Role of Dietary Potassium in the Hyperaldosteronism and Hypertension of the Remnant Kidney Model

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Abstract. The remnant kidney model of progressive renal disease is marked by arterial hypertension, especially when produced by nephrectomy and partial infarction. Hyperaldosteronism sustains much of the hypertension, but the stimuli to the increased aldosterone levels are uncertain. It is hypothesized that the hyperaldosteronism attending this model stems from the combination of fixed dietary potassium load in the face of reduced filtration on the one hand, and persistent renin secretion from the scarred remnant kidney on the other. This hypothesis predicted that dietary potassium restriction would lower aldosterone and BP in this model. To test this prediction, two groups of rats with a remnant kidney were studied. Group 1 consumed 0.4 ± 0.06 mEq (mean ± SD) of potassium chloride daily, and group 2 ate 4.8 ± 1.0 mEq daily. Two sham-operated groups with intact kidneys also were studied. Group 3 consumed 1.7 ± 0.2 mEq daily and group 4 ate 15.2 ± 1.4 mEq daily. These levels of intake were designed to provide at least as much potassium per liter of GFR in the sham groups as in the remnant kidney rats. Systolic BP (SBP), 24-h protein excretion, plasma aldosterone levels, 24-h urinary aldosterone excretion, and plasma renin activity (PRA) were determined in all groups at 2 wk. At 4 wk, after SBP and protein excretion measurements, remnant kidneys were perfusion-fixed for morphometric analysis. SBP was normal in both sham-operated groups at the time-fixed for morphometric analysis. SBP was normal in both sham-operated groups and was not different between the two groups with remnant kidneys at either 2 or 4 wk. Both plasma and 24-h urinary aldosterone excretion at 2 wk followed potassium intake (120 ± 124 versus 580 ± 442 pg/ml for plasma aldosterone, group 1 versus group 2, P = 0.003, and 2.6 ± 1.8 versus 23.2 ± 9.8 ng/d for urinary aldosterone, group 1 versus group 2, P = 0.0001). PRA, however, followed a reverse pattern in which dietary potassium restriction resulted in higher levels (16 ± 6 versus 6 ± 3 ng angiotensin I/ml per h, group 1 versus group 2, P = 0.01). A similar pattern for PRA and aldosterone excretion was also observed in the sham groups, in which lower potassium intake also resulted in a significantly higher PRA and lower aldosterone excretion. The constancy of BP in the sham groups likely reflects their lack of nephron reduction and greater sodium excretory capacity. Morphometric analysis in remnant animals revealed no significant difference between the two dietary groups in the prevalence of glomerular sclerosis, glomerular volume, or interstitial volume. It is concluded that dietary potassium is a potent determinant of hypertension in the remnant kidney model probably through the actions of aldosterone and that the high aldosterone secretion in this model is a function of the dietary potassium load. In this model, reduction in nephron number is also critical in promoting hypertension in conjunction with hyperaldosteronism.

The renin-angiotensin-aldosterone system participates in the progressive pathophysiology of many experimental and human renal diseases (1–5). Actions of angiotensin II (AngII) in the kidney have been posited as the major mechanism for maintenance of injurious elevations in glomerular pressure, and reductions in glomerular pressure have been attributed, at least in part, to removal of the intrarenal effects of AngII (1–3). However, systemic hypertension and even nonhemodynamic but intrarenal actions of AngII, such as growth-promoting effects, enhancement of ammoniagenesis, and fibroproliferative consequences, also may contribute to progressive renal injury, and relief from them reduces injury (1–3,5).

Hyperaldosteronism also occurs in the remnant kidney model (6). Its suppression with angiotensin-converting enzyme (ACE) inhibitors and AngII blockers results in a significant improvement in hypertension, perselectivity, and glomerular sclerosis (6). The stimuli to this sustained hyperaldosteronism, however, are not well delineated because chronic renal disease is usually accompanied by low-to-normal plasma renin activity (1,2,7). Likewise, the available measurements of circulating renin and AngII do not suggest extraordinary systemic activation of this system in the remnant kidney model (1,7,8). Mitigation of hyperaldosteronism in this model with ACE inhibitors and AngII receptor blockers results in a marked increase in serum potassium (6). This finding suggests that the heightened aldosterone levels may serve as an adaptive response to sus-
tained dietary potassium intake in the setting of reduced renal mass.

We hypothesized that a diet low in potassium would therefore lower aldosterone production and thereby reduce hypertension in the remnant kidney model.

Materials and Methods

Adult male Sprague Dawley rats weighing 225 to 300 g underwent right nephrectomy and infarction of approximately two-thirds of the left kidney by ligation of two segmental renal arteries or sham laparotomy. Three days postablation, plasma creatinine was measured by the modified Jaffe reaction (Beckman Instruments, Brea, CA). By intention, two remnant groups were created with equivalent plasma creatinine levels. The two remnant groups received a semi-synthetic powder diet that was potassium-deficient. The protein content was 23.4% and the sodium content was 174 mEq/kg (Teklad Premier Laboratory Diets, Madison, WI). Potassium chloride was added to the semi-synthetic diet at two different levels as follows. Group 1 (Low K+ diet – Remnant): KCl 25 mEq/kg synthetic diet (n = 20); group 2 (Normal K+ diet – Remnant): KCl 250 mEq/kg synthetic diet (n = 15).

These diets were designed to provide approximately 0.5 mEq and 5.0 mEq KCl per rat per day in group 1 and group 2, respectively. The higher level of potassium intake (5.0 mEq KCl/d) approximates that provided by standard rat diets with the usual daily food ingestion (approximately 20 g/d).

The two sham-operated groups were fed as follows: Group 3 (Low K+ diet – Sham): KCl 115 mEq/kg synthetic diet (n = 6); group 4 (High K+ diet – Sham): KCl 900 mEq/kg synthetic diet (n = 6). These diets were designed to provide daily dietary K+ loads per liter GFR, as estimated from the creatinine clearance, that were even higher than those of the comparable remnant kidney groups. All animal procedures were in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

Two and four weeks after assignments to groups, the rats were placed in metabolic cages for collection of urine and stool for 24 h and determination of food intake. Sham-operated rats (groups 3 and 4) were studied for only 2 wk and were all sacrificed at that time for the same studies as for groups 1 and 2. Systolic BP was measured in the awake state by the tail-cuff method. Total urinary protein excretion was studied for only 2 wk and was all sacrificed at that time for the same studies as for groups 1 and 2. Twenty-four-hour urinary aldosterone excretion was also measured at 2 wk. Plasma aldosterone was assayed by RIA on trunk blood obtained 2 and 4 g/d, group 1 versus group 2) yielding calculated potassium intakes of 0.4 ± 0.06 and 4.8 ± 1.0 mEq/d, P < 0.01) (Table 1 and 2). Creatinine clearance was 0.9 ± 0.3 and 1.0 ± 0.2 L/d for groups 3 and 4, respectively. Daily potassium load, expressed as daily KCl intake per liter GFR, as estimated from the creatinine clearance, was lower in group 1 (0.45 ± 0.2 vs. 4.8 ± 1.6 mEq/L GFR, P = 0.0001). Weight gain and hematocrit were also comparable between the four groups.

Two-Week Results

Remnant Animals (Groups 1 and 2). The 24-h food intake was similar between the two remnant groups (17 ± 2 versus 19 ± 4 g/d, group 1 versus group 2) yielding calculated potassium intakes of 0.4 ± 0.06 and 4.8 ± 1.0 mEq/d, P < 0.01) (Tables 1 and 2). Creatinine clearance was 0.9 ± 0.3 and 1.0 ± 0.2 L/d for groups 3 and 4, respectively. Daily potassium load, expressed as daily KCl intake per liter GFR, as estimated from the creatinine clearance, was lower in group 1 (0.45 ± 0.2 versus 4.8 ± 1.6 mEq/L GFR, P = 0.0001). Weight gain and hematocrit were also comparable between these two groups. Although plasma sodium was similar in the two groups, plasma potassium was lower in group 1 (3.4 ± 0.8 versus 4.4 ± 0.4 mEq/L, P = 0.0001). In parallel with plasma potassium levels, urinary and fecal potassium excretion were significantly lower in group 1 (0.06 ± 0.04 versus 2.5 ± 0.6 mEq/d for urinary potassium, P = 0.0001, and 0.02 ± 0.01 versus 0.07 ± 0.05 for fecal potassium, P < 0.001). Also, fractional excretion of potassium was lower in group 1 (2.6 ± 1.8% versus 53 ± 9%, P = 0.0001). Urinary Na+ excretion was comparable between the two groups (1.4 ± 0.3 versus 1.6 ± 0.4 mEq/d, group 1 versus group 2). The similar weight gain and sodium excretion that were observed support the measurements of food intake in (PAS). The remnant kidney, adrenal glands, and heart were weighed at the time of sacrifice.

The prevalence of glomerular sclerosis was determined on PAS-stained sections of the kidneys in a blinded manner. For each rat, at least 100 glomerular profiles were assessed for the presence or absence of any sclerosis. The results are expressed as the percentage of glomeruli having any sclerotic component. Morphometric analysis was based on the method of point counting as described previously (9). For measurement of mean glomerular volume (MOV), a grid containing a tessellation of points 6.0 mm apart was used. The mean glomerular volume was defined as follows: MOV = (P × A)1/3 × B/k, where P is the average number of points per profile, A is the area in square micrometers represented by each point, B = 1.38 and represents a correction factor that assumes glomeruli are spherical, and k = 1.01 represents a correction factor that assumes the variation in glomerular volume has a coefficient of variation of 10%. For the measurement of fractional interstitial volume, grid tessellations were 4.0 cm apart. The coarse-to-fine point ratio was 1.9. Percent cortical interstitial volume was taken as equal to the sum of fine points falling on the interstitium (excluding tubules and luminal space) divided by the sum of fine points falling on whole kidney profile. Blood vessels and the infarctive scar region were excluded from this analysis.

Statistical Analyses

Statistical analyses were performed by unpaired t test. All results are given as mean ± 1 SD. A P value ≤0.05 was considered significant.

Results

Three days postablation, serum creatinine was similar by design between the two remnant groups (0.9 ± 0.2 for group 1 versus 0.9 ± 0.1 mg/dl for group 2). Groups 3 and 4 had normal serum creatinines (0.4 ± 0.1 mg/dl for both groups). Initial weight loss and hematocrit were also comparable between the four groups.

Two-Week Results

Remnant Animals (Groups 1 and 2). The 24-h food intake was similar between the two remnant groups (17 ± 2 versus 19 ± 4 g/d, group 1 versus group 2) yielding calculated potassium intakes of 0.4 ± 0.06 and 4.8 ± 1.0 mEq/d, P < 0.01) (Table 1 and 2). Creatinine clearance was 0.9 ± 0.3 and 1.0 ± 0.2 L/d for groups 3 and 4, respectively. Daily potassium load, expressed as daily KCl intake per liter GFR, as estimated from the creatinine clearance, was lower in group 1 (0.45 ± 0.2 versus 4.8 ± 1.6 mEq/L GFR, P = 0.0001). Weight gain and hematocrit were also comparable between these two groups. Although plasma sodium was similar in the two groups, plasma potassium was lower in group 1 (3.4 ± 0.8 versus 4.4 ± 0.4 mEq/L, P = 0.0001). In parallel with plasma potassium levels, urinary and fecal potassium excretion were significantly lower in group 1 (0.06 ± 0.04 versus 2.5 ± 0.6 mEq/d for urinary potassium, P = 0.0001, and 0.02 ± 0.01 versus 0.07 ± 0.05 for fecal potassium, P < 0.001). Also, fractional excretion of potassium was lower in group 1 (2.6 ± 1.8% versus 53 ± 9%, P = 0.0001). Urinary Na+ excretion was comparable between the two groups (1.4 ± 0.3 versus 1.6 ± 0.4 mEq/d, group 1 versus group 2). The similar weight gain and sodium excretion that were observed support the measurements of food intake in (PAS). The remnant kidney, adrenal glands, and heart were weighed at the time of sacrifice.
Table 1. Systemic, metabolic, and hemodynamic effects of dietary potassium in rats with partial renal ablation: 2 wk postablation

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial Weight (g)</th>
<th>Final Weight (g)</th>
<th>Food Intake (g/d)</th>
<th>CCr (L/d)</th>
<th>K⁺ Intake (mEq/L GFR)</th>
<th>Plasma K (mEq/L)</th>
<th>Urinary K (mEq/d)</th>
<th>Stool K (mEq/d)</th>
<th>Urinary Na⁺ (mEq/d)</th>
<th>Uprot.V (mg/d)</th>
<th>SBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 20)</td>
<td>261 ± 15</td>
<td>303 ± 25</td>
<td>17 ± 2</td>
<td>0.9 ± 0.3</td>
<td>0.45 ± 0.2</td>
<td>3.4 ± 0.8</td>
<td>0.06 ± 0.04</td>
<td>0.02 ± 0.01</td>
<td>1.4 ± 0.3</td>
<td>135 ± 93</td>
<td>140 ± 26</td>
</tr>
<tr>
<td>2 (n = 15)</td>
<td>275 ± 9</td>
<td>306 ± 11</td>
<td>19 ± 4</td>
<td>1.0 ± 0.2</td>
<td>4.8 ± 1.6</td>
<td>4.4 ± 0.4</td>
<td>2.5 ± 0.6</td>
<td>0.07 ± 0.05</td>
<td>1.6 ± 0.4</td>
<td>121 ± 63</td>
<td>170 ± 34</td>
</tr>
</tbody>
</table>

<sup>a</sup>C₄, creatinine clearance; Uprot.V, 24-h urinary protein excretion; SBP, systolic blood pressure.

<sup>b</sup>P < 0.001.

Table 2. Systemic, metabolic, and hemodynamic effects of dietary potassium in rats with partial renal ablation: 4 wk postablation

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial Weight (g)</th>
<th>Final Weight (g)</th>
<th>Food Intake (g/d)</th>
<th>Plasma K (mEq/L)</th>
<th>Urinary K (mEq/d)</th>
<th>Stool K (mEq/d)</th>
<th>Urinary Na⁺ (mEq/d)</th>
<th>Uprot.V (mg/d)</th>
<th>SBP (mmHg)</th>
<th>Adrenal Glands (mg)</th>
<th>Remnant Kidney Weight (g)</th>
<th>Heart Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 12)</td>
<td>261 ± 15</td>
<td>372 ± 34</td>
<td>20 ± 3</td>
<td>3.3 ± 0.6</td>
<td>0.11 ± 0.1</td>
<td>0.09 ± 0.1</td>
<td>1.7 ± 0.1</td>
<td>216 ± 135</td>
<td>153 ± 25</td>
<td>67 ± 8</td>
<td>2.6 ± 0.8</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>2 (n = 10)</td>
<td>278 ± 9</td>
<td>353 ± 15</td>
<td>18 ± 4</td>
<td>4.8 ± 0.7</td>
<td>2.9 ± 0.6</td>
<td>0.17 ± 0.1</td>
<td>1.6 ± 0.2</td>
<td>148 ± 109</td>
<td>197 ± 27</td>
<td>64 ± 5</td>
<td>2.1 ± 0.4</td>
<td>1.7 ± 0.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Abbreviations as in Table 1.

<sup>b</sup>P < 0.01.
indicating that the two groups were indeed ingesting similar amounts of the diet. Awake systolic BP was significantly lower in group 1 than group 2 (140 ± 26 versus 170 ± 34 mmHg, \( P = 0.0005 \)). Twenty-four-hour urinary protein excretion (Uporot.V) was not different between the two groups (135 ± 93 versus 121 ± 63 mg/d, group 1 versus group 2).

The weights of the remnant kidneys, adrenal glands, and hearts from rats sacrificed at 2 wk were not statistically different between the two groups (data not shown). Plasma aldosterone levels at 2 wk were lower in group 1 compared to group 2 (120 ± 124 versus 580 ± 442 pg/ml, \( P = 0.03 \)). Twenty-four-hour urinary aldosterone excretion was also lower in group 1 (2.6 ± 1.8 versus 23.2 ± 9.8 ng/d, \( P = 0.0001 \)). Plasma renin activity (PRA), however, was higher in group 1 compared to group 2 (16 ± 6 versus 6 ± 3 ng angiotensin I/ml per h, \( P = 0.01 \)) (Table 3).

**Sham Animals (Groups 3 and 4).** Food intake and weight gain were similar in the two groups and comparable to the remnant groups (3.6 mmHg) (Table 4). The 24-h food intake was also similar between the two sham groups (113 ± 62 versus 117 ± 20 mmHg) (Table 4). PRA and 24-h aldosterone excretion followed the pattern observed at 2 wk, namely, lower potassium intake resulted in a lower SBP (153 ± 25 versus 197 ± 27 mmHg, group 1 versus group 2, \( P = 0.0006 \)). A clear dissociation between SBP and proteinuria also persisted through the latter part of the study period (216 ± 135 versus 148 ± 109 mg/dl, group 1 versus group 2). The difference, however, did not reach statistical significance. Weights of remnant kidneys, adrenal glands, and hearts were not different between the two groups (2.6 ± 0.8 versus 2.1 ± 0.4 g for kidney weight, 67 ± 8 versus 64 ± 5 mg for combined adrenal weight, and 1.6 ± 0.2 versus 1.7 ± 0.2 g for heart weight, all group 1 versus group 2). Glomerular volume, fractional interstitial volume, and the prevalence of glomerular sclerosis were all numerically higher in group 2; the differences, however, did not reach statistical significance (\( P = 0.16, 0.14, \) and 0.22 for glomerular volume, cortical interstitial volume, and sclerosis, respectively)

**Discussion**

These studies demonstrate that potassium restriction reduces BP in the remnant kidney model, while even wider absolute and per GFR variation in potassium intake had no impact on the measurements of food intake and confirm the equivalence of dietary intakes. Systolic BP was normal and not different between the two sham groups (113 ± 13 versus 117 ± 20 mmHg) (Table 4). PRA and 24-h aldosterone excretion followed the same pattern observed in the remnant groups (3.6 ± 1.1 versus 1.5 ± 0.5, ng angiotensin I/ml per h, \( P = 0.0002, 7.7 ± 2.6 \) versus 49.2 ± 18.8 ng/d, \( P = 0.0003 \)), group 3 versus group 4 for PRA, and 24-h urinary aldosterone excretion, respectively) (Table 3). The average plasma aldosterone level was numerically higher in group 4 than group 3, but the two values were not statistically distinguishable.

**Four-Week Results**

Both remnant groups (groups 1 and 2) continued to display weight gains and similar hematocrit levels at 4 wk (Table 2). In addition, serum creatinine remained similar in the two groups: 0.8 ± 0.2 versus 1.1 ± 0.8 mg/dl. Calculated daily potassium intake based on food ingestion at 4 wk was 0.5 ± 0.1 mEq/d in group 1 and 4.5 ± 0.9 mEq/d in group 2 (\( P < 0.01 \)). Plasma, urinary, and fecal potassium paralleled dietary potassium intake (3.3 ± 0.6 versus 4.8 ± 0.7 mEq/L for plasma potassium, \( P = 0.0001, 0.11 \) ± 0.1 versus 2.9 ± 0.6 mEq/d for urinary potassium, \( P = 0.0001, \) and 0.09 ± 0.1 versus 0.17 ± 0.1 mEq/d, \( P = 0.09 \) for stool potassium). Twenty-four-hour sodium excretion remained similar in the two groups (1.7 ± 0.1 versus 1.6 ± 0.2 mEq/d).

Systolic BP followed the pattern observed at 2 wk, namely, lower potassium intake resulted in a lower SBP (153 ± 25 versus 197 ± 27 mmHg, group 1 versus group 2, \( P = 0.0006 \)). A clear dissociation between SBP and proteinuria also persisted through the latter part of the study period (216 ± 135 versus 148 ± 109 mg/dl, group 1 versus group 2). The difference, however, did not reach statistical significance. Weights of remnant kidneys, adrenal glands, and hearts were not different between the two groups (2.6 ± 0.8 versus 2.1 ± 0.4 g for kidney weight, 67 ± 8 versus 64 ± 5 mg for combined adrenal weight, and 1.6 ± 0.2 versus 1.7 ± 0.2 g for heart weight, all group 1 versus group 2). Glomerular volume, fractional interstitial volume, and the prevalence of glomerular sclerosis were all numerically higher in group 2; the differences, however, did not reach statistical significance (\( P = 0.16, 0.14, \) and 0.22 for glomerular volume, cortical interstitial volume, and sclerosis, respectively)

**Table 3. Renin and aldosterone studies at 2 wk**

<table>
<thead>
<tr>
<th>Category</th>
<th>PRA (ng AngII/mg per h)</th>
<th>Plasma Aldosterone (pg/ml)</th>
<th>24-Hour Urinary Aldosterone (ng/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remnants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group 1 (n = 12)</td>
<td>16 ± 6(^b)</td>
<td>120 ± 124(^b)</td>
<td>2.6 ± 1.8(^c)</td>
</tr>
<tr>
<td>group 2 (n = 10)</td>
<td>6 ± 3</td>
<td>580 ± 442</td>
<td>23.2 ± 9.8</td>
</tr>
<tr>
<td>Sham</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group 3 (n = 6)</td>
<td>3.6 ± 1.1(^c)</td>
<td>183 ± 85</td>
<td>7.7 ± 2.6(^c)</td>
</tr>
<tr>
<td>group 4 (n = 6)</td>
<td>1.5 ± 0.5</td>
<td>288 ± 277</td>
<td>49.2 ± 18.8</td>
</tr>
</tbody>
</table>

\(^{a}\) PRA, plasma renin activity; AngII, angiotensin II.

\(^{b}\) \( P < 0.03, \) group 1 versus 2 and group 3 versus 4.

\(^{c}\) \( P < 0.005, \) group 1 versus 2 and group 3 versus 4.
systolic BP in the control groups. This antihypertensive property of potassium restriction in the remnant rats may be explained by the attenuation of their hyperaldosteronism with potassium restriction.

The mechanism by which aldosterone determines systemic hypertension in the remnant kidney model is not entirely clear. However, salt retention under the direction of mineralocorticoids would seem an obvious possibility and may indeed contribute through extracellular volume expansion in generating systemic hypertension. However, the hypertension of this model has been remarkably unresponsive to wide changes in dietary sodium intake (9–11). Thus, it is reasonable to consider other pathways by which aldosterone could sustain elevated BP in this model. Direct effects of aldosterone on the vasculature have been demonstrated. Notably, AngII receptor levels increase in cultured smooth muscle cells with aldosterone treatment (12), and increases in vascular endothelin have been reported after systemic administration of mineralocorticoids to animals (13). Furthermore, it is possible that other direct pressor mechanisms may occur with aldosterone; however, these would necessarily be rather slow in onset because acute administration of the mineralocorticoid does not immediately elevate pressure. Considerable data indicate that central nervous system actions of aldosterone activate pressor mechanisms (14). For example, infusion of aldosterone into the cerebrospinal fluid at very low rates (rates well below those that cause hypertension when administered systemically) over several days led to heightened arterial pressures in experimental animals (14,15). These or other “non-volume” actions of aldosterone may contribute to the elevated arterial pressures observed in the remnant kidney model. Interestingly, aldosterone receptor blockade with spironolactone has only a modest hypotensive effect in remnant animals (6).

The reported effects of dietary potassium on hypertension in other models have been variable and likely depend on the underlying mechanism of the hypertension (16–21). In the one-clip, two-kidney model of hypertension, a model with some similarities to the infarctive remnant, moderate potassium restriction ameliorated the hypertension even when started after establishment of the renovascular hypertension (21). However, in other models and in some populations of patients with primary hypertension, potassium supplementation lowers BP (17,18,20,22). To our knowledge, the effect on potassium intake on BP has not been studied in patients with renal parenchymal hypertension. However, the present studies raise the possibility that potassium restriction might mitigate this form of hypertension.

Despite the clear differences in BP on the two levels of potassium intake in the remnant kidney animals, there was no discernible effect of dietary potassium on their proteinuria or renal structural injury. Perhaps the elevation in PRA on the lower potassium diet and the likely associated increase in AngII vitiates the effects of lower BP. That is, AngII might have promoted injury in the potassium-restricted group through its intrarenal vasoconstrictive as well as fibroproliferative properties (1–3,5). Indeed, this reciprocal augmentation of PRA may be analogous to studies comparing ACE inhibitors

### Table 4.

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial Weight (g)</th>
<th>Final Weight (g)</th>
<th>Food Intake (g/d)</th>
<th>Plasma K (mEq/L GFR)</th>
<th>Urinary K (Uprot.V mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (α = 0)</td>
<td>254 ± 4</td>
<td>306 ± 6</td>
<td>15 ± 2</td>
<td>0.7 ± 0.2</td>
<td>0.2 ± 0.0</td>
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<tr>
<td>4 (α = 0)</td>
<td>254 ± 4</td>
<td>302 ± 11</td>
<td>17 ± 2</td>
<td>1.6 ± 0.5</td>
<td>0.8 ± 0.3</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Group</th>
<th>K+ Intake (mEq/L GFR)</th>
<th>SBP (mmHg)</th>
<th>Adrenal Glands</th>
<th>C Cr (L/d)</th>
<th>Urinary Na+ (mmol/g)</th>
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<td>3 (α = 0)</td>
<td>254 ± 4</td>
<td>113 ± 13</td>
<td>15 ± 3</td>
<td>0.8 ± 0.2</td>
<td>10.4 ± 2.1</td>
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<tr>
<td>4 (α = 0)</td>
<td>254 ± 4</td>
<td>117 ± 20</td>
<td>25 ± 8</td>
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</tr>
</tbody>
</table>

| Abbreviations as in Table 1. | b P < 0.01. | c P < 0.05. |
with antihypertensive therapy composed of reserpine, hydralazine, and thiazide (1). In such studies comparing these therapies in the remnant kidney model, the triple drug treatment and ACE inhibitor have been equally effective in controlling systemic hypertension, but only the agents interrupting AngII production were effective in blocking proteinuria and glomerulosclerosis (1). Stimulation of intrarenal AngII by the triple drug regimen has been viewed as a likely mechanism whereby renal injury is sustained. Such a scenario may pertain to the potassium-restricted rats and explain their persistent disease. Taking the results of the present studies together with those obtained in our previous studies demonstrating the role of aldosterone in this model, we conclude that either intrarenal AngII or aldosterone is sufficient to provoke proteinuria and structural damage in this model, but aldosterone is key in maintaining its arterial hypertension (6).

The stimuli to the hyperaldosteronism of the remnant kidney model are illuminated by the present results. It is well known that both potassium and AngII have important effects on aldosterone secretion (23–29). The stimulatory effect of potassium intake can be direct and occur in the absence of other secretagogues. AngII can also independently provoke aldosterone secretion (24,25,30). However, potassium and AngII when acting together produce multiplicative or synergistic stimulation of aldosterone secretion (27,29,31). Previous studies have shown that PRA in the remnant derives from the edges of the infarctive scar of the remnant kidney (2,7,32). We propose that maintenance of PRA from this site, in conjunction with the dietary potassium burden, synergistically spurs aldosterone secretion. Two previous lines of evidence had also supported the notion that hyperaldosteronism of the remnant kidney model arises in part from the requirement for potassium balance in the setting of reduced renal mass. First, as noted above, administration of enalapril and losartan to rats with a remnant kidney resulted in a fall in aldosterone level, but this was accompanied by a rise in serum potassium, a finding consistent with the notion that the heightened aldosterone maintained potassium balance (6). Second, contrasting the “pyleectomy” and infarction models of the remnant kidney, the former displayed a lower PRA and a lower aldosterone but at the expense of a higher serum potassium (32). Finally, the present studies demonstrate a particularly potent effect of potassium in determining aldosterone levels in this model.

The sham-operated rats, in contrast to those with remnant kidneys, showed no effect of dietary potassium on BP. With major reductions in potassium intake, small decreases in BP occasionally have been demonstrated in normal animals and these are exacerbated when the animals are simultaneously maintained on a low sodium diet (22,28). The relative stability of BP across a range of potassium intakes in the sham-operated animals may be related to any of several differences between them and the rats with partial renal ablation. First, plasma levels of aldosterone were not so widely separated by the levels of potassium intake in the sham-operated animals as were those in the rats with a remnant kidney. In fact, the plasma levels were not statistically different between the two sham groups even though excretion rates and adrenal weights were higher with the higher potassium diet. Second, the suppression of renin on the higher potassium diets tended to be greater in the sham-operated animals than in the remnant. Suppression of PRA by potassium loading has been well documented, but perhaps the scar-derived renin secretion from the remnant kidney is more resistant to potassium’s inhibitory actions (33). In this regard, the vasopressor and salt-retentive actions of AngII would be expected to be least in the sham-operated animals that had the lowest PRA. Third, natriuresis is an expected consequence of potassium loading, and may militate against the salt-retaining actions of aldosterone. This natriuresis may be expressed to a greater degree with a full complement of nephrons (18,34). Indeed, the classic minirenalocorticoïd—salt or “DOCA-salt”—model of hypertension requires nephron reduction, at least to the level of nephrectomy, to achieve hypertension (35). Hence, the hypertensive actions of aldosterone are likely to be much diminished with the normal filtration and excretory capacity of the sham-operated rats (36).

In conclusion, this set of studies demonstrates that potassium restriction lowers aldosterone production and arterial pressure in the remnant kidney model. The lack of effect on proteinuria and glomerular sclerosis may be due to the concomitant increase in PRA, and intrarenal AngII, which could offset the protection expected from the lower systemic BP. Finally, these results provide support for the hypothesis that the arterial hypertension and hyperaldosteronism of this model are dependent on dietary potassium.

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