Potassium Depletion Ameliorates Hypertension in Spontaneously Hypertensive Rats

STUART L. LINAS AND ROCHELLE MARZEC-CALVERT

SUMMARY The hemodynamic effect of moderate K⁺ depletion in hypertension is unknown. Since severe K⁺ depletion reduces systemic vascular resistance in normotensive rats, we determined the effect of K⁺ depletion on the natural history of hypertension in spontaneously hypertensive rats (SHR). Wistar-Kyoto rats (WKY) and SHR were fed a K⁺-replete, a moderately K⁺-depleted, or a severely K⁺-depleted diet. After 6 weeks, systemic vascular resistance was reduced by 25% in WKY on the severely K⁺-depleted diet while mean arterial pressure and systemic vascular resistance were comparable in WKY on the other two diets. In SHR on the severely K⁺-depleted diet for 6 weeks, muscle K⁺ was reduced by 23% and growth rate by 65%. In SHR on the moderately K⁺-depleted diet, growth rate was reduced by 23% after 3 weeks. By 6 weeks, however, muscle K⁺ was reduced by 5 to 6% and growth rate was comparable to that in SHR receiving the K⁺-replete diet. The administration of either K⁺-depleted diet prevented the development of hypertension (systolic blood pressure: severely-depleted, 116 ± 4; moderately-depleted, 122 ± 3; K⁺-replete, 155 ± 5 mm Hg; p < 0.001 compared with both K⁺-depleted groups) and reversed established hypertension (systolic blood pressure: severely-depleted, 116 ± 4; moderately-depleted, 128 ± 3; K⁺-replete, 171 ± 5 mm Hg; p < 0.001 compared with both K⁺-depleted groups). The protective effect of K⁺ depletion was mediated by a 40% reduction in systemic vascular resistance. These results suggest that K⁺ depletion has a potent antihypertensive effect in SHR. The vasodilative effect of moderate K⁺ depletion also appears to be specific for hypertension since it did not occur in normotensive WKY.

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KEY WORDS • hypokalemia • electrolytes • hemodynamics • angiotensin

For many years sodium was the only electrolyte considered relevant to the control of blood pressure in patients with essential hypertension. While recent studies have demonstrated that other electrolytes such as calcium and chloride may also be of importance in the pathogenesis of hypertension, there have been few experimental studies on the hemodynamic effects of potassium in hypertension. This paucity of information on potassium is surprising since potassium is the major intracellular cation and since many of the 30 million hypertensive patients in the United States are treated with diuretic agents and manifest mild hypokalemia and a decrease in total body potassium.

Although there have been few studies on the effect of potassium in hypertensive animals, there have been hemodynamic studies on the effects of potassium in normotensive animals. Acute hypokalemia, as occurs when vessels or limbs from normokalemic animals are perfused with hypokalemic solutions, results in vasoconstriction. In contrast, chronic, severe total body potassium depletion induced by diet or dialysis, or both, results in a decrease in systemic vascular resistance (SVR) and mean arterial pressure (MAP). Unfortunately, severe potassium depletion results in growth retardation as well as a decrease in total body potassium, and the vasodilative effect of severe potassium depletion has not been dissociated from this growth retardation.

Despite information in normotensive rats indicating that potassium depletion could lower blood pressure, many investigators have suggested that potassium depletion results in hypertension and advocate potassium supplementation therapy in patients treated for hypertension who become hypokalemic.

To determine the physiological importance of potassium depletion in hypertension, we developed a model...
of moderate potassium depletion that did not impair growth over prolonged periods. With the use of this model, we found that moderate dietary potassium depletion prevented and reversed angiotensin-mediated hypertension in the two-kidney, one clip model of renovascular hypertension in the rat. Since moderate potassium depletion had such a potent vasodilative effect in angiotensin II-mediated hypertension, we questioned whether potassium depletion could have a broader antihypertensive effect. The purpose of the current study was to determine if moderate potassium depletion could alter the natural history of hypertension in spontaneously hypertensive rats (SHR), which exhibit a form of hypertension that has many features in common with human essential hypertension.

Materials and Methods

Male 8-week-old Wistar-Kyoto rats (WKY) and SHR (Charles River Breeding Laboratories, Wilmington, MA, USA) were used for study. All rats were maintained on standard rat chow (Wayne Laboratory, Wayne, IN, USA) for 1 week. At that time, systolic blood pressure (SBP) was determined and animals were placed on the following diets:

1. A severely potassium-depleted diet (ICN Pharmaceutical, Cleveland, OH, USA) containing potassium, 5 mEq/kg, and supplemented with magnesium.
2. A moderately potassium-depleted diet that was prepared by adding 54 mEq KCl to the severely potassium-depleted diet.
3. Two different potassium-replete diets: one prepared by adding a mixture of potassium salts, 240 mEq/kg, to the severely potassium-depleted diet and the other consisting of standard rat chow containing potassium, 260 mEq/kg.

Magnesium was added to each diet (other than standard rat chow) because the basic potassium-depleted diet is deficient in magnesium. The final composition of these diets has been reported. Since in preliminary studies we determined that the natural history of hypertension was the same in both groups of potassium-replete rats, data for the two groups of potassium-replete rats have been combined.

Effect of Potassium Depletion in WKY

To study the effect of moderate and severe potassium depletion on normotensive animals, eight WKY receiving the potassium-replete diet were compared with eight WKY receiving the moderately potassium-depleted diet and six WKY receiving the severely potassium-depleted diet. The SBP and weight gain were determined after 3 and 6 weeks. Plasma potassium, muscle potassium, and systemic hemodynamics were determined after 6 weeks of the respective diets.

Effect of Potassium Depletion in SHR

To study the effect of moderate and severe potassium depletion on the development of hypertension, 23 rats receiving the potassium-replete diet were compared with 23 rats receiving the moderately potassium-depleted diet and 13 rats receiving the severely potassium-depleted diet. SBP and weight gain were determined after 3 and 6 weeks in all animals. In six animals in each group, systemic hemodynamics, plasma potassium, and muscle potassium were determined after 6 weeks (15-17 weeks of age) of the respective diets. In other rats, plasma sodium, potassium, calcium, and muscle potassium were also determined after 6 weeks.

To study the effect of moderate and severe potassium depletion on established hypertension, 44 additional SHR on the potassium-replete diet with a SBP of 150 mm Hg or higher (15-17 weeks) were continued on the potassium-replete diet (n = 15) or placed on the moderately (n = 18) or severely (n = 11) potassium-depleted diets. SBP and weight were monitored for 6 additional weeks. Systemic hemodynamics, plasma potassium, and muscle potassium were determined after 6 weeks in six rats in the potassium-replete group, six in the moderately depleted group, and five in the severely potassium-depleted group. In additional animals, sodium, potassium, chloride, calcium, and muscle potassium were also determined after 6 weeks.

The SBP was measured in unanesthetized animals by the tail-cuff plethysmography method using a pneumatic sensing device (Narco Biosystems, Houston, TX, USA). For hemodynamic studies, potassium-replete and potassium-depleted animals were anesthetized with pentobarbital (40-60 mg/kg i.p.). Each animal was cannulated with tapered PE-350 tubing through the femoral artery for blood pressure recording and blood collection and into the left ventricle through the right carotid artery for microsphere injection. Cardiac output was determined by the reference sample method using plastic microspheres (3M, St. Paul, MN, USA) smaller than 8.8 ± 0.6 μm in diameter labeled with 85Sr as adapted for use in our laboratory. Microspheres were suspended in normal saline and sonicated within 30 seconds of injection. In preliminary studies and in studies by others, it has been shown that there is less than 3% recirculation of 8.8-μm microspheres through the pulmonary circulation. For plasma and muscle determinations, animals were anesthetized with pentobarbital and the left femoral artery was cannulated with polyethylene tubing. Plasma was obtained for determination of sodium, potassium, chloride, and calcium. A 1-g sample of psoas muscle was taken for determination of muscle potassium content. Plasma sodium and potassium were measured with an IL 343 Flame Photometer (Instrumentation Laboratories, Lexington, MA, USA). Chloride was measured with a chloridimeter (Buchler-Cotlove, Fort Lee, NJ, USA). Muscle potassium was determined after nitric acid digestion. Calcium was measured by atomic absorption spectrophotometry (Model 290B; PerkinElmer, Norwalk, CT, USA).

Statistical analysis was performed using one-way and two-way analysis of variance. Multiple comparisons were made using Scheffe's test. Data are expressed as the mean ± SEM.
Results

Effect of Potassium Depletion in WKY

After 3 and 6 weeks of the respective diets, SBP was comparable in the three groups. Animals receiving the severely potassium-depleted diet did not grow normally, gaining 10.2 ± 2.3 g over the 6 weeks of study. At 3 weeks, animals receiving the moderately potassium-deficient diet had gained 65% of the weight gained by animals on the potassium-replete diet (initial weight, 215 ± 4 vs 212 ± 4 g, respectively; change in weight, 26.3 ± 2.2 vs 40.2 ± 1.8 g, respectively; \( p < 0.05 \)). By 6 weeks, cumulative weight gain was comparable between the two groups (52.5 ± 3.2 vs 56.8 ± 4.1 g, respectively; \( p = \text{NS} \)). Table 1 demonstrates the effects of the potassium depletion on electrolytes and systemic hemodynamics. The WKY fed the severely potassium-depleted diet had marked decreases in both plasma and muscle potassium. There was a 25% reduction in SVR, while cardiac index was increased by 17%. In contrast to the vasodepressor effects of severe potassium depletion, moderate potassium depletion resulted in a 9% decrease in muscle potassium but did not result in vasodilatation or an increase in cardiac index.

Effect of Potassium Depletion in SHR

Figure 1 demonstrates the effect of potassium depletion on developing hypertension in the SHR. In potassium-replete rats, SBP reached 144 ± 2 mm Hg at 3 weeks and 155 ± 5 mm Hg at 6 weeks. Hypertension was less severe in rats fed either of the potassium-depleted diets. In the severely potassium-depleted group, SBP reached 114 ± 4 mm Hg at 3 weeks and 116 ± 4 mm Hg at 6 weeks (both, \( p < 0.001 \) compared with the potassium-replete group). In the moderately potassium-depleted group, SBP reached 121 ± 2 mm Hg at 3 weeks and 122 ± 3 mm Hg at 6 weeks (both, \( p < 0.001 \) compared with the potassium-replete group).

Table 2 demonstrates the hemodynamic mechanism of the protective effect of potassium depletion. The increase in MAP in potassium-replete rats resulted from an increase in SVR of 72% as compared with that in normotensive WKY. In contrast, the administration of either potassium-depleted diet prevented the increase in MAP and SVR observed in potassium-replete animals.

Weight gain in rats with spontaneous hypertension is shown in Figure 2 and Table 3. Animals receiving the severely potassium-depleted diet did not grow normally during the 6-week study period. At 3 weeks, animals fed the moderately potassium-depleted diet had gained 77% of the weight of animals fed the potassium-replete diet. By 6 weeks, however, cumulative weight gain was comparable between the two groups. At the time of death, there were no statistically significant differences among groups in plasma concentrations of sodium, chloride, or calcium. In contrast, plasma potassium was not significantly reduced in moderately potassium-deficient rats but was profoundly reduced in severely potassium-depleted animals. The decrease in plasma potassium was associated with a decrease in muscle potassium in both potassium-depleted groups: 5% in the moderately potassium-depleted group and 23% in the severely potassium-depleted group. Thus, the administration of the severely potassium-depleted diet resulted in severe potassium depletion and growth retardation.

Table 1. Effect of Potassium Depletion on Plasma Potassium, Muscle Potassium, and Systemic Hemodynamics in Normotensive WKY

<table>
<thead>
<tr>
<th>Variable</th>
<th>( K^+ )-replete (( n = 8 ))</th>
<th>Moderate ( K^+ ) depletion (( n = 8 ))</th>
<th>Severe ( K^+ ) depletion (( n = 6 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma ( K^+ ) (mEq/L)</td>
<td>4.07 ± 0.1</td>
<td>3.70 ± 0.1</td>
<td>2.01 ± 0.1*</td>
</tr>
<tr>
<td>Muscle ( K^+ ) (mEq/L)</td>
<td>383 ± 7</td>
<td>353 ± 9†</td>
<td>294 ± 18†</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>114 ± 2</td>
<td>117 ± 2†</td>
<td>100 ± 3*</td>
</tr>
<tr>
<td>Cardiac index (ml/min-kg(^{-1}))</td>
<td>318 ± 14</td>
<td>311 ± 10</td>
<td>372 ± 14†</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml·min(^{-1})·kg(^{-1}))</td>
<td>0.36 ± 0.02</td>
<td>0.38 ± 0.01</td>
<td>0.27 ± 0.02‡</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*\( p < 0.001 \), †\( p < 0.05 \), ‡\( p < 0.01 \), compared with values in potassium-replete WKY.
TABLE 2. Effect of Potassium Depletion on Plasma Potassium, Muscle Potassium, and Systemic Hemodynamics in Developing SHR

<table>
<thead>
<tr>
<th>Variable</th>
<th>K⁺-replete</th>
<th>Moderate K⁺ depletion</th>
<th>Severe K⁺ depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma K⁺ (mEq/L)</td>
<td>4.19 ± 0.1</td>
<td>3.98 ± 0.1</td>
<td>1.85 ± 0.1*</td>
</tr>
<tr>
<td>(10)</td>
<td>(11)</td>
<td>(11)</td>
<td></td>
</tr>
<tr>
<td>Muscle K⁺ (mEq/kg)</td>
<td>385 ± 7</td>
<td>366 ± 8</td>
<td>297 ± 8*</td>
</tr>
<tr>
<td>(23)</td>
<td>(22)</td>
<td>(7)</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>147 ± 3</td>
<td>115 ± 3*</td>
<td>113 ± 5*</td>
</tr>
<tr>
<td>Cardiac index (ml/min·kg⁻¹)</td>
<td>238 ± 10</td>
<td>301 ± 15†</td>
<td>295 ± 6†</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml·min⁻¹·kg⁻¹)</td>
<td>0.62 ± 0.03</td>
<td>0.38 ± 0.02*</td>
<td>0.42 ± 0.02†</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Numbers in parentheses refer to the number of animals for that determination. Hemodynamic studies were performed in six animals in each group.

*p < 0.001, †p < 0.05, compared with values in potassium-replete SHR.

Contrast, the administration of the moderately potassium-depleted diet resulted in more moderate potassium depletion and, after the initial 3 weeks, a normal growth pattern.

The effect of potassium depletion on established hypertension in the SHR is depicted in Figure 3. A protective effect of potassium depletion was observed at 2 weeks and was still present after 6 weeks. Table 4 demonstrates the effect of the potassium depletion on systemic hemodynamics in SHR with established hypertension. The protective effect of moderate potassium depletion on MAP was mediated by a 42% decrease in SVR. The effect of potassium depletion on growth in SHR with established hypertension is depicted in Table 3 and Figure 4. As in the earlier studies, severely potassium-depleted rats did not grow normally, gaining just 35% of the weight of potassium-replete rats over the 6 weeks of study. In contrast, while weight gain in moderately potassium-depleted rats at 2 weeks was 41% of potassium-replete rats, by 3 and 6 weeks weight gain was comparable in moderately potassium-depleted and potassium-replete animals. At death there were no statistically significant differences among groups in plasma sodium, chloride, or calcium concentration. In contrast, plasma potassium was profoundly reduced in severely potassium-depleted SHR and modestly reduced in moderately potassium-depleted rats. The decrease in plasma potassium was associated with a 22% decrease in muscle potassium in severely potassium-depleted rats and a 6% decrease in muscle potassium in moderately potassium-depleted rats (see Table 4).

Discussion

The hemodynamic effects of potassium depletion in hypertension are debated. Beginning with Thomas Addison, potassium depletion has been implicated as a cause of hypertension. While numerous epidemiological studies have reported an inverse relationship between dietary potassium and blood pressure, there have been few experimental studies on the hemodynamic effects of potassium depletion in hypertension. However, the published experimental data suggest that the effect of potassium depletion on blood pressure control in hypertension is variable. For exam-

![Figure 2. Effect of moderate (KD-M; n = 23) and severe (KD-0; n = 13) potassium depletion on weight gain in SHR prior to the development of hypertension. KR refers to potassium-replete animals (n = 23). The p values refer to comparisons between severely potassium-depleted and either moderately potassium-depleted or potassium-replete animals.](http://hyper.ahajournals.org/)

![Figure 3. Effect of moderate potassium-depleted (KD-M; n = 23) and severe potassium-depleted (KD-0; n = 13) diets on plasma potassium concentration and muscle potassium concentration in SHR. KR refers to potassium-replete animals (n = 23). The p values refer to comparisons between severely potassium-depleted and either moderately potassium-depleted or potassium-replete animals.](http://hyper.ahajournals.org/)

**TABLE 3. Effect of Potassium Depletion on Absolute Body Weight in SHR**

<table>
<thead>
<tr>
<th>Weight of SHR (g)</th>
<th>K⁺-replete (n = 23)</th>
<th>Moderate K⁺ depletion (n = 23)</th>
<th>Severe K⁺ depletion (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing hypertension</td>
<td>228 ± 3</td>
<td>227 ± 3</td>
<td>227 ± 3</td>
</tr>
<tr>
<td>3 weeks</td>
<td>264 ± 3</td>
<td>255 ± 4</td>
<td>233 ± 3*</td>
</tr>
<tr>
<td>6 weeks</td>
<td>280 ± 4</td>
<td>280 ± 5</td>
<td>246 ± 3†</td>
</tr>
<tr>
<td>Established hypertension</td>
<td>276 ± 4</td>
<td>277 ± 5</td>
<td>277 ± 6</td>
</tr>
<tr>
<td>2 weeks</td>
<td>293 ± 4</td>
<td>284 ± 6†</td>
<td>281 ± 6†</td>
</tr>
<tr>
<td>3 weeks</td>
<td>306 ± 5</td>
<td>308 ± 8‡</td>
<td>296 ± 6*‡</td>
</tr>
<tr>
<td>6 weeks</td>
<td>333 ± 4</td>
<td>336 ± 6†</td>
<td>297 ± 5‡</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*‡p < 0.05, †p < 0.001, compared with values in moderately potassium-depleted and potassium-replete SHR; §p < 0.05, compared with values in potassium-replete SHR.
hysteria, hypertension in the deoxycorticosterone acetate-salt model is associated with severe potassium depletion. In contrast, severe potassium depletion has been found to prevent the development of angiotensin-mediated hypertension. Moreover, severe potassium depletion has been shown to decrease systemic resistance in normotensive dogs and rats. In each of these studies, however, the vasodilative effect of severe potassium depletion was not dissociated from the growth retardation that is known to be associated with severe potassium depletion.

We have recently developed a more moderate model of potassium depletion that resulted in a 6 to 8% decrease in muscle potassium and, after an initial lag in weight gain, did not alter growth. With the use of this model, we found that moderate potassium depletion prevented the development of angiotensin II-mediated hypertension in the rat with two-kidney, one clip renovascular hypertension and reversed established two-kidney, one clip renovascular hypertension. Our current studies suggest that moderate potassium depletion may have a broader antihypertensive effect. In this regard potassium reversal reversed a form of hypertension in SHR that is not considered to be primarily angiotensin II-mediated. Our initial studies in SHR were carried out in severely potassium-depleted rats because this model of potassium depletion had been used frequently. Although severe potassium depletion reversed developing and established hypertension, the SHR fed the severely potassium-depleted diet did not grow normally. In addition, severe potassium depletion resulted in growth retardation and vasodilation in normotensive WKY (see Table 1). In contrast to severely potassium-depleted rats, after an initial lag in growth, SHR fed the moderately potassium-depleted diet grew at the same rate as rats fed a normal potassium diet. In association with a 5 to 6% decrease in muscle potassium in SHR fed the moderately potassium-restricted diet, SBP was reduced by 21% in the studies on early hypertension and by 25% in the studies on established hypertension. Since the vasodilative effect of moderate potassium depletion was also observed between 3 and 6 weeks when SHR fed the

**TABLE 4.** Effect of Potassium Depletion on Plasma Potassium, Muscle Potassium, and Systemic Hemodynamics in SHR with Established Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>K⁺-replete</th>
<th>Moderate K⁺ depletion</th>
<th>Severe K⁺ depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma K⁺ (mEq/L)</td>
<td>4.24 ± 0.2 (9)</td>
<td>3.76 ± 0.2 (10)*</td>
<td>2.1 ± 0.1 (10)</td>
</tr>
<tr>
<td>Muscle K⁺ (mEq/kg)</td>
<td>380 ± 9 (13)</td>
<td>357 ± 9 (17)*</td>
<td>301 ± 13 (6)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>168 ± 4 (17)</td>
<td>123 ± 3 (17)†</td>
<td>118 ± 4 (6)†</td>
</tr>
<tr>
<td>Cardiac index (ml/min·kg⁻¹)</td>
<td>221 ± 6</td>
<td>281 ± 9†</td>
<td>303 ± 8†</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml·min⁻¹·kg⁻¹)</td>
<td>0.76 ± 0.04</td>
<td>0.44 ± 0.02†</td>
<td>0.39 ± 0.03†</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Numbers in parentheses refer to the number of animals for that determination. Hemodynamic studies were performed in six potassium-replete, six moderately potassium-depleted, and five severely potassium-depleted animals.

*p < 0.05, †p < 0.001, compared with values in potassium-replete animals.
moderately potassium-depleted diet grew at a faster rate than SHR fed the potassium-replete diet (see Figures 2 and 4), the protective effect of moderate potassium depletion could be dissociated from the sustained growth retardation of severe potassium depletion. However, since there was an initial lag in weight gain in SHR fed the moderately potassium-depleted diet, it is possible that an initial lag in growth may have been required to observe the vasodilative effect of moderate potassium depletion in the SHR. Furthermore, despite comparable decreases in muscle potassium in SHR and WKY, the vasodilative effect of moderate potassium depletion was not observed in normotensive WKY (see Table 1). Thus, the vasodepressant effect of moderate potassium depletion was specific for hypertension.

The protective effect of potassium depletion was mediated by a 40% reduction in SVR. In earlier studies in normotensive, severely potassium-depleted rats, we found that the vasodilative effect of potassium depletion was associated with a selective decrease in pressor responsiveness to angiotensin II as pressor responsiveness to norepinephrine was preserved. We demonstrated that angiotensin II binding to its putative membrane receptor was increased and concluded that the decrease in vascular reactivity was caused by a postreceptor abnormality. Recently, we found that potassium depletion was protective in the angiotensin II–dependent phase of two-kidney, one clip renovascular hypertension and postulated that the protective effect of potassium depletion in this setting was mediated by a postreceptor defect. The current studies in SHR extend these observations. The results suggest 1) that potassium depletion may have broader antihypertensive effects than angiotensin II–mediated hypertension and 2) since the increase in systemic resistance in SHR may be mediated by a number of factors in addition to angiotensin II, the mechanism of the vasodilative effect of potassium depletion may be broader than the angiotensin II postreceptor defect we initially proposed.

The diets used for these studies are deficient in phosphorus as well as potassium. It seems unlikely, however, that the protective effect of the diets was caused by phosphorus deficiency since the hemodynamic profile of phosphorus deficiency (increased SVR, decreased cardiac index, pressor resistance to angiotensin II and norepinephrine) differs markedly from the hemodynamic profile of phosphorus deficiency (increased SVR, increased cardiac index, selective pressor resistance to angiotensin II but not norepinephrine). The vasodilative effect of chronic potassium depletion is paradoxical since acute hypokalemia causes contraction of vascular smooth muscle. It is not known whether chronic potassium depletion protects directly at vascular smooth muscle to inhibit the contractile response or in the central nervous system to reverse the increase in neural outflow causing vascular contraction in the SHR. Further studies will be required to determine which of these protective mechanisms occurs in the potassium-depleted SHR.

In contrast to our findings, recent studies have demonstrated that potassium supplementation can lower blood pressure in patients with essential hypertension and in experimental models of hypertension including the SHR. Although a protective effect of both potassium depletion and potassium supplementation seems paradoxical, the mechanism of protection of these divergent maneuvers appears to differ. In most studies, potassium supplementation has been found to ameliorate hypertension by causing an increase in urinary sodium excretion. In contrast, since total body sodium and plasma volume are increased in potassium depletion, the protective effect of potassium depletion is independent of changes in sodium and volume and is related to potassium depletion per se.

In summary, we have demonstrated that potassium depletion reverses both early and established hypertension in the SHR. The vasodilative effect of severe potassium depletion occurred in normotensive and hypertensive rats and was associated with profound growth retardation. The vasodilative effect of moderate potassium depletion only occurred in the setting of hypertension and after an initial lag in growth, at a time when growth was not impaired. Since moderate potassium depletion has now been shown to reverse renovascular hypertension and spontaneous hypertension in the rat, we conclude that potassium depletion may have a broader antihypertensive effect than has been recognized previously.

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