Potassium Feeding Reduces Hyperactive Central Nervous System Pressor Responses in Dahl Salt-Sensitive Rats

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SUMMARY Dahl showed that feeding KCl prevents the rise in blood pressure caused by a high NaCl diet in salt-sensitive Dahl “S” rats. Such S rats when normotensive on a low NaCl diet have a 2 to 3 times greater pressor response than Dahl “R” rats to intracerebroventricular hypertonic saline (600 mOsm/liter) or angiotensin II (AII) (500 ng). Does dietary KCl prevent NaCl hypertension in S rats partly by abolishing these hyperactive central nervous system (CNS) pressor responses? The effect of potassium-loading on CNS pressor responses was studied in S rats on a low (0.3%) NaCl diet. Drinking a 2% KCl solution reduced the CNS pressor responses in S rats to both AII and hypertonic saline by 44% (p < 0.025) and brought them down almost as low as in R rats. KCl added to the low NaCl dry diet also decreased the CNS pressor responses in S rats to AII and to hypertonic saline by 39% (p < 0.01) and 59% (p < 0.02) respectively. K-citrate added to the low NaCl diet was generally as effective as KCl in reducing CNS pressor responses. K-citrate reduced the angiotensin pressor response by 44% (p < 0.001) and the hypertonic saline pressor response by 46% (p < 0.05). Thus, potassium feeding greatly diminished the hyperactive CNS pressor responses in S rats. This CNS action may well explain a good part of the protective effect of KCl against NaCl hypertension in S rats.

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KEY WORDS • hypertonic saline pressor response • angiotensin II pressor response • blood pressure regulation • NaCl hypertension • CNS pressor response • potassium • diet

INCREASING evidence suggests the participation of the central nervous system (CNS) in several forms of experimental hypertension including DOCA-salt, renal, and Kyoto spontaneous hypertension. This is also the case in Dahl salt-sensitive “S” rats, which become severely hypertensive when fed a high NaCl diet but remain normotensive on a low NaCl diet. Vascular resistance increases after NaCl feeding in Dahl S rats, and cutting peripheral sympathetic nerves abolishes half of this increase. In addition, destruction of peripheral sympathetic nerves with 6-hydroxydopamine prevents the onset of NaCl hypertension in Dahl S rats. A previous study in this laboratory demonstrated that the pressor responses to hypertonic saline and angiotensin II (AII) introduced into the lateral brain ventricle were twice as great in Dahl S rats as in Dahl salt-resistant “R” rats, even when both strains are normotensive on a low NaCl diet. These Dahl R rats remain normotensive on high salt intakes. Thus neurogenic mechanisms seem to contribute to the NaCl-induced hypertension in Dahl S rats.

The causal relationship between dietary salt intake and the development of certain types of hypertension in experimental animals and in human subjects is well recognized. On the other hand, some other studies indicate that increases in dietary potassium effectively counter the adverse effects of an increased sodium intake. Louis et al. revealed a blood pressure (BP) lowering effect of supplemental dietary potassium in the Kyoto spontaneously hypertensive rats (SHR) fed excess sodium. Dahl et al. showed that feeding KCl prevented the rise in BP induced by a high NaCl (4.5%) diet in S rats (see fig. 1). Such a protective effect of potassium against hypertension might be present in man, also. The mechanism of these effects of potassium remains unknown, however.

Dietary KCl could prevent NaCl hypertension in Dahl S rats partly by reducing the neurogenic component of the NaCl-induced hypertension. This hyperactive neurogenic component may be partly revealed by the hyperactive CNS pressor responses in Dahl S rats. To test this general relationship, we studied the effect of potassium-loading on the CNS pressor responses in Dahl S rats. Our results show that potassium-loading with either KCl or K-citrate diminishes the hyperactive CNS pressor responses in S rats and brings them down almost to those seen in R rats.

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Male Dahl S and R rats were all fed a low (0.3%) NaCl diet. At about 10 weeks of age, 18 S and 9 R rats began to drink only a 2% KCl solution ad libitum instead of tap water. In some rats, the intake of KCl solution was measured every day. For control rats, 19 S and nine R drank tap water throughout this experiment.

Experiment 2

Male Dahl S and R rats were also used in this study. At the age of 4 weeks, 12 S and 12 R rats began to eat a low (0.3%) NaCl diet supplemented with KCl (5.1%). Another group of 11 S and 12 R rats were fed a low NaCl diet supplemented with K-citrate (7.4%). KCl and K-citrate were added to the low NaCl dry diet such that the molar K/Na ratios were equal in both cases. Another group of 11 S and 11 R rats were given a low NaCl diet alone, without any added potassium and served as controls. All rats drank tap water ad libitum.

Implantation of Brain Cannula

After 4 weeks on a special diet or drink, a cannula was implanted into the lateral brain ventricle of each rat under pentobarbital anesthesia. This cannula was made of 22-gauge stainless steel tubing and was 14 mm long. Coordinates for the implanted cannula with respect to the bregma (flat skull) were: posterior, 0.5 mm; lateral, 1.0 mm; and 3.5 to 3.7 mm deep from the dura. A 27-gauge stylus was placed in the guide cannula. Following surgery, the rats were treated prophylactically with 30,000 U penicillin, i.m. Rats in Experiment 1 continued to drink either the KCl solution or tap water. Rats in Experiment 2 were given low NaCl diet alone or low NaCl diet with added KCl or K-citrate continuously.

Blood Pressure Measurement

Blood pressure was measured twice without anesthesia by the tail-cuff method on two different days just before the final testing day.

Test of CNS Pressor Responses

After 6 weeks on a special diet or drink, rats were lightly anesthetized with pentobarbital (30 mg/kg, i.p.) and placed on a heating pad maintained at 37°C. The femoral artery was catheterized with PE 50 tubing filled with heparinized saline. The femoral artery catheter was connected to a Statham P-23 ID transducer, and mean BP was recorded continuously on a Grass 79D recorder. In Experiment 2, another catheter was implanted into the femoral vein. Injections into the lateral brain ventricle were done through the brain cannula using an injection cannula constructed of 27-gauge stainless steel tubing. For injections, the cannula ended at the tip of the implanted guide cannula and was connected via PE 20 tubing to a remote 10 µl Hamilton syringe. First, 2 µl of hypertonic NaCl solution (600 mOsm/liter) and second, 500 ng of All in 2 µl of isotonic saline were injected. At least 30 minutes separated each injection. Injection of isotonic saline was omitted in this study because it did not induce any pressor response whatsoever in any rat in previous experiments (fig. 2). The doses of hypertonic saline and All were deliberately...
kept low enough to prevent large rises in BP that could cause perturbation of physiologic responses. A pressor response was defined as the peak BP increase over the preinjection baseline. Rats in this study were anesthetized and had no increase in drinking following the injections. Hence, the pressor responses here did not include the usual increase in BP associated with drinking. At the end of a given experiment, India ink was injected through the brain ventricle, and the brain was removed for verification of the cannula sites.

When rats have been given 6-hydroxydopamine into the lateral brain ventricle, many catecholaminergic neurons are destroyed. In such rats, one can inject 500 ng of All into the lateral brain ventricle without producing any pressor response whatsoever. This result appears to rule out the possibility that All placed in the lateral brain ventricle exerts a pressor effect only after it has leaked out into the systemic circulation. Much evidence indicates that All in the lateral brain ventricle acts on specific receptors located in the CNS.

Test of Peripheral Pressor Responses

In Experiment 2, the pressor response to intravenous (i.v.) doses of All (50 ng/kg) dissolved in dextrose solution was also studied after completion of CNS pressor responses. This dose was selected to produce a roughly similar pressor response.

Plasma Potassium Concentration

Blood was drawn from the femoral artery catheter after testing, and plasma K concentration was measured using flame photometry.

Statistics

Values are given as means ± se of the means. Statistical comparisons were made with the Student's t test. The 5% probability level was used as the criterion of significance.

Results

Experiment 1

Intake of KCl Solution

On the average, each S rat drank 64 ml of 2% KCl solution per day for 6 weeks. The average for R rats was 67 ml of KCl per day.

Body Weight

Body weight on the final testing day was almost the same between the two groups of S rats (341 ± 12 g vs 340 ± 12 g). The control R rats weighed more than the R rats on 2% KCl (372 ± 16 g vs 327 ± 12 g; p < 0.05).

Blood Pressure

Blood pressure in all groups remained normal during a low NaCl diet (table 1). There was no difference in BP between S rats on tap water and S rats on 2% KCl. Both groups of S rats showed a slightly higher systolic pressure than did R rats.

Pressor Responses

When 500 ng of All or 2 µl of hypertonic saline were injected into the lateral brain ventricle, the control S rats invariably had a pressor response (fig. 2). On the other hand, the control R rats usually had a comparatively smaller rise in BP. The control S rats showed a 2.5-fold greater rise in BP than the control rats after All (11.7 vs 4.8 mm Hg; p < 0.01 (fig. 3). The control S rats also showed a threefold greater rise in BP than the control R rats after hypertonic saline (5.5 vs 1.7; p < 0.01) (fig. 4). However, the pressor responses in S rats on 2% KCl were +6.6 mm Hg and +3.1 mm Hg after intracerebroventricular injection of All and hypertonic saline, respectively (figs. 3, 4). These responses were significantly (44%) smaller than those in control S rats (p < 0.025) but were not significantly different from those in control R rats. In R rats, the 2% KCl drink did not significantly influence the CNS pressor responses (figs. 3, 4).

Table 1. Effects of Drinking 2% KCl on Systolic Blood Pressure, Plasma K Concentration, and Pressor Responses to Intracerebroventricular Angiotensin II (All) (500 ng) and Hypertonic NaCl (600 mOsm/liter)

<table>
<thead>
<tr>
<th>Rat group</th>
<th>n</th>
<th>Systolic BP (mm Hg)</th>
<th>Plasma K (mEq/liter)</th>
<th>All (600 ng)</th>
<th>NaCl (600 mOsm/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahl S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td>130 ± 2</td>
<td>3.8 ± 0.1</td>
<td>11.7 ± 1.6</td>
<td>5.5 ± 0.9</td>
</tr>
<tr>
<td>2% KCl</td>
<td>18</td>
<td>133 ± 3</td>
<td>4.0 ± 0.1</td>
<td>6.6 ± 1.0*</td>
<td>3.1 ± 0.5*</td>
</tr>
<tr>
<td>Dahl R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9</td>
<td>117 ± 3;*</td>
<td>4.2 ± 0.2</td>
<td>4.8 ± 1.2†</td>
<td>1.7 ± 0.2†</td>
</tr>
<tr>
<td>2% KCl</td>
<td>9</td>
<td>116 ± 2;†</td>
<td>4.4 ± 0.2</td>
<td>4.3 ± 1.8†</td>
<td>1.7 ± 0.3†</td>
</tr>
</tbody>
</table>

Values are given as means ± SEM.

*p < 0.025 compared to control S rats.
†p < 0.01 compared to control S rats.
‡p < 0.005 compared to control S rats.
EFFECT OF POTASSIUM ON CNS PRESSOR RESPONSES

Plasma K Concentration

Rats on KCl tended to have a slightly higher plasma K concentration than control rats, but these small differences were not statistically significant (table 1).

Experiment 2

Body Weight

The S rats loaded with KCl or K-citrate weighed somewhat less than control S rats (control, 297 ± 6 g; KCl, 273 ± 9 g; p < 0.01 compared to control; K-citrate, 262 ± 6 g, p < 0.01 compared to control). On the other hand, there was no significant difference in weight among the three groups of R rats (control, 266 ± 12 g; KCl, 275 ± 8 g; K-citrate, 247 ± 11 g).

Blood Pressure

There was no difference in systolic BP among the three groups of S rats, and also among the three groups of R rats. All groups of S rats had slightly higher BP than any group of R rats (table 2).

TABLE 2. Effects of Potassium Feeding on Systolic Blood Pressure, Plasma K Concentration, and Pressor Responses to Intracerebroventricular (i.v.t.) Angiotensin II (AII) (500 ng) and Hypertonic NaCl (600 mOsm/liter), and Intravenous (i.v.) AII (50 ng/kg)

<table>
<thead>
<tr>
<th>Rat group</th>
<th>n</th>
<th>Systolic BP (mm Hg)</th>
<th>Plasma K (mEq/liter)</th>
<th>i.v.t. AII (500 ng)</th>
<th>i.v.t. NaCl (600 mOsm/liter)</th>
<th>i.v. AII (50 ng/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahl S</td>
<td></td>
<td></td>
<td></td>
<td>i.v.t. AII</td>
<td>i.v.t. NaCl</td>
<td>i.v. AII</td>
</tr>
<tr>
<td>Control</td>
<td>11</td>
<td>133 ± 3</td>
<td>3.7 ± 0.1</td>
<td>11.1 ± 1.0</td>
<td>7.1 ± 1.4</td>
<td>39.9 ± 5.0</td>
</tr>
<tr>
<td>KCl</td>
<td>12</td>
<td>136 ± 1</td>
<td>3.7 ± 0.1</td>
<td>6.8 ± 1.0†</td>
<td>2.9 ± 0.7†</td>
<td>27.5 ± 3.2*</td>
</tr>
<tr>
<td>K-citrate</td>
<td>11</td>
<td>137 ± 2</td>
<td>3.9 ± 0.2</td>
<td>6.2 ± 0.7†</td>
<td>3.8 ± 0.8*</td>
<td>32.0 ± 3.8</td>
</tr>
<tr>
<td>Dahl R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>11</td>
<td>123 ± 2‡</td>
<td>3.6 ± 0.1</td>
<td>5.1 ± 1.0‡</td>
<td>2.1 ± 0.3§</td>
<td>23.7 ± 3.8†</td>
</tr>
<tr>
<td>KCl</td>
<td>12</td>
<td>117 ± 2‡</td>
<td>3.8 ± 0.2</td>
<td>5.3 ± 0.7‡</td>
<td>2.5 ± 0.3†</td>
<td>24.4 ± 3.0†</td>
</tr>
<tr>
<td>K-citrate</td>
<td>12</td>
<td>119 ± 2‡</td>
<td>3.7 ± 0.1</td>
<td>5.1 ± 0.6‡</td>
<td>1.6 ± 0.2§</td>
<td>19.1 ± 3.6‡</td>
</tr>
</tbody>
</table>

Values are given as means ± SEM.

*p < 0.05 compared to control S rats.
†p < 0.02 compared to control S rats.
‡p < 0.01 compared to control S rats.
§p < 0.005 compared to control S rats.
¶p < 0.001 compared to control S rats.
CNS Pressor Responses

Intracerebroventricular AII increased BP +11.1 mm Hg in control S rats; +6.8 mm Hg in S rats on KCl; +6.2 mm Hg in S rats on K-citrate; and +5.1 in control R rats (table 2) (fig. 5). Thus, KCl decreased the angiotensin pressor response of S rats by 39% (p < 0.01) and K-citrate decreased it by 44% (p < 0.001). The intracerebral hypertonic saline increased BP +7.1 mm Hg in control S rats, +2.9 mm Hg in S rats on KCl, +3.8 mm Hg in S rats on K-citrate, +2.1 in control R rats (fig. 6). Thus, KCl decreased the hypertonic saline pressor response of S rats 59% (p < 0.02) and K-citrate decreased it 46% (p < 0.05). On the other hand, in the R rats, neither KCl nor K-citrate had any clear effect on the pressor responses to hypertonic saline (KCl, +2.5 ± 0.3; K-citrate, +1.6 ± 0.2 mm Hg) and AII (KCl, +5.3 ± 0.7; K-citrate, +5.1 ± 0.6 mm Hg).

Pressor Responses to Intravenous Angiotensin II

KCl decreased the pressor response to i.v. AII in S rats by 31% (p < 0.05). K-citrate decreased it 20%, but this change was not significant (table 2). Neither KCl nor K-citrate had any effect on the pressor response to i.v. AII in R rats (table 2).

Plasma K Concentration

No significant difference in plasma potassium was found among all the groups in Experiment 2 (table 2).

Discussion

We found significantly greater pressor responses to CNS hypertonic saline and AII in the Dahl S rats compared with the Dahl R rats when they were both fed low NaCl diets and both drank tap water. This finding is consistent with the previous study in this laboratory. Similar potentiated pressor responses to intracerebroventricular injection of AII or intracisternal injection of hypertonic saline have also been reported in Kyoto SHR rats. But hypertension had already been established in these SHR rats, and structural changes in the arterial walls as indicated by Folkow et al. were presumed to be present. These structural changes could have accounted for the potentiated pressor responses.

It is intriguing that Dahl S rats have enhanced CNS pressor responses on a low sodium diet even though the BP is within the normal range. These potentiated pressor responses in S rats could contribute to their heightened susceptibility to NaCl-induced hypertension. This finding provides another facet to the participation of the CNS in NaCl hypertension in Dahl S rats.

In the current Experiment 1, central pressor responses in Dahl S rats given 2% KCl solution for drinking were significantly lower than those in control S rats and almost the same as those seen in control R rats. Drinking KCl seems to have an inhibitory effect on the hyperactive CNS pressor responses in S rats. In Experiment 2, both KCl and K-citrate added to the
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dry chow greatly diminished the hyperactive CNS pressor responses in S rats. K-citrate was generally as effective as KCl. Taken together, potassium itself seems to have played an important role in this moderation of hyperactive CNS pressor responses in S rats.

Since Meneely et al.'s report that the life-shortening effects of a moderately high sodium diet could be prevented by supplements of dietary potassium, some subsequent studies indicating the antihypertensive effect of potassium in rats can be found. There is also evidence that dietary potassium may be anti-hypertensive in man. A recent report showed that subjects with high BP had relatively low urinary potassium concentrations and lower potassium/creatinine ratios. Blacks had higher BP levels and consistently less dietary potassium and urinary potassium excretion than whites.

The mechanism by which potassium moderates hypertension has not yet been made clear. Reid and Laragh found that the increased pressor response to intravenous AII in rats maintained on a high sodium diet did not occur among rats receiving KCl in addition to NaCl. Campbell and Schmitz showed that the pressor response to intravenous AII was significantly reduced in rats on a high potassium diet compared to rats on a normal potassium diet. In our Experiment 2, pressor responses to intravenous AII were attenuated in S rats on KCl or on K-citrate, although the change was not significant in the latter case. Such moderation of the intravenous AII pressor response by potassium might suggest possible pathways by which KCl exerts its antihypertensive effect in Dahl S rats. Intravenous AII would reach roughly the same sites as the AII produced in the lungs by the converting enzyme, including arteriolar receptors as well as CNS receptors. And, of course, AII is being continuously released into arterial blood.

The current study clearly indicates that hypertensive CNS pressor responses in Dahl S rats could be largely corrected with either KCl or K-citrate supplementation. It is conceivable that such an inhibitory effect of potassium on the hyperactive CNS pressor responses will turn out to be one of the main mechanisms by which potassium prevents the development of NaCl-induced hypertension in Dahl S rats.

It is uncertain how potassium manages to suppress the CNS pressor responses to hypertonic saline and AII in S rats only. Several possibilities should be considered. First, it is probable that hypertonic saline or AII placed in the lateral brain ventricle need to act upon their specific receptors in order to elicit CNS pressor responses. Potassium may affect the number or the binding affinities of these brain receptors.

Second, increased sympathetic activity is involved in the centrally mediated pressor response to hypertonic saline. The central pressor response to AII is the result of both vasopressin release and increased sympathetic activity. Therefore, potassium may influence either vasopressin release or sympathetic outflow. We do not have a direct measure of vasopressin release or sympathetic activity, but Battarbee et al. indicated that potassium supplementation reduced the urinary excretion of norepinephrine and epinephrine. If this is the case, potassium may suppress the sympathetic outflow. This effect on sympathetic outflow could be exerted within the CNS or on the actual sympathetic nerve endings.

Third, potassium may reduce the reactivity of the peripheral arterioles to vasoconstrictor agents such as norepinephrine and AII. Potassium has been reported to have both direct and indirect effects on the vascular system.

Fourth, baroreceptor function may be altered by a small change in electrolyte concentration. Saum et al. reported that an increase in extracellular potassium in his in vitro aortic arch-aortic nerve preparation reduced the threshold of the response to pressure and may increase baroreceptor sensitivity. A recent report suggests that a high potassium intake in humans ameliorates the BP rise after mental stress or norepinephrine infusion by improving baroreceptor function. With regard to this, it is noteworthy that Gordon et al. at this meeting reported a distinctly reduced baroreceptor activity in Dahl S rats.

Fifth, potassium may influence central pressor responses indirectly by augmenting renal sodium excretion and thereby reducing body sodium content. High NaCl diets enhance further the CNS pressor responses in Dahl S rats when compared on the basis of absolute increase in BP. A sodium-deficient diet diminishes the hyperactive CNS pressor response to AII in SHR rats. Potassium has been shown to have natriuretic activity. A decrease in exchangeable body sodium after potassium loading has been reported. If potassium does indeed induce natriuresis, it may change the CNS pressor responses. Along this line, a previous study in our laboratory has indicated that the long-term use of thiourea diuretics, which reduce body sodium content, did not change whatsoever the CNS pressor responses to intracerebroventricular AII or hypertonic saline in an ordinary strain of rats. However, the responses in Dahl S rats could be quite different.

In conclusion, Dahl S rats even when normotensive on a low NaCl diet have markedly hyperreactive CNS pressor responses. When a high potassium intake was begun in these normotensive S rats, it almost normalized these hyperreactive CNS pressor responses, bringing them down almost to the level seen in R rats. Such an inhibitory effect of potassium feeding on the CNS pressor responses could explain a good part of the protective effect of KCl against NaCl-induced hypertension in Dahl S rats.

References
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