and plasma were analyzed for creatinine (Beckman creatinine analyzer; Beckman Instruments, Fullerton, CA) and Na and K (IL 941 flame photometer). Creatinine clearance was determined by standard methods and was expressed per 100 g body wt. The urinary ratios of Na/K in milliequivalents per day and in milliequivalents per 100 grams body weight per day are shown in Table 2.

Urine albumin was measured by an immunonephelometric technique (34,35) that had not been previously applied to rat albumin measurements. In order to assess if the antihuman albumin (Atlantic Antibodies, Stillwater, MN) in this assay could be used to measure rat albumin, we performed the following: human albumin and rat albumin of highest purity were obtained from Sigma Chemical Co. (St. Louis, MO). Serial dilutions, as well as individually weighted samples, were then prepared in the assay buffer, analyzed, and compared with human calibrator serum (Atlantic Antibodies). In all instances, nearly superimposable curves were obtained with linear regression coefficients of ≥97% for each assay and with correlation coefficients between human and rat albumin concentrations exceeding 95%.

**Histopathology**

Kidneys were bisected and totally submitted for microscopic evaluation by an examiner unaware of the animal's strain or diet. The Formalin-fixed tissues were paraffin embedded and stained with hematoxylin and eosin. Sections were scanned vertically between cortex and medulla. One hundred consecutive glomeruli were evaluated for global or segmental sclerosis, necrosis, thrombosis, and increased cellularity. Also recorded were tubular atrophy, dilation, and regeneration; tubular casts; interstitial fibrosis and inflammation; and vascular

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**TABLE 1. Effect of 8.5-month dietary intake of low and high Na+ and/or K+ on body weight and SBP**

<table>
<thead>
<tr>
<th>Dietary Group</th>
<th>Diet (Na/K)</th>
<th>WKY Rats</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP (1 mo)</td>
<td>SBP (5 mo)</td>
<td>SBP (9.5 mo)</td>
</tr>
<tr>
<td>I</td>
<td>1:1</td>
<td>108 ± 25</td>
<td>143 ± 15</td>
</tr>
<tr>
<td>II</td>
<td>1:15</td>
<td>106 ± 30</td>
<td>130 ± 55</td>
</tr>
<tr>
<td>III</td>
<td>15:1</td>
<td>113 ± 22</td>
<td>143 ± 26</td>
</tr>
<tr>
<td>IV</td>
<td>15:15</td>
<td>115 ± 46</td>
<td>136 ± 20</td>
</tr>
</tbody>
</table>

<sup>a</sup> All values are mean ± SD; N = 8 rats in each dietary group except for 9.5 months SHR Diet III (N = 6) and SHR Diet IV (N = 7). Note that SBP was significantly lower in WKY rats as compared with that in SHR both at 5 and 9 months and for each dietary group (P < 0.0001).

<sup>b</sup> P < 0.001, Diet I versus IV.

<sup>c</sup> P < 0.01, Diet I versus II.

<sup>d</sup> P < 0.01, Diet II versus IV.
intimal edema, fibrosis, and inflammation. The severity of pathologic changes was further assessed on a semiquantitative grading scale as follows: Grade I, one to five foci of tubular and/or glomerular changes present; Grade II, more than five but less than 10 foci present; Grade III, any number of foci of glomerular and/or tubular alterations plus vascular changes.

**Statistical Analysis**

A three-way analysis of variance was used in order to investigate differences between the three grouping variables of strain (WKY rats and SHR), Na diet (low and high), and K diet (low and high) in relation to the variables of interest. The variables of interest included albumin excretion rate (AER), plasma creatinine, body weight, calorie and protein intake, plasma Na and K concentrations, urinary Na/K ratios, and creatinine clearance. Each variable of interest was investigated separately. For each of these variables, the following effects were investigated: (1) the main effects of strain, Na diet, and K diet and (2) the interactions of Na diet and strain, K diet and strain, Na diet and K diet, and strain and Na diet and K diet. All statistical assumptions were met with the exception of homogeneity of variances for a few of the variables (urinary AER and body weight). When this assumption was not met, a ranked analysis of variance was used. Scheffe's post-hoc procedure was used where appropriate. All tables contain the actual data.

A repeated measures analysis of variance was used in order to investigate differences between strain, Na diet, and K diet in relation to the three time-related blood pressure measurements. Because the assumption of sphericity was not met, a conservative univariate model was used.

Fisher's exact test was used in order to compare SHR and WKY rat strains with the number of kidneys with pathologic changes. A log-linear analysis was used in order to investigate the effects of Na diet, K diet, and strain on histopathologic grade (Table 4).

**RESULTS**

It should be noted that two SHR on Diet III died at 4 and 5 months of life, whereas one SHR on Diet IV died at 9 months of life. Because of lack of histological data, these three animals were not included in the Results. Table 1 shows the body weights of the SHR and WKY rats maintained on each of the four described dietary regimens of Na and K. At 9.5 months of age, WKY rats and SHR strains on high-Na diets (Diet IV and III) had lower body weights than did those on low-Na diets (Diet I and II; P = 0.028).

Blood pressures are also shown in Table 1. At the onset of the study, both strains of rats had similar

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**TABLE 2.** Estimated calorie and protein intake (see Text) and the effect of dietary variation of NaCl and KCl over 8.5 months on plasma Na⁺ and K⁺ concentrations and on urinary Na⁺ and K⁺ excretion.

<table>
<thead>
<tr>
<th>Dietary Group</th>
<th>Total Calories</th>
<th>Protein Content</th>
<th>Urinary Na⁺/K⁺ (mgCl/100 gm BW)</th>
<th>Plasma Na⁺ (mEq/L)</th>
<th>Plasma K⁺ (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY Rats 1</td>
<td>45 ± 15 (115.5)</td>
<td>2.3 ± 0.7 (0.59)</td>
<td>145 ± 6</td>
<td>2.7 ± 0.18</td>
<td>1.23 ± 0.25</td>
</tr>
<tr>
<td>WKY Rats 2</td>
<td>37 ± 14 (105.5)</td>
<td>2.1 ± 0.6 (0.54)</td>
<td>146 ± 6</td>
<td>2.6 ± 0.23</td>
<td>1.22 ± 0.16</td>
</tr>
<tr>
<td>WKY Rats 3</td>
<td>42 ± 11 (115.5)</td>
<td>1.9 ± 0.6 (0.56)</td>
<td>148 ± 5</td>
<td>2.4 ± 0.16</td>
<td>1.07 ± 0.02</td>
</tr>
<tr>
<td>WKY Rats 4</td>
<td>35 ± 11 (115.5)</td>
<td>1.9 ± 0.6 (0.56)</td>
<td>149 ± 5</td>
<td>3.1 ± 0.37</td>
<td>1.02 ± 0.05</td>
</tr>
</tbody>
</table>

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All values are means ± SD. For each dietary group except for 9.5-months, SHR Diet I = 0 and SHR Diet IV (IV = 7). Note: The sodium and potassium intakes were estimated from the urinary excretion of Na as described in Methods.
SBP; however, by 4 months on their respective diets (i.e., 5 months of age), the SBP trends had been well established and statistically reflected the levels recorded at the completion of the study. Thus, SBP was higher both at 5 months and at 9 months of age in SHR as compared with WKY rats on comparable diets \((P < 0.001)\). At high-Na intake, both strains of rats had a statistically insignificant rise in SBP, which was not lowered by high-K supplementation.

Calorie intake at 9.5 months of age ranged from 31 to 68 kcal/day, and protein intake ranged from 1.6 to 2.4 g/day. These ranges in intakes became narrower with correction for body weight (Table 2) because body weight paralleled calorie intake in both WKY rats and SHR; with the possible exception of SHR on Diet II, a low body weight was invariably explained by low calorie and low protein intake in both strains of rats. There were no differences in calorie and protein intakes or in body weight between WKY rats and SHR on comparable diets.

Plasma electrolyte concentrations at the age of 9.5 months (Table 2) ranged between 145 and 154 mEq/L for Na and 2.6 and 3.1 mEq/L for K in both WKY rats and SHR. Although there were not statistical differences in the plasma Na values between dietary groups or strains, such differences were present in plasma K. The higher K diets (Table 2; Diets II and IV) were associated with a 9 to 15% increase in mean serum K concentrations in both strains of rats \((P < 0.05)\). Diets I and II and \(P < 0.01\) for Diets III versus IV). The urinary ratio of Na/K (Table 2) closely reflected the intake of these ions. However, the excreted electrolytes did not reflect the exact ratio of dietary load of Na and K. This finding is in accord with that of previous studies in SHR in which the urinary recovery of these ions ranged from 70 to 95% (26). Although the estimated caloric and protein intakes shown in Table 2 are not adjusted to reflect such lower Na excretion rates, the urinary Na output and, therefore, food intake was indistinguishable in WKY rats and SHR on comparable diets.

Creatinine and AER values are shown in Table 3. Serum creatinine concentrations ranged from 0.2 to 0.4 mg/dL in all animals (median, 0.3 mg/dL). The creatinine clearance was similar in all groups and was not significantly affected by dietary changes in Na or K or by SBP. SHR had higher AER than did WKY rats at all levels of dietary intakes \((P < 0.0001)\). Rats of either rat strain maintained on low-Na diets had lower AER than did rats on high-Na diets \((P < 0.035)\). Both Na and K intakes significantly affected AER independent of rat strain \((P < 0.0001)\); however, these effects on AER occurred in opposing directions with high-Na diets increasing AER and high-K diets reducing AER. Notice that SHR on high-Na intake had a significant reduction in AER with K supplementation (Diets III versus IV; \(P < 0.01\)).

### Histopathology

Global sclerosis was seen in only four kidneys (all SHR) and represented 2.5% of the 400 glomeruli examined from the affected kidneys. Segmental sclerosis was noted in seven kidneys (five SHR and two WKY rats) involving 1% of the glomeruli examined. Glomeruli in 14 kidneys (12 SHR and 2 WKY rats) exhibited mesangial expansion, foam cells, occasional thrombi, and slightly increased cellularity. Nearby tubules were distended with proteinaceous material or were atrophic. Such affected glomerulotubular complexes were sporadic but tended to localize to the juxtamedullary portion of the cortex. Thirty (2.1%) of the 1400 glomeruli counted in these animals had these changes. Foci of tubular atrophy and/or casts with or without glomerular changes were noted in 30 kidneys (26 SHR and 4 WKY rats). Focal interstitial fibrosis was seen in three kidneys (all SHR). Interstitial inflammation was present in 21

### TABLE 3. Plasma creatinine, creatinine clearance, and AER according to dietary intake of Na\(^+\) and K\(^{+}\)

<table>
<thead>
<tr>
<th>Group</th>
<th>WKY Rats</th>
<th></th>
<th>SHR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma Creatinine (mg/dL)</td>
<td>Creatinine Clearance (mL/min/100 g body wt)</td>
<td>AER (µg/min/100 g body wt)</td>
<td>Plasma Creatinine (mg/dL)</td>
</tr>
<tr>
<td>I</td>
<td>0.32 ± 0.09</td>
<td>0.79 ± 0.28</td>
<td>0.08 ± 0.02</td>
<td>0.35 ± 0.08</td>
</tr>
<tr>
<td>II</td>
<td>0.27 ± 0.07</td>
<td>0.90 ± 0.26</td>
<td>0.11 ± 0.03</td>
<td>0.24 ± 0.07</td>
</tr>
<tr>
<td>III</td>
<td>0.30 ± 0.09</td>
<td>0.85 ± 0.28</td>
<td>0.18 ± 0.06</td>
<td>0.32 ± 0.07</td>
</tr>
<tr>
<td>IV</td>
<td>0.32 ± 0.04</td>
<td>0.76 ± 0.12</td>
<td>0.12 ± 0.04</td>
<td>0.32 ± 0.07</td>
</tr>
</tbody>
</table>

\(a\) All values are mean and SD; \(N = 8\) rats in each dietary group except for 9.5 months SHR Diet III \((N = 6)\) and SHR Diet IV \((N = 7)\).

\(b\) \(P < 0.035\); Diets I plus II versus Diets III plus IV.

\(c\) \(P < 0.0001\); Diet I versus III and Diet II versus II.

\(d\) \(P < 0.01\); Diet II versus IV and Diet III versus IV.
kidneys (17 SHR and 4 WKY rats). Arterial walls showed thickening of five kidneys (three SHR and two WKY rats), onion skinning in one SHR kidney, and vacuolization of vascular smooth muscle in the media in nine kidneys (five SHR and four WKY rats). Typical pathologic changes found in the more affected kidneys (Dietary Group III) are depicted in Figure 1.

Comparison of the SHR and WKY rat groups as a whole showed that SHR had a significantly greater number of kidneys affected with pathologic changes in the glomeruli (12:2), tubules (17:0), and interstitium (17:4) (all comparisons were significant at \( P < 0.001 \) by Fisher's exact test). However, the semiquantitative histopathologic grading was far more representative of the extent of renal injury than was the statistical analysis of the total number of lesions present among the different dietary groups. These data, which are summarized in Table 4, indicate that 28 of the 32 WKY animals had no pathologic findings at all and 3 others had only Grade I changes, contrasting with only 3 of 29 SHR with no evidence of renal injury. Among SHR, all six animals on the high-Na–low-K diet had either Grade II or III changes compared with SHR on the high-Na–high-K diet, none of which had Grade III changes and five of which had none or minor (Grade I) alterations. Log-linear analysis showed a significant association between rat strains, dietary Na and K intakes, and histopathologic grade. As with AER, a high-Na diet was associated with a greater number of and more severe histopathologic changes (\( P < 0.001 \)), whereas K supplementation was associated with significantly fewer such alterations (\( P < 0.001 \)) in SHR only.

**DISCUSSION**

In recent years, there has been a resurgence of interest in defining the role of dietary factors that, beyond NaCl, could affect the development of hypertension or of hypertensive end-organ damage. Various electrolytes have been implicated in their relationship to essential hypertension, including potassium, calcium, and sodium.

This study suggests that in comparison to high-Na diets, low-Na diets are perhaps associated with a limited reduction in mean SBP in WKY rats (20%) and in SHR (10%), but these SBP reductions are not statistically significant. Even if real, however, the increases in SBP related to higher Na intake in both rat strains are not reduced by dietary K supplementation. These results are in contrast to those of studies in rats (19) and short-term controlled trials in human subjects with mild or moderate hypertension in whom KCl supplementation (96 mEq/day) prevented the blood pressure rise associated with high Na administered concurrently (7,12). On the other hand, our data are consistent with those obtained by Treasure et al. in their two-kidney, one-clip Goldblatt hypertensive rats, despite the much lower absolute intakes of Na and K used in that study (26). Indeed, an antihypertensive action of K administration accompanied by a reduction in urinary Na/K ratio in humans (1–6,7,12,16) or in animals (19–21,24) has been demonstrated mainly in forms of hypertension that are dependent on Na intake rather than the Na-independent SHR model used in this current study. The reduction of the urinary molar ratio of Na/K and the absolute minimum ratios that may protect against the deleterious effects of the chronic ingestion of excessive Na have not been determined in humans or in animals. The data presented here demonstrate that the higher dietary K intake selected in our studies was sufficient to produce significant and comparable elevations in serum K concentrations as were those measured in previous human and animal studies. From our data, it does not appear that it is the reduction in dietary Na/K ratio that affects blood pressure: if high Na was associated with increased SBP, this occurred at both high (15:1) and low (1:1) ratios (Table 2; Diets III and IV); and the SBP in animals on the low-Na–low-K diet was not further reduced by K supplementation, affecting a 15-fold reduction in the Na/K ratio (Table 2; Diet I versus II). In our study, K supplementation had little or no effect on SBP in either rat strain.

We observed no protection by K against systolic hypertension. Instead, the remarkable finding is the substantial (fourfold; \( P < 0.001 \)) increase in AER that occurred in SHR on high Na intake without concomitant high K intake (Table 3; Group III) and the decline in AER (2.5-fold; \( P < 0.01 \)) in the absence of a reduction in SBP with K supplementation (Table 3; Diet IV). These data clearly demonstrate a disassociation of SBP and AER, whereas the albuminuria-sparing effect of K supplementation is apparent especially in animals with high Na intake. The beneficial effect of high K ingestion on AER was qualitatively similar in WKY rats, but the magnitude of AER reduction was not statistically significant. These results strongly suggest that sodium exacerbates and potassium mitigates at least the early, subclinical glomerular alterations via mechanisms other than changes in SBP. A converse but analogous disassociation between systemic hypertension and renal injury occurred in studies in which prolonged pharmacologic lowering of SBP in SHR did not prevent the progression of albuminuria and renal injury (36). Deterioration in renal function has also been reported in humans with well-controlled essential hypertension over a mean follow-up of 58 ± 34 months (± SD) (37).

The microalbuminuria in our study may be a predictor for renal damage. Despite the focality of the histopathologic alterations, the SHR as a group had a greater prevalence of glomerular, tubular, and interstitial changes as compared with WKY rats (\( P < \)
0.001). More revealing, however, were the graded pathologic changes (Table 4) that demonstrated a marked difference in renal injury between WKY rats and SHR. Although WKY rats had few alterations as a group, SHR exhibited marked changes especially on the high-Na–low-K diet (Group III) with fewer and less severe changes occurring with K+ supplementation (Group IV). Thus, a greater degree of renal injury corresponded to higher AER. Furthermore, the fact that SBP at levels comparable to those measured at 9.5 months of age were already established by 5 months of age (Table 1) argues against a SBP-lowering effect of K that may have prevented baroinjury during the earlier experimental period in SHR Group IV. These data, however, do not completely exclude the possibility that transient dietary effects on blood pressure, between 1 and 5 months of age, could have caused the effects seen at 9.5 months of age.
TABLE 4. Effect of low and high sodium and potassium intake on renal histology

<table>
<thead>
<tr>
<th>Dietary Group</th>
<th>Rat Strain</th>
<th>N</th>
<th>Histopathologic Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>None I II III</td>
</tr>
<tr>
<td>I</td>
<td>WKY</td>
<td>8</td>
<td>0 0 0</td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>8</td>
<td>0 6 2</td>
</tr>
<tr>
<td>II</td>
<td>WKY</td>
<td>8</td>
<td>0 0 0</td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>8</td>
<td>1 7 0</td>
</tr>
<tr>
<td>III</td>
<td>WKY</td>
<td>8</td>
<td>6 1 1</td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>6</td>
<td>0 0 3</td>
</tr>
<tr>
<td>IV</td>
<td>WKY</td>
<td>8</td>
<td>6 2 0</td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>7</td>
<td>2 3 2</td>
</tr>
<tr>
<td>Total Numbers</td>
<td>WKY</td>
<td>32</td>
<td>28 3 1 0</td>
</tr>
<tr>
<td></td>
<td>SHR</td>
<td>29</td>
<td>3 16 7 3</td>
</tr>
</tbody>
</table>

* The grading system used in described in Methods.

* P < 0.001: WKY versus SHR strains.

* P < 0.001: SHR, Diet III versus IV.

The mechanisms proposed to explain the antihypertensive action of K have been recently reviewed (18,27,38). The available data suggest that the antihypertensive action of K is primarily mediated by its effect on the renal proximal tubule (39,40) to produce natriuresis in both rats (20–22,41,42) and in controlled human studies (12,43), thereby attenuating extracellular fluid expansion, increase in cardiac output, and the rise in blood pressure induced by high dietary Na intake. However, in the absence of systemic hypertension or increase in glomerular hydrostatic pressure, tubular dysfunction would not result in significant high-molecular-weight proteinuria or albuminuria. Thus, direct glomerular injury may better explain such proteinuria. Workman and Paller (44) have shown that a 16 mm Hg fall in mean arterial pressure in SHR by K supplementation was mediated by reductions in systemic vascular resistance, and not by stimulation of the renin-angiotensin system or due to changes in the pressor effect of angiotensin II and norepinephrine, which have been shown to induce proteinuria in rats (45,46) and in hypertension in humans (47–49). K supplementation may directly reduce systemic vascular resistance by affecting vascular smooth muscle sensitivity to circulating pressor hormones. Suppression of circulating concentrations of renin (24,42,43) and angiotensin II (50) by K supplementation may attenuate such effects. However, in marked contrast to several studies cited, Linas and Marzec-Calvert have shown a hypotensive action of K depletion in SHR, which is also mediated by marked attenuation of systemic vascular resistance (51). Little is known about the effects of K on the contractile elements of mesangial cells and on glomerular arteriolar smooth muscle, which modulate RBF and pressure at the glomerular level. Although renal nerve modification and reduction in renal vascular resistance has been shown to alleviate renal injury in the presence of hypertension in SHR (52), on the aggregate, the disparate results obtained in hypertensive species of animals and in humans have not provided a mechanism that satisfactorily explains the glomeruloprotective effect of K on the Na-independent SHR model of essential hypertension. Lastly, an importance for anion (Cl−) intake in improving blood pressure, AER, and histopathologic injury in KCl-supplemented animals in this study is unlikely: in our studies, the effects of this anion appear to be minimized by the fact that Diets II and III had similar Cl− content yet both WKY rats and SHR on such diets differed markedly in SBP, AER, and tissue injury.

An additional finding of this study is the apparent homology between human and rat albumin, which permits measurement of the latter through the use of antihuman albumin. This very simple and sensitive immunonephelometric technique greatly simplifies the measurement of small concentrations of urinary rat albumin, which is currently being assayed by electrophoretic and other more cumbersome methods (53).

In this study, there were no ill effects associated with the low-Na diets with or without K supplementation. After 8.5 months of such dietary control, both WKY rats and SHR demonstrated a somewhat better nutritional status, especially on the low-Na–low-K diet, as compared with those on diets high in Na. Indeed, the three rats that died before the completion of the study were SHR on high sodium intake: two on low potassium and one on high potassium. Whether retardation of renal injury and longevity can be improved by longer treatment with a low-Na–low-K diet cannot be answered by this study. The early studies showing that KCl supplementation improved survival in animals with chronic NaCl toxicity did not find a correlation with blood pressure effects (54). Thus, such increased survival in these volume-expanded animals could be associated with the glomeruloprotective properties of KCl independent of reductions in systemic arterial pressure due to KCl.

It is noteworthy that our findings are analogous to those of Tobian et al. (29,30), showing a deleterious effect of Na and a protective effect of K on stroke in hypertensive rats, also unrelated to the effect of blood pressure. Thus, damage to multiple target organs may be affected by dietary cations in hypertension and this may also apply to humans (27).

In summary, our studies indicate that the modest rise in SBP associated with high Na intake is not prevented by K supplementation in either WKY rats or in SHR. A high dietary Na/K ratio appears to promote renal end-organ damage for which albuminuria is an early marker. This intriguing disassocia-
tion between the effects of dietary Na and K on blood pressure and on hypertension-related albuminuria and renal end-organ injury deserves further investigation.

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