Dietary Potassium and the Development of Hypertension in Two-Kidney, One Clip Goldblatt Hypertensive Rats

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SUMMARY Experiments were designed to test the hypothesis that a decrease in the molar ratio of sodium to potassium (from 5 to 0.2) in a diet of constant total electrolyte content would decrease renin and aldosterone levels or result in a diuresis and natriuresis that would attenuate the development of hypertension in two-kidney, one clip Goldblatt hypertensive rats. Measurements of blood pressure, renin-angiotensin-aldosterone activities, and metabolic balance were compared for groups of clipped or sham-clipped rats that were maintained on diets of altered sodium-potassium content initiated at the time of clipping. Four weeks of dietary treatment following application of a 0.25 mm clip to one renal artery resulted in significantly higher plasma renin activity for animals on the 1:5 Na/K ratio diet, (13.5 ± 2.3 ng Al/ml • hr, compared to 5.6 ± 0.7 ng Al/ml • hr for rats on the 1:1 Na/K diet, or 7.1 ± 0.8 ng Al/ml • hr for rats on the 5:1 Na/K ratio diet, p < 0.05). Urinary free aldosterone was also significantly (p < 0.01) higher in animals on the 1:5 Na/K diet (22.5 ± 1.3 ug/24 hrs compared to 10.9 ± 1.3 ug/24 hrs on the 1:1 Na/K ratio diet and 14.4 ± 0.5 ug/24 hrs on the 5:1 Na/K diet). Variations in plasma renin activity and aldosterone induced by altering the ratio of sodium to potassium in the diet were not associated with detectable differences in the level of blood pressure between the dietary sets of animals that had either been clipped or sham-clipped. Nine days after placement of a 0.2 mm clip on one renal artery in different groups of rats, the mean systolic blood pressure for animals on the 1:1 Na/K ratio diet was 141 ± 4 mm Hg, that for animals on the 1:5 Na/K ratio diet was 141 ± 7 mm Hg, and that for animals on the 5:1 Na/K ratio diet was 144 ± 3 mm Hg. There were no significant differences in blood pressure at any time during the period of study between any of the diet treatment groups. Metabolic balance studies failed to reveal significant differences in weight gain, food intake, water consumption, urine output, or fractional recovery of sodium or potassium between any of the dietary sets for the clipped group or the sham group of animals. These results indicate that altered molar ratios of dietary Na/K do not affect the course of blood pressure in the two-kidney, one clip Goldblatt hypertensive rat when total electrolyte content for the various diets is maintained at a constant level. (Hypertension 5: 521-528, 1983)

KEY WORDS • hypertension • potassium • two-kidney, one clip Goldblatt hypertensive rat • renin-angiotensin • molar dietary Na/K ratio • aldosterone • diuresis

The effect that alterations of dietary electrolytes have upon the development of hypertension has been controversial for many years. Potassium salts were classified as diuretic agents in the pharmacopeia from two centuries ago, and it was this property of potassium compounds that prompted Addison1 to use them for the treatment of hypertension in humans as early as 1928. The addition of potassium to diets of high sodium content has been observed to increase survival in the Dahl salt-sensitive strain of rats.2 Studies in humans have also suggested that the ratio of Na/K in the diet may be important in the development of hypertension and decreasing this ratio may be a means of reducing blood pressure.3, 4 Changes of dietary sodium and potassium are known to alter renin and aldosterone secretion; it is possible that attenuation of secretion rates or activities of this system are responsible for the decrease in blood pressure produced by a diet with a low Na/K ratio. However, the mecha-
nism of any antihypertensive effect of increased potassium intake remains undefined.

Two-kidney, one clip hypertension in rats is generally accepted as a form of hypertension where the elevated blood pressure is angiotensin-dependent early in the evolution of the high blood pressure. Further, our recent observations suggest that altered excretory behavior of the kidney opposite the stenosis might also contribute to the hypertension in this model. Since two-kidney, one clip hypertension in rats may be dependent on both angiotensin and volume factors and since both of these mechanisms could be affected by dietary electrolyte composition, it seemed an ideal model to use to test the hypothesis that a diet of high potassium content achieved by altering the molar ratio of Na/K would modify the development of hypertension. Particularly, we were interested in testing this hypothesis with an experimental design that would not result in increased solute intake possibly leading to a solute diuresis. For this reason, we designed diets of altered Na/K contents but which did not result in increased total solute intake for our rats. Since the renin-angiotensin system is thought to play a major role in the development of hypertension in this model, we expected that if an antihypertensive action of potassium was mediated by altered activity of this system it should be reflected by reduced plasma renin activity or renal renin activities. Suzuki et al. have suggested that diets of increased potassium content result in diuretic responses that are associated with attenuation of the level of hypertension. To assess the possible diuretic responses following our dietary interventions and to be certain that we achieved the altered urinary excretion patterns of electrolyte that would be expected to follow altered electrolyte intake, the effects of these dietary modifications were also examined in metabolic balance studies.

Methods

Male Sprague Dawley rats weighing 60–80 g were anesthetized with pentobarbital Na+ (Nembutal; 50 mg/kg, i.p.), the right kidney was exposed via a flank incision and a silver clip was placed around the right renal artery. After an overnight recovery period, the animals were placed in individual metabolic cages in a room with constant temperature and humidity, which was lighted automatically from 6 a.m. to 6 p.m. The animals remained in the metabolic cages except for the periods when they were removed for blood pressure measurements and weighing. All rats were provided with a measured amount of tap water each day allowing calculation of water intake daily. Animals were pair fed; the food allowance was gradually increased each day to allow for growth. Measurement of food consumption daily allowed computation of daily electrolyte intake.

Systolic blood pressures were measured every 3 days in conscious animals that were warmed to 37°C using an electrosphygmometer and physiograph recorder (Narco Bio Systems, Inc., Houston, Texas, Model PE 300). The average of six blood pressure measurements was taken as the blood pressure value for that day. All blood pressure measurements were performed at the same time of day to minimize any possible influence of a diurnal variation on the blood pressure data.

Specially formulated low sodium, low potassium diets were obtained from I.C.N. Nutritional, Cleveland, Ohio. Three diets were prepared; all had identical chloride and total cation contents but with varying molar ratios of sodium and potassium. The diet for Set 1 contained a 1:1 Na/K ratio of 0.3 mmol NaCl/g and 0.3 mmol KCl/g; the diet for Set 2 contained a 1:5 Na/K molar ratio of 0.1 mmol NaCl/g and 0.5 mmol KCl/g; the diet for Set 3 contained a 5:1 Na/K molar ratio with 0.5 mmol NaCl/g and 0.1 mmol KCl/g. All animals were allowed deionized water to drink ad libitum. Food and water intake were measured daily. Urine was collected for 24 hours for 2 full days out of every 3-day period; collections on the 3rd day were omitted since that 24-hour period was interrupted for blood pressure measurements. Urinary sodium and potassium were determined with a flame photometer (Model 443, Instrumentation Laboratories, Lexington, Massachusetts). Urinary chloride was measured on a digital chloridometer (Buchler Instruments, Fort Lee, New Jersey) and urinary osmolality was determined with a vapor pressure osmometer (Model 5730B; Wescor Inc., Logan, Utah). Twenty-four-hour urinary excretions of each electrolyte and osmolality were computed from these measurements and the urine volumes.

Three experimental groups of animals were used. Group 1 containing 66 animals had a 0.25 mm clip placed around the right renal artery. Group 1 was subdivided into three sets of 22 animals each; each set of animals was fed one of the three diets described above. Metabolic balance data were obtained in each dietary set of the Group 1 animals. Group 2 consisted of 33 animals that were sham-clipped. The sham group of animals was treated identically to those in Group 1 except that the clip was removed after placing it around the renal artery for 30 seconds. The sham group was also divided into three dietary sets of 11 animals each; each subset was treated with one of the diets described above. A third group of animals was examined that had a 0.2 mm clip placed around the right renal artery to produce hypertension of more rapid onset. Group 3 consisted of 21 animals; sets of seven animals were treated with each of the three different diets.

Plasma renin activity (PRA) and kidney renin activity were determined in 10 animals from each of the three dietary sets of animals which had either been clipped (Group 1, 0.25 mm clip) or sham-clipped (Group 2) 4 weeks after the introduction of the diet. All of the blood samples and kidneys were obtained at the same time of day to minimize any possible effects of circadian variation. The animals were decapitated and blood was collected into chilled tubes containing EDTA (disodium ethylene diamine tetracetate, 1 mg/ml). The kidneys were then quickly removed, frozen in an acetone/dry ice mixture, weighed and stored at...
-20°C until the extraction and assay for renin activity was performed. The blood was immediately centrifuged at 4°C; the plasma was removed and stored at -20°C until it was analyzed.

Tissue renin activity was determined by radioimmunoassay after extraction of the homogenized kidney. This involved incubation of an aliquot of the tissue homogenate with a fixed amount of renin substrate. The subsequent angiotensin I generated was assayed and the tissue renin activity was calculated as nanograms of angiotensin I per milligram of wet weight of kidney per hour of incubation (ng AI (mg • hr). The renin substrate pool was obtained from the plasma of a dog that had been nephrectomized 48 hours prior to sacrifice. The pooled plasma was subjected to transient acidification to reduce the activity of angiotensinases. Recovery of added angiotensin I after incubation at 37°C for 24 hours was 92.5% and linear angiotensin I generation with time was documented. Plasma renin activities were determined by radioimmunoassay. For 1 day of each week, urine was collected for 24 hours for aldosterone measurement. We used radioimmunoassay to measure free aldosterone since it is considered to reflect most accurately the variations of aldosterone secretion in the rat.

After 5 weeks on each diet, a group of 12 animals from each set in Group 1 was anesthesized with pentobarbital, and blood was removed from the femoral artery for the determination of plasma sodium and potassium concentration.

Values for blood pressure for each subset of animals at each time were averaged and the mean was used for comparisons. Observations were analyzed with analysis of variance accomplished with a general linear models procedure-regression program (Wilk's criterion) on a computer (IBM 371). Some of the observations were subjected to least squares curve-fitting procedures on a computer. Data are presented as mean ± SEM. Significance was accepted as a p value ≤ 0.05.

Results

Figure 1 shows the weight gain for all groups of animals with time. When these data were expressed as the best-fit regression equation of weight gain with time, the slopes of the equations were not significantly different between any of the dietary sets for the Group 1 animals. The slopes of the regression equations for each of the subsets of animals in Group 1 were 0.238 ± 0.007 on the Na/K 1:1 diet, 0.225 ± 0.008 for the Na/K 1:5 diet, and 0.222 ± 0.006 on the Na:K 5:1 diet (p > 0.20). Similarly, the slopes observed for growth rate for the sham clipped animals of Group 2 were not different for any of the three dietary sets, nor were they different from any dietary treatment set observed for Group 1. Animals of the three dietary treatment sets of Group 3 grew at rates similar to those of Group 1 and Group 2.

The data for blood pressure measurements for the three dietary subsets for each of the three groups of animals are shown in figure 2 as a function of time after clamping. The initial mean systolic pressures for animals from the three dietary subsets of Group 1 were not different. Blood pressure did not begin to rise above control values until 27 days post clamping when the weights of the animals ranged from 130 to 150 g. There was a gradual increase in blood pressure from 27 days onward that was similar for all three dietary sets of Group 1. At 54 days after clamping, the mean systolic pressure was 146 ± 6 mm Hg in animals on the Na/K 1:1 diet, 148 ± 7 mm Hg on the Na/K 1:5 diet, and 150 ± 11 mm Hg on the Na/K 5:1 diet.

The time of onset, rate of rise, and final blood pressures achieved in the dietary subsets were not significantly different. The initial blood pressures for the
three sets of rats of Group 2 were not different from each other, nor were they different from those of Group 1 or Group 3. The animals from Group 2 showed no significant change in blood pressure over the 54 days of the study, and there was no significant difference in blood pressure between any of the dietary subsets. The time course for the development of hypertension in Group 3 animals that had received the smaller clip (0.2 mm) was accelerated compared to that for animals that had a 0.25 mm clip (Group 1). The blood pressure began to rise 6 days after clipping when their body weights ranged between 100 to 110 g. Similar to the observations in Group 1 animals, the times of onset, rates of rise, and final levels of blood pressure achieved were not significantly different for any of the dietary subsets of Group 3. Thirty-six days after clipping, the blood pressure for Group 3 animals on the Na/K 1:1 diet was 153 ± 7 mm Hg; for animals on the Na/K 1:5 diet, 151 ± 6 mm Hg; and for animals on the Na/K 5:1 diet, 159 ± 10 mm Hg.

Urinary excretion of sodium and potassium are shown in figure 3. The marked differences in the urinary excretion of sodium and potassium between each set of six animals reflects the dietary intake closely. When the excreted electrolytes were expressed as the fraction of the measured intakes, recoveries ranged between 70% and 95%. There were no significant differences of fractional recoveries for sodium, potassium, or chloride between any of the dietary sets. Of note is the fact that the high potassium diet did not result in a detectable diuresis or natriuresis regardless
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FIGURE 4. Plasma renin activity and renal renin content four weeks post clipping. Each bar in the top panel represents data for 10 animals of each dietary set of clipped (0.25 mm clip) rats of Group 1. The data shown in the bottom panel represent the observations for 10 animals of each dietary set of sham clipped animals of Group 2. Values for plasma renin activity are shown on the left panel, and those for kidney renin contents of the stenotic (to the left) and the contralateral kidneys (to the right) are shown on the right panel. The notation for all of the different diet treatment groups is shown on the lower panel. Data are mean values ± SEM. * = significant differences from other dietary sets of that Group (p < 0.01).

Measurements of plasma renin activity (PRA) and renal renin activity obtained 4 weeks after clipping for animals that had been either clipped (Group 1, 0.25 mm) or sham-clipped (Group 2) are shown in figure 4. The PRA value for animals on the Na/K 1:5 diet was different from that for animals on either of the other two dietary subsets of Group 1. The clipped animals (Group 1) on the Na/K 1:5 diet had a mean PRA of 13.5 ± 2.3 ng Al/ml · hr, a value that was significantly greater than that for animals on the Na/K 1:1 ratio diet, 5.6 ± 0.7 ng Al/ml · hr, or that for animals on the Na/K 5:1 diet, 7.1 ± 0.8 ng Al/ml · hr (p < 0.01). The PRA for the dietary subsets of the sham-clipped animals (Group 2) showed trends that were directionally similar to those of the same dietary subsets for Group 1 animals. However, the absolute values of PRA each subset of Group 1 and Group 2 were different (p < 0.05). The average PRA value for Group 2 animals on the Na/K 1:5 diet was 8.1 ± 1.5 ng Al ml · hr, a value not significantly different from the average PRA value for animals on the Na/K 1:1 diet, 4.7 ± 0.8 ng Al/ml · hr, or that for animals on the Na/K 5:1 diet, 3.9 ± 1.9 ng Al/ml · hr. When all data for Groups 1 and 2 were examined, there were significant differences in PRA as a result of each of the dietary interventions (p < 0.05).

Renal renin activity was significantly higher in the clipped (right) kidney of all dietary sets of Group 1 when compared to the nonclipped (left) side (fig. 4). There were no significant differences in the renal renin activities for kidneys of the same side between the dietary sets. However, there was no indication that the dietary subsets failed to exhibit the same pattern of response for each treatment within Group 1 and Group 2 (analysis of variance). There were no differences in renal renin activity between the two kidneys of the sham-clipped animals (Group 2) for any dietary treatment set.

Twenty-four-hour urinary free aldosterone excretions for the 5-week period of study for Group 1 are shown in figure 5. After the 2nd week on the respective diets, the free aldosterone excretion for animals on the Na/K 1:5 diet was significantly higher (7.5 ± 1.0 µg/24 hrs) than that for animals on the Na/K 1:1 diet (4.0 ± 0.7 µg/24 hrs; p < 0.05). There was no significant difference between aldosterone excretions for animals on the Na/K 5:1 diet (5.1 ± 1.4 µg/24 hrs) and those on the Na/K 1:1 diet (p > 0.10). For all dietary sets of Group 1, the urinary aldosterone excretion reached maximum values 3 weeks after application of the clip.
to the renal artery. After 5 weeks on the diets, the urinary aldosterone excretions for all three dietary sets of Group 1 were not significantly different (12.0 ± 2.7 µg/24 hrs for animals on the Na/K 1:5 diet, 8.0 ± 1.4 µg/24 hrs on the Na/K 1:1 diet, and 7.7 ± 2.1 µg/24 hrs on the Na/K 5:1 diet). Average values for plasma electrolytes measured after 4 weeks of exposure to the various diets are shown in table 2. Plasma potassium was significantly higher in the animals on the low sodium-high potassium diet ratio compared to that for the other dietary subsets but there were no differences in plasma sodium between any of the dietary subsets.

**Discussion**

The decrease in molar ratio of Na/K in the diets used in this study (from 5 to 0.2) was similar to those previously found to modify blood pressure in salt dependent forms of hypertension. However, the total solute content remained constant in all of the diets in the present protocol, in contrast to earlier studies where the total solute intake was increased by the addition of KCl to diets of normal or increased sodium chloride content, the total solute content remained constant in all of the diets in the present protocol. The sodium content of standard rat chows ranges from 0.15-0.23 mmoles/g and the potassium chloride content ranges from 0.16-0.28 mmoles/g, resulting in molar ratios of Na/K for standard rat chows of 0.5 to 0.91. Therefore, the total electrolyte content of the diets used in this study are only slightly above the range of normal dietary electrolyte content for the rat.

The development of hypertension in the two-kidney, one clip Goldblatt hypertensive rat was not affected by manipulations of the dietary Na/K ratio. This observation was seen consistently in both the more rapid development of hypertension following application of the 0.2-mm clip to one renal artery and during the slower development of hypertension when the larger diameter 0.25-mm clip was used. The blood pressures of sham-clipped animals, which remained at normal normotensive levels, were also not affected by the alteration of dietary Na/K ratios. These findings differ substantially from those reported by Suzuki et al. However, it should be noted that the experimental designs of the two studies are not comparable. Suzuki et al. added potassium chloride to the rats' drinking water, which reduced the molar Na/K ratio from approximately 0.6 on the normal diet to 0.35 in the treated group; however, this also increased greatly the total electrolyte intake for the animals. The present experiments utilized diets that did not increase the total electrolyte intake and which also allowed much larger variations in the molar ratios for dietary Na/K. There was very little difference between the absolute amount of potassium administered in Suzuki's high KCl group

### Table 1. Metabolic Studies for Group I Animals

<table>
<thead>
<tr>
<th></th>
<th>1st Week</th>
<th>2nd Week</th>
<th>3rd Week</th>
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<tr>
<td></td>
<td>Na:K 1:1</td>
<td>Na:K 1:5</td>
<td>Na:K 5:1</td>
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<td></td>
<td>Na:K 1:1</td>
<td>Na:K 1:5</td>
<td>Na:K 5:1</td>
</tr>
<tr>
<td></td>
<td>Na:K 1:1</td>
<td>Na:K 1:5</td>
<td>Na:K 5:1</td>
</tr>
<tr>
<td>Total water intake mls</td>
<td>±12 ± 12</td>
<td>±5.9 ± 7.7</td>
<td>±7.7 ± 7.7</td>
</tr>
<tr>
<td>Sodium intake mEq</td>
<td>8.7 ± 0.9</td>
<td>3.2* ± 0.2</td>
<td>16* ± 1.2</td>
</tr>
<tr>
<td>Potassium intake mEq</td>
<td>8.7 ± 0.9</td>
<td>3.1* ± 0.1</td>
<td>3.1* ± 0.2</td>
</tr>
<tr>
<td>Urine volume mls</td>
<td>66.9 ± 0.9</td>
<td>59.3 ± 1.1</td>
<td>61.5 ± 5.2</td>
</tr>
<tr>
<td>Sodium excretion mEq</td>
<td>4.9 ± 0.4</td>
<td>2.3* ± 0.3</td>
<td>12.0* ± 1.9</td>
</tr>
<tr>
<td>Potassium excretion mEq</td>
<td>5.5 ± 0.4</td>
<td>9.7* ± 0.3</td>
<td>2.1* ± 0.3</td>
</tr>
<tr>
<td>Chloride excretion mEq</td>
<td>12.3 ± 0.4</td>
<td>13.3 ± 0.3</td>
<td>11.7 ± 0.6</td>
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<tr>
<td>Osmolal excretion mOsm/mEq</td>
<td>24.9 ± 3.4</td>
<td>20.9 ± 2.5</td>
<td>22.7 ± 3.4</td>
</tr>
</tbody>
</table>

Each number represents the average of mean accumulation of the 4 day collection period within each week from 6 animals in each dietary set. The SEM is printed below.

**Values significantly different from the Na:K=1:1 diet group: p < 0.01; p < 0.051.**

### Table 2. Measured Plasma Electrolytes for Group I Rats after 5 Weeks of Diet Exposure

<table>
<thead>
<tr>
<th>Diet</th>
<th>Na:K 1:1</th>
<th>Na:K 1:5</th>
<th>Na:K 5:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na⁺] plasma</td>
<td>134 ± 1.56</td>
<td>131 ± 1.23</td>
<td>136 ± 1.3</td>
</tr>
<tr>
<td>[K⁺] plasma</td>
<td>3.74 ± 0.10</td>
<td>4.29 ± 0.24*</td>
<td>3.71 ± 0.14</td>
</tr>
</tbody>
</table>

*Plasma potassium concentration was significantly higher in Na/K 1:5 diet group than either of other diet groups (p < 0.01). Data represent observations (x ± sem) for 12 animals of each dietary set of Group 1 measured 5 weeks after clipping.
(approximately 7 mmoles/day) and the quantities that we observed to be ingested by the high KCl group of the present experiments (up to 10 mmoles/day) at comparable times in the respective studies. Therefore, it would appear that the absolute amount of potassium is not important in the mediation of any antihypertensive effect. Furthermore, differences in the amount of potassium do not explain the differences between the results observed by Suzuki and coworkers and the results of these experiments.

Suzuki and coworkers reported 7 that the addition of potassium to the drinking water was associated with a marked diuresis and natriuresis; it was suggested that this contributed to the fall in blood pressure that they observed. Simultaneous reduction of the NaCl intake when the KCl intake is high may prevent the natriuresis that has been observed by others when high potassium intakes have been superimposed on normal NaCl intakes. 21 Metabolic balance studies undertaken during the administration of large amounts of potassium support this supposition as it has been shown 14, 15 that the diuretic and natriuretic effects of potassium are transient and limited by the extent to which overall sodium balance can be perturbed. Therefore, the diuretic activity of potassium reported by others may be a reflection of the overall increased solute intake used in those protocols rather than any diuretic action of potassium directly. The solute load in all of the diets utilized in our experiments was identical as evidenced by the equivalent chloride excretion for all dietary sets at any point in time (table 1). Renal excretory ability as reflected by urine volume/24 hrs and osmolar excretion was not different for any of the dietary sets suggesting that these diets have no gross deleterious effect upon renal function.

Plasma renin activity was significantly increased in the clipped animals of Group 1 on the Na/K 1:5 diet (i.e., the low sodium, high potassium diet). Despite this increase of PRA, blood pressure for this set was not significantly different from that of the other dietary sets of Group 1. It is surprising that blood pressure is not directly related to PRA in this model of hypertension where blood pressure is usually angiotensin-dependent. However, earlier studies have reported 18 that PRA may not correlate with blood pressure in two-kidney, one clip Goldblatt hypertensive rats when they are exposed to a salt-restricted diet.

An alternative explanation 19 for the failure of blood pressure to increase with increasing PRA is that the high potassium content of the diet may alter the sensitivity of vascular receptors to the effects of angiotensin. In support of this possibility is the observation 18 that high potassium diets decrease the number of angiotensin receptors in vascular smooth muscle. Thus, the dose response relationships for angiotensin vascular receptors may be altered, and blood pressure may be largely unaffected, even though PRA is increased. Although potassium can suppress renin secretion directly, 12, 19, 21 the simultaneously lowered sodium content of this diet is obviously able to override this suppressive effect, resulting in PRA that are relatively increased. A low sodium, high potassium diet in humans is also associated with increased PRA. 22, 23 The results of the observations of PRA by Suzuki et al. 7 are rather surprising in that, PRA was not increased but actually suppressed, despite the dramatic natriuresis that they observed following the introduction of potassium to the animals drinking water. This suppression of renin activity may have been one of the factors responsible for the attenuated rise in blood pressure observed during potassium administration in their experiments; however, the mechanism responsible for the decreased PRA is not evident. It is possible that the suppression of PRA in this setting is the result of the greatly increased total electrolyte or chloride intake. 23 In summary, it seems likely that the differences in total electrolyte content of the diets in the two studies are responsible for the variant results.

There are two mechanisms that could account for the increased urinary aldosterone excretion in the animals of Group 1 treated with the low sodium, high potassium diet. The first possibility is that the expected increases in angiotensin activity following the marked increase of PRA on this diet stimulates adrenal mineralocorticoid release. The second possibility is that the high potassium diet and the resulting increases in systemic potassium concentrations could stimulate aldosterone release from the adrenal directly. It is interesting that, in all the dietary sets, aldosterone excretion reached a maximum 3 weeks after placing the clip on the renal artery and thereafter declined. This pattern of aldosterone excretion may reflect the changes in activity of the renin-angiotensin system with time that we have observed and that others have reported to occur in the two-kidney, one clip Goldblatt hypertensive rat. 24, 25
In conclusion, lowering the dietary ratio of sodium to potassium when the solute content of the diet is maintained at a normal level increases PRA and aldosterone excretion rates but does not influence the pattern of development of high blood pressure in a two-kidney, one clip model of Goldblatt hypertension in rats. Furthermore, a diuretic effect of potassium is not apparent when the total solute content of the diet is maintained at a normal level. However, it is possible that diuretic effects of increased dietary potassium intake or high total solute intake itself are responsible for the reduction in blood pressure observed when potassium is added to high salt diets in salt dependent forms of hypertension. It could also be that ingestion of a diet of high potassium content in the setting of normal total solute intake results in subtle but significant volume depletion that increases PRA; the net effect of these two phenomena would maintain blood pressure at the same hypertensive level. In other experiments, higher Na\(^+\) intakes may have allowed maintenance of the crucial volume factor and allowed high potassium to reduce blood pressure by attenuating activity of the renin-angiotensin axis directly. However, it is also possible that potassium acts through other mechanisms that were not evaluated in these experiments, such as by modifying the contribution of the nervous system to hypertension\(^{26,27}\) or by antagonizing the effect of the putative natriuretic hormone.\(^{29-31}\)

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