Effect of Dietary Chloride on Salt-Sensitive and Renin-Dependent Hypertension

SHIRLEY A. WHITESCARVER, BRAD J. HOLTZCLAW, JAN H. DOWNS, COBERN E. OTT, JAMES R. SOWERS, AND THEODORE A. KOTCHEN

SUMMARY  We have previously reported that 1) selective dietary sodium loading (without chloride) does not produce hypertension in rats of the Dahl salt-sensitive strain (DS) and 2) selective chloride loading (without sodium) lowers plasma renin activity in the intact Sprague-Dawley rat maintained on a low NaCl diet. The present study examined the effect of selective dietary chloride loading on two models of hypertension: the DS and the renin-dependent one-kidney, one clip Sprague-Dawley rat. The DS were pair-fed (n = 7/group) a “normal” NaCl, a high NaCl (4%), or a “normal” sodium-high chloride diet for 11 weeks. From Week 7 until the end of the experiment, the high NaCl-fed animals had higher (p < 0.05) blood pressures than animals fed either the normal NaCl or normal sodium-high chloride diet, which were not different from each other. Thus, in the DS, hypertension depends on high dietary intakes of both sodium and chloride. In one-kidney, one clip hypertensive rats, selective chloride loading failed to lower plasma renin activity (9 ± 1 vs 7 ± 1 ng angiotensin I/ml/hr) or to prevent hypertension (160 ± 10 vs 166 ± 9 mm Hg). Thus, selective dietary chloride loading (without sodium) does not alter blood pressure in either salt-sensitive or renin-dependent hypertension. (Hypertension 8: 56-61, 1986)

KEY WORDS  • Dahl salt-sensitive rat • sodium chloride • one-kidney, one clip hypertension

ELEVATED arterial pressure is related to a high dietary NaCl intake in some hypertensive persons. One animal model of salt-sensitive hypertension is the Dahl salt-sensitive rat strain (DS). Developed by Louis K. Dahl and colleagues, DS are Sprague-Dawley rats inbred for their predisposition to become hypertensive on a high NaCl diet. For years, interest in salt-sensitive hypertension has focused primarily on the sodium ion. However, we have recently reported that selective sodium loading (without concomitant chloride) fails to produce hypertension in DS. Similar observations have been described by Kurtz and Morris and confirmed by us in another NaCl-dependent model of hypertension — the deoxycorticosterone acetate (DOCA)-salt treated rat. In the present study, to further evaluate the importance of chloride for NaCl-dependent hypertension, we compared the effects of dietary NaCl loading and selective chloride loading (without concomitant sodium) on blood pressure in DS.

We have previously reported that inhibition of renin release by NaCl in the intact Sprague-Dawley rat is specifically related to chloride. Thus, we hypothesized that, in the absence of sodium loading, selective chloride loading might inhibit renin release and hence lower blood pressure in a renin-dependent model of hypertension. To evaluate this hypothesis, we also studied the effects of selective chloride loading on plasma renin activity and blood pressure in NaCl-deprived Sprague-Dawley rats with one-kidney, one clip hypertension. In this model, elevated arterial pressure is renin-dependent rather than "sodium"-dependent.

Materials and Methods

Salt-Sensitive Hypertension

Twenty-one male DS were obtained (Brookhaven National Laboratory, Upton, NY, USA) at weaning and maintained on regular Purina rat chow (1% NaCl; St. Louis, MO, USA) for 3 weeks. At 7 weeks of age the animals were divided into three groups of seven
and fed one of the following diets: a 1% NaCl diet ("normal" NaCl), a 4% NaCl diet (high NaCl), or a "normal" sodium–high chloride diet (Table 1). The normal and the high NaCl diets were prepared by adding 0.36 g of sodium phosphate, 0.34 g of sodium bicarbonate, 0.70 g of calcium carbonate, and either 0.60 or 3.69 g of sodium chloride, respectively, to 100 g of a sodium-deficient diet (sodium, 0.002 mEq/g; chloride, 0.14 mEq/g; TD 170840; Teklad, Madison, WI, USA). The normal sodium–high chloride diet (high chloride) was made equimolar in chloride to the high NaCl diet by adding 1.5 g of glycine chloride and 0.2 g of calcium chloride to 100 g of a normal sodium–high chloride diet prepared by Teklad (sodium, 0.17 mEq/g; chloride, 0.60 mEq/g; TD 83346); this diet was equimolar in sodium to the normal NaCl food. All diets were equimolar in calcium and potassium.

During the 11-week study, the animals were housed in individual metabolic cages. Sodium, potassium, and chloride balances were calculated as dietary intake minus urinary excretion. Urine was collected under mineral oil to prevent evaporation. To ensure similar dietary intake, the animals were pair-fed and the high chloride–fed animals served as leaders. All groups received distilled water ad libitum. Weight was recorded weekly and electrolyte balances were calculated. At the end of 5 weeks, the animals were decapitated and plasma renin activity (PRA) and renal renin content (RRC) were determined.

Electrolyte content of the diets and muscles was analyzed after nitric acid digestion. All sodium and potassium concentrations were measured with an IL flame photometer (Instrumentation Laboratories, Morris Plains, NJ, USA). Chloride concentrations were measured with a Buchler chloridometer (Nuclear Chemical, St. Louis, MO, USA). Plasma protein concentrations were measured with a National Protometer (Baltimore, MD, USA); arterial blood samples were obtained for measurement of ionized calcium, protein, pH, carbon dioxide (Pco2) and oxygen (Po2) tension, and plasma electrolyte and creatinine concentrations. Thigh muscles were removed for determination of tissue electrolytes, and kidneys were harvested for measurement of catecholamine content.

### Renin-Dependent Hypertension

Thirty-two Sprague-Dawley rats were housed in metabolic cages and maintained on low NaCl chow (sodium, 0.004 mEq/g; chloride, 0.002 mEq/g; ICN Pharmaceuticals, Irvine, CA, USA). One week later, all animals were unilaterally nephrectomized and a 0.22-mm silver clip was placed on the remaining renal artery. After operation, the experimental group (n = 16) was fed a low sodium–normal chloride (0.14 mEq/g) diet prepared by adding 1.5% glycine chloride to the low NaCl chow. The control group (n = 16) was fed the low NaCl chow for the duration of the 5-week study. The animals were pair-fed, and the glycine chloride–fed group served as leaders. As in the first study, systolic blood pressures were measured twice weekly and electrolyte balances were calculated. At the end of 5 weeks, the animals were decapitated and plasma renin activity (PRA) and renal renin content (RRC) were determined.

Electrolyte content of the diets and muscles was analyzed after nitric acid digestion. All sodium and potassium concentrations were measured with an IL flame photometer (Instrumentation Laboratories, Morris Plains, NJ, USA). Chloride concentrations were measured with a Buchler chloridometer (Nuclear Chemical, St. Louis, MO, USA). Plasma protein concentrations were measured with a National Protometer (Baltimore, MD, USA); arterial pH, Pco2, and Po2 were determined with an IL blood gas analyzer. Creatinine concentrations were measured using a colorimetric method (Sigma Chemical, St. Louis, MO, USA). The PRA was measured in quadruplicate with the radioimmunoassay procedure of Haber et al.11 For the measurement of RRC, renin was extracted from the whole kidney by the method of Haas et al.12 and incubated with excess sheep substrate; the generated angiotensin I then was assayed as previously described.13 Kidney catecholamines were extracted, separated by high-performance liquid chroma-

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### Table 1: Electrolyte Content of the Three Diets (Determined After Nitric Acid Digestion), Starting and Ending Weights, Muscle Electrolyte Content, and Cumulative Electrolyte Balance of DS on These Diets

<table>
<thead>
<tr>
<th>Diet</th>
<th>Food electrolyte content (mEq/g)</th>
<th>Body weight (g)</th>
<th>Cumulative electrolyte balance (mEq/100 g body wt for 11 wk)</th>
<th>Muscle electrolyte content (μEq/g dry wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na+</td>
<td>K+</td>
<td>Cl-</td>
<td>Start of study</td>
</tr>
<tr>
<td>High NaCl (n = 7)</td>
<td>0.70</td>
<td>0.25</td>
<td>0.75</td>
<td>241.4</td>
</tr>
<tr>
<td></td>
<td>±9.8</td>
<td>±6.7</td>
<td>±7.5</td>
<td>±1.75*</td>
</tr>
<tr>
<td>Normal NaCl (n = 7)</td>
<td>0.17</td>
<td>0.25</td>
<td>0.24</td>
<td>228.3</td>
</tr>
<tr>
<td></td>
<td>±8.7</td>
<td>±4.7</td>
<td>±5.0</td>
<td>±0.45</td>
</tr>
<tr>
<td>High Cl (n = 7)</td>
<td>0.17</td>
<td>0.26</td>
<td>0.72</td>
<td>226.6</td>
</tr>
<tr>
<td></td>
<td>±8.0</td>
<td>±7.0</td>
<td>±5.1</td>
<td>±0.48</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*p < 0.01, †p < 0.05, compared with the other two groups.
Results

Salt-Sensitive Hypertension

Overall, the systolic blood pressure of the DS rats fed the high NaCl diet was significantly ($p < 0.001$) higher than that of both the normal NaCl-fed and the high chloride-fed animals, which were not significantly different from each other (Figure 1). In addition, the rate of increase in blood pressure of the high NaCl-fed animals was significantly greater than that in the other two groups ($p < 0.001$). From the seventh week until the end of the experiment, mean systolic blood pressure of the high NaCl-fed animals was significantly greater ($p \leq 0.05$) than that of the animals fed either the normal NaCl or the high chloride diet. At no time did the systolic blood pressure of the latter two groups differ significantly. At the end of the experiment, direct-intra-arterial mean pressures confirmed the difference in systolic blood pressure among the groups. Mean arterial pressures of the high NaCl-fed group (142 ± 4 mm Hg) were significantly higher ($p < 0.05$) than either the normal NaCl-fed group (129 ± 2 mm Hg) or high chloride-fed group (128 ± 4 mm Hg), which were not significantly different from each other.

Weight gain during the 11-week study was comparable on all diets; there were no statistically significant differences in beginning or ending weights among the groups (Table 1). The cumulative 11-week sodium balance of the high NaCl-fed animals was significantly more positive ($p < 0.01$) than that of the normal NaCl-fed or high chloride-fed animals, which were not significantly different from each other. Animals fed a high NaCl diet had a significantly greater positive sodium balance beginning within the first week compared with that in the other two groups, although blood pressure was not significantly elevated until the seventh experimental week. Chloride balances of both the high chloride-fed and high NaCl-fed animals were significantly more positive ($p < 0.05$) than those of the normal NaCl-fed group and were not different from each other. Potassium balance of the high NaCl-fed group was significantly less positive than that in the other two groups ($p < 0.05$). Muscle sodium, potassium, and chloride contents did not differ among groups.

At the end of the study, there were no statistically significant differences among the groups in plasma concentrations of sodium, potassium, chloride, or total protein (Table 2). Although plasma ionized calcium concentration was lower in the high NaCl-fed animals, the values were not significantly different. Arterial pH, Pco$_2$, Po$_2$, and creatinine clearance did not differ among the three groups. Arterial hematocrit and plasma volumes at the end of the study also were not different among groups. Heart rates of anesthetized animals and kidney contents of norepinephrine, epinephrine, and dopamine also did not differ among groups (Table 3).

Renin-Dependent Hypertension

The addition of 1.5% glycine chloride to a low NaCl diet neither inhibited renin release nor prevented the development of hypertension in one-kidney, one clip Sprague-Dawley rats (Table 4). There were no group differences in weight gain, systolic blood pressure, or plasma creatinine levels between the groups at the end of the 5-week period. Although the chloride balance was significantly more positive in the glycine chloride-fed animals ($p < 0.01$), neither PRA nor RRC was significantly suppressed as compared to values in the low NaCl-fed controls.

Discussion

We have previously reported that sodium loading with anions other than chloride fails to produce hypertension in two models of salt-sensitive hypertension—the DS$^4$ and rats with DOCA-salt hypertension.$^6$ To determine whether such a diet has a hypotensive effect unrelated to lack of chloride, this diet was fed to one-kidney, one clip rats.$^5$ The diet failed to alter the development of hypertension in this renin-dependent model, indicating that a lack of dietary chloride, rather than some other effect of the diet itself, was important in protecting against the development of hypertension in the DS.
TABLE 2. Plasma Values and Creatinine Clearance for the DS at the End of the 11-Week Study

<table>
<thead>
<tr>
<th>Diet</th>
<th>Na⁺ (mEq/L)</th>
<th>K⁺ (mEq/L)</th>
<th>Cl⁻ (mEq/L)</th>
<th>Ca²⁺ (mg/dl)</th>
<th>Protein (g/dl)</th>
<th>C₅O₂ (ml/min)</th>
<th>Arterial pH</th>
<th>P⁰₂ (mm Hg)</th>
<th>P⁰₂ (mm Hg)</th>
<th>Hematocrit (%)</th>
<th>Plasma volume (ml/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High NaCl</td>
<td>143.5 ± 0.6</td>
<td>4.4 ± 0.2</td>
<td>104.9 ± 2.3</td>
<td>2.29 ± 0.03</td>
<td>5.4 ± 0.1</td>
<td>0.87 ± 0.05</td>
<td>7.43 ± 0.01</td>
<td>44.6 ± 0.5</td>
<td>87.2 ± 2.1</td>
<td>45.1 ± 1.0</td>
<td>4.08 ± 0.11</td>
</tr>
<tr>
<td>Normal NaCl</td>
<td>142.8 ± 0.6</td>
<td>4.7 ± 0.2</td>
<td>102.6 ± 2.2</td>
<td>2.35 ± 0.02</td>
<td>5.6 ± 0.1</td>
<td>1.16 ± 0.11</td>
<td>7.39 ± 0.01</td>
<td>46.8 ± 0.7</td>
<td>87.2 ± 2.6</td>
<td>44.7 ± 3.8</td>
<td>3.89 ± 0.07</td>
</tr>
<tr>
<td>High Cl</td>
<td>143.6 ± 0.4</td>
<td>4.7 ± 0.1</td>
<td>105.0 ± 1.3</td>
<td>2.40 ± 0.02</td>
<td>5.6 ± 0.1</td>
<td>0.93 ± 0.10</td>
<td>7.40 ± 0.01</td>
<td>46.0 ± 0.8</td>
<td>90.0 ± 1.4</td>
<td>45.7 ± 3.9</td>
<td>3.90 ± 0.10</td>
</tr>
</tbody>
</table>

Values are means ± SEM. C₅O₂ = creatinine clearance, P⁰₂ = carbon dioxide tension, P⁰₂ = oxygen tension

TABLE 3. Renal Norepinephrine, Epinephrine, and Dopamine Content and Anesthetized Heart Rate of DS on the Various Diets

<table>
<thead>
<tr>
<th>Diet</th>
<th>Norepinephrine (ng/g tissue)</th>
<th>Epinephrine (ng/g tissue)</th>
<th>Dopamine (ng/g tissue)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High NaCl</td>
<td>165.10 ± 14.07</td>
<td>6.71 ± 3.29</td>
<td>12.12 ± 1.24</td>
<td>401 ± 12</td>
</tr>
<tr>
<td>Normal NaCl</td>
<td>149.42 ± 7.80</td>
<td>7.96 ± 1.89</td>
<td>12.78 ± 0.48</td>
<td>385 ± 8</td>
</tr>
<tr>
<td>High Cl</td>
<td>150.43 ± 6.65</td>
<td>9.99 ± 2.58</td>
<td>11.20 ± 0.78</td>
<td>388 ± 9</td>
</tr>
</tbody>
</table>

Values are means ± SEM

TABLE 4. Effect of Selective Chloride Loading (Without Sodium Loading) on Weight, Systolic Blood Pressure, Plasma Renin Activity, Renal Renin Content, and Electrolyte Balances in Rats with One-Kidney, One Clip Hypertension

<table>
<thead>
<tr>
<th>Diet</th>
<th>Body weight (g)</th>
<th>Blood pressure (mm Hg)</th>
<th>Creatinine (mg/dl)</th>
<th>PRA (ng L/1 ml/hr)</th>
<th>RRC (U/g)</th>
<th>Net balance (mEq/5 wk)</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cl⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low NaCl (n = 16)</td>
<td>184 ± 3</td>
<td>223 ± 2</td>
<td>115 ± 2</td>
<td>166 ± 9</td>
<td>0.7 ± 0.1</td>
<td>1231 ± 123</td>
<td>-1405</td>
<td>23</td>
<td>894</td>
</tr>
<tr>
<td>Low NaCl + 1.5%</td>
<td>179 ± 1</td>
<td>222 ± 1</td>
<td>115 ± 1</td>
<td>160 ± 10</td>
<td>0.6 ± 0.1</td>
<td>94 ± 9</td>
<td>999 ± 99</td>
<td>0.517</td>
<td>27</td>
</tr>
<tr>
<td>GlyCl (n = 16)</td>
<td>179 ± 4</td>
<td>222 ± 4</td>
<td>115 ± 4</td>
<td>160 ± 10</td>
<td>0.6 ± 0.1</td>
<td>94 ± 9</td>
<td>999 ± 99</td>
<td>0.517</td>
<td>27</td>
</tr>
</tbody>
</table>

Results are means ± SEM. PRA = plasma renin activity, ANG I = angiotensin I, RRC = renal renin content, Gly = glycine

*Before clipping and institution of diets.
†Five weeks after clipping and institution of diets
‡p < 0.01, compared with low NaCl diet

In the present study, we evaluated the effect of selective dietary chloride loading, without sodium loading, on the development of hypertension in the DS. Selective chloride loading, like selective sodium loading, failed to produce hypertension, whereas animals fed a comparably high chloride intake provided as NaCl did become hypertensive. Thus, we conclude that the concomitant administration of sodium and chloride is required to produce hypertension in this salt-sensitive model.

We also evaluated the effect of selective chloride loading on a renin-dependent model of hypertension, the one-kidney, one clip Sprague-Dawley rats maintained on a low NaCl diet. The renin dependency of this model has been documented previously. 9, 11 We have reported that dietary chloride loading (in the absence of sodium loading) suppresses renin activity in the intact Sprague-Dawley rat. 7 Furthermore, adding glycine chloride to a low NaCl diet reduces plasma renin activity in the unilaterally nephrectomized rat. 17 In this study, however, selective chloride loading did not inhibit renin release and failed to decrease blood pressure in this renin-dependent model of hypertension. In contrast to our results with glycine chloride, Suzuki et al. 18 have reported that potassium chloride loading prevents two-kidney, one clip hypertension in the rat. This protective effect was attributed primarily to the natriuretic effect of potassium.

In DS, the rate of blood pressure rise depends on both the NaCl content of the diet and the age at which high NaCl feeding is instituted. 19 Our previous study of selective sodium loading and the current study of selective chloride loading were performed in DS of identical ages. In our earlier study, animals fed a high NaCl diet received 7% NaCl. In the current study, the amount of NaCl fed to the high NaCl diet group was...
limited by the amount of chloride tolerated by the group fed the normal sodium–high chloride diet. In preliminary studies, animals receiving a normal sodium intake did not consistently consume diets with a chloride content in excess of 0.75 mEq/g (chloride content of a 4% NaCl diet). Higher chloride contents also resulted in acidosis and decreased weight gain. Consequently, to maintain equimolar contents of chloride in the high NaCl and normal sodium–high chloride diets, the high NaCl diet used in the current study contained 4% NaCl. In our earlier study, animals fed 7% NaCl became hypertensive within 3 weeks, a finding consistent with previous reports. In the current study, hypertension developed more slowly in animals fed 4% NaCl; however, in DS fed the normal NaCl diet, systolic blood pressures in our previous (136 ± 1 mm Hg) and current (130 ± 3 mm Hg) studies were similar.

It is unlikely that the failure of arterial pressure to increase in DS and to decrease in one-kidney, one clip Sprague-Dawley rats fed glycine chloride is related to an effect of glycine per se. Although direct application of pharmacological concentrations of glycine (20% glycine) to the medulla of the cat brain has been reported to decrease arterial pressure and although glycine is the neurotransmitter of inhibitory interneurons in the spinal cord, we are unaware of ingested amino acids having an effect on the central or peripheral sympathetic nervous system. In the present experiment, the 1.5% glycine chloride feeding had no effect on heart rate or kidney catecholamine content in DS. Furthermore, elevated blood pressure in the one-kidney, one clip model can be lowered by sympathetic nervous system antagonists; failure of 1.5% dietary glycine chloride to lower blood pressure in this model suggests that dietary glycine does not inhibit nervous system activity.

The observation that the development of hypertension is dependent on the dietary intake of sodium and chloride has implications for the mechanism by which a high NaCl intake produces hypertension in the susceptible host. By comparing animals fed high NaCl diets with those selectively fed either sodium (previous study) or chloride alone, we found that the development of hypertension was unrelated to differences in weight gain or to selective increases in sodium or chloride balance. However, an increase in net sodium and chloride balance preceded the elevation of arterial pressure in DS fed a high NaCl diet. Although plasma volumes at the termination of the experiment did not differ among groups, it is possible that the elevated arterial pressure of NaCl-fed animals was related to an early, transient elevation of plasma volume or to an expanded extracellular fluid volume. Although extracellular fluid volume was not measured in this study, we have previously demonstrated that elevated arterial pressure in NaCl-fed DOCA-salt hypertensive rats is associated with an expanded extracellular fluid volume.

Sodium chloride-induced hypertension is also associated with increased peripheral resistance, and various investigators have attributed this increased resistance to a transient increase of plasma volume, alterations of sodium and calcium transport in vascular smooth muscle, neurogenic vasoconstriction, or increased responsiveness to vasoconstrictor agents. Recently, Ferrari et al. have shown an impairment in the cardiopulmonary baroreflex function in prehypertensive DS. They also have reported that a high NaCl diet potentiates baroreceptor discharge in Dahl salt-resistant rats, but not in DS. Because of the contribution of this reflex to the inhibition of efferent renal sympathetic activity, Ferrari et al. hypothesized that an elevation of renal sympathetic nerve activity may lead to inappropriately high renal vascular resistance. Our study does not address the mechanism by which high NaCl intake causes hypertension, but it does emphasize the importance of both chloride and sodium for NaCl-sensitive hypertension.

We have previously suggested that inhibition of renin release by chloride in the intact Sprague-Dawley rat is related to an effect of NaCl cotransport in the thick ascending limb of the loop of Henle. Failure of chloride loading to inhibit renin release in one-kidney, one clip rats indicates that the primary mechanism for stimulation of renin release in these animals is related to some other mechanism (e.g., the renal baroreceptor or renal nerves). Indeed, several studies have suggested a predominant role for the renal baroreceptor when renal perfusion pressure is reduced below the autoregulatory range. Renin release also has been reported recently to be stimulated by decreased perfusion pressure, even in the absence of a functional macula densa.

In summary, neither sodium nor chloride loading alone produced hypertension in the DS. Our findings indicate that the combination of sodium with chloride is responsible for the development of hypertension in this salt-sensitive model. In addition, in contrast to findings in the intact Sprague-Dawley rat, selective chloride loading did not inhibit renin secretion and thus failed to prevent hypertension in a one-kidney, one clip model of hypertension. Although the mechanisms of hypertension in the DS and the one-kidney, one clip Sprague-Dawley rat are different, selective dietary chloride loading (without sodium) failed to alter arterial pressure in either model.

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