Prevention and Reversal of Cataracts in Genetically Hypertensive Rats Through Sodium Restriction

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We previously described the Dahl salt-sensitive rat as a potential model of cataractogenesis in which cataract formation is associated with hypertension. Cataractous lesions were characterized by a marked lenticular and aqueous humor electrolyte imbalance. In the present study the effects of chronic dietary sodium restriction on cataract formation were evaluated in salt-sensitive rats to determine whether or not modification of the hypertensive process might reduce the incidence of cataracts in this genetic model. In addition, the possibility that early cataractous lesions in adult hypertensive salt-sensitive rats might be reversed by acute sodium restriction was evaluated. Chronic dietary sodium restriction modified the development of hypertension and prevented cataract formation in salt-sensitive rats. Furthermore, acute dietary sodium restriction (1 week) completely and consistently reversed early cataractous lesions (pinpoint opacities) in adult hypertensive salt-sensitive rats. Both the prevention and reversal of cataracts were associated with normalization of the lenticular and aqueous humor parameters measured. These data suggest that cataractogenesis is not the consequence of sustained arterial hypertension, but rather that initiation of both hypertension and cataract formation in this genetic model may be the result of extracellular fluid volume state. Invest Ophthalmol Vis Sci 30:2356-2360, 1989.

The Dahl salt-sensitive rat is a model of the genetic hypertension consistently induced in rats of this strain when a high sodium diet is administered beginning at weanling age.1 The control salt-resistant rat, developed simultaneously, is a strain in which a high sodium diet does not induce hypertension.1 Since chronic sodium restriction initiated at weanling age markedly attenuates the development of hypertensive disease in the salt-sensitive rat, it has been postulated that expansion of extracellular fluid volume plays a pivotal role in the development of hypertension in this genetic model. In earlier studies we described a high incidence of cataract formation in Dahl salt-sensitive hypertensive rats (DS) obtained from Brookhaven National Laboratories (Upton, NY) over a period of four years.1 Cataractous lesions in salt-sensitive rats were associated with marked changes in lenticular content of sodium and potassium, as well as increased lenticular water content and decreased lens dry weight.1 These lenticular changes, characteristic of several other cataractous lesions unrelated to hypertension2,3 were associated with changes in aqueous humor sodium and potassium concentrations. The latter finding was suggestive of a possible defect in ion transport processes at the lens or ciliary epithelia in salt-sensitive hypertensive rats. Furthermore, salt-sensitive rats that did not develop cataractous lesions demonstrated lesser but significant changes in aqueous humor potassium content in contrast to values in Dahl salt-resistant control rats (DR).1 This alteration supported the concept that a specific ion transport defect at the lens or ciliary processes might be a characteristic of salt-sensitive hypertension. Nevertheless, these earlier studies did not directly address the possibility of a relationship among sodium intake, salt sensitivity, cataractogenesis, and hypertension in this genetic model.

In the present study we evaluated the possibility that modification of the hypertensive process through chronic dietary sodium restriction beginning at weanling age influences cataractogenesis in the Dahl salt-sensitive rat. In separate studies we also evaluated the possibility that acute sodium restriction reverses early cataractous lesions in adult hypertensive salt-sensitive rats. The latter experiment was based on
studies reporting reversibility of diabetic cataracts when hyperglycemia is controlled prior to the development of mature cataracts. Therefore, the present studies were designed to evaluate the possibility that cataractogenesis in salt-sensitive rats might be directly related to the hypertensive process in this model of genetic hypertension.

Materials and Methods

Weanling female DS and DR were purchased from Brookhaven National Laboratories. The rats were housed in a room with an ambient temperature of 26°C with a light–dark cycle of 12 hours. Sixty DS and 40 DR were maintained on a sodium-restricted diet (0.01% sodium; ICN Nutritional Biochemicals, Cleveland, OH) and tap water ad libitum beginning at the age of 5 weeks. An additional 40 DS and 30 DR were maintained on a high sodium diet (0.9% sodium chloride in place of drinking water) and standard rat chow (0.46% sodium; Purina, St. Louis, MO) beginning at the age of 5 weeks, to induce hypertension in the DS. Systolic blood pressure was measured weekly by tail-cuff plethysmography (Narco Bio-Systems, Houston, TX) in the conscious restrained rat. Cataract formation was assessed in all rats through weekly visual inspection with the aid of an ophthalmoscope. Biweekly slit-lamp microscopy (Haag-Streit, Bern, Switzerland) was carried out in all rats. For this purpose the pupils of each rat were dilated through topical administration of 0.02% mydriacil (Alcon, Humacao, Puerto Rico). When slit-lamp microscopy revealed subcapsular fine (pinpoint) opacities in DS maintained on a high sodium diet, these rats were immediately placed on a sodium-restricted diet for one week (acute sodium restriction). At the same time, an equal number (eight) of age-matched DR maintained on a high sodium diet were also changed to a sodium-restricted diet for one week. Slit-lamp microscopy was repeated and systolic blood pressure measured in these groups of rats. The animals were then sacrificed for lenticular and aqueous humor analysis.

Generally, we have observed that cataract formation in hypertensive DS kept on a high sodium diet occurs between the ages of 16 and 24 weeks. Therefore, ten DS and ten DR that had been maintained on a sodium-restricted diet from weanling age were sacrificed at the age of 25 weeks, since prior to this time lens opacities were not detected in any DS. These chronically sodium-restricted rats were sacrificed for lenticular and aqueous humor analysis. The remainder of chronically sodium-restricted rats were studied by slit-lamp microscopy up to the age of 36 weeks to evaluate the possibility that cataract formation might occur at a later age in sodium-restricted DS.

Aqueous humor was collected from the anterior ocular chamber immediately upon decapitation of rats. Glass pipettes designed in our laboratory for this purpose were inserted tangentially into the anterior chamber. Samples were analyzed for sodium and potassium concentrations. Samples were analyzed for sodium and potassium concentrations. Results

During chronic dietary sodium restriction, cataract formation was not observed in either DS or DR. Slit-lamp microscopy consistently revealed lens transparency in both groups of rats up to the age of 36 weeks. Systolic blood pressure (Fig. 1) was greater in DS than in DR at any given age, but during chronic dietary sodium restriction blood pressure in DS was maintained below 140 mmHg and was relatively constant with increasing age. Therefore, chronic dietary sodium restriction prevented the progressive rise in
blood pressure with increasing age and also prevented cataract formation in DS. Under these conditions, aqueous humor sodium and potassium concentrations (Table 1) in DS were similar to those observed in DR, in contrast to the previously reported increase in aqueous humor potassium concentration even in hypertensive DS that did not develop cataracts following chronic sodium loading. Furthermore, no differences in lenticular water content, sodium content or potassium content were observed between DS and DR maintained on a sodium-restricted diet from weanling age (Table 1). It is notable, however, that lenticular content of both sodium and potassium during chronic dietary sodium restriction was significantly greater than control values previously reported in DR during chronic sodium loading. In addition, although lenticular dry weight was similar between DS (20.70 ± 0.20 mg) and DR (20.86 ± 0.10 mg) during chronic dietary sodium restriction, these values were significantly lower than those previously reported in control DR maintained on a high sodium diet.

The incidence of cataract formation in hypertensive DS maintained on a high sodium diet was 35%. Early changes in lens transparency were noted in some DS by the age of 16 weeks. These early changes were confirmed by slit-lamp microscopy that revealed anterior pin point opacities in this subgroup of DS. Yet pinpoint opacities were not observed in all DS that developed cataracts (DSc). This discrepancy appeared because the generally precipitous development of mature cataracts in DSc precludes the identification in every rat of the early pinpoint opacification state when slit-lamp microscopy is carried out on a biweekly basis. Transparent crystalline lenses were observed in all DR throughout the study. Under these conditions the development of hypertension in DS was reflected by the progressive rise in systolic blood pressure with increasing age (Fig. 2), and in DSc preceded cataract formation. In addition, the rise in blood pressure was greater in DS that later developed cataractous lesions than it was in DS that did not develop cataracts. Peak blood pressure was observed in DS at the age of 23 to 26 weeks, whereas comparable blood pressure was observed in DSc by the age of 10 to 12 weeks.

Once early cataractous changes were observed in hypertensive DS, these rats and an equal number (eight) of chronically sodium-loaded, age-matched DR were placed on a sodium-restricted diet. One week later, slit-lamp microscopy revealed lens transparency in all rats. The reversal of cataracts in DSc through acute sodium restriction was not associated with any change in systolic blood pressure in either DSc (high salt: 195 ± 5 vs sodium restriction: 192 ± 8 mmHg) or DR (high salt: 98 ± 3 vs sodium restriction: 95 ± 3 mmHg). After one week of dietary sodium restriction, aqueous humor sodium and potassium concentrations (Table 2) were similar in DSc with reversed lenticular lesions and DR. In addition, lenticular water content, sodium content, and potassium content were similar in DSc after reversal of cataracts and DR (Table 2). Lenticular dry weight was also similar in DSc (21.18 ± 0.40 mg) and DR (21.79 ± 0.10 mg). Control values of these lenticular parameters during acute sodium restriction in the present study were comparable to those previously reported in DR following chronic sodium loading.

A separate group of DSc with mild cataractous lesions was also studied, except that these rats were not placed on a sodium-restricted diet. This group of rats was studied to determine lens electrolyte content and water content when mild cataractous lesions were

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**Table 1. Aqueous humor electrolyte concentrations and lenticular contents in adult salt-sensitive and salt-resistant rats during chronic dietary sodium restriction**

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<thead>
<tr>
<th></th>
<th>Aqueous humor</th>
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<th>Lens</th>
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<tbody>
<tr>
<td></td>
<td>Na⁺ (mEq/L)</td>
<td>K⁺</td>
<td>Na⁺ content (mEq/kg dry weight)</td>
</tr>
<tr>
<td>Group</td>
<td></td>
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<tr>
<td>DS</td>
<td>134 ± 3</td>
<td>4.0 ± 0.1</td>
<td>30.3 ± 5</td>
</tr>
<tr>
<td>DR</td>
<td>136 ± 3</td>
<td>3.7 ± 0.1</td>
<td>31.5 ± 9</td>
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For all values measured, there is no statistically significant difference between corresponding values in DS and DR.
Fig. 2. Systolic blood pressure (SBP) in salt-sensitive rats that eventually developed cataracts (squares), salt-sensitive rats that did not develop cataracts (triangles), and salt-resistant rats (circles), maintained on a high sodium diet beginning at the age of 5 weeks. Asterisks denote values significantly different (P < 0.001) from corresponding values in DR. Daggers denote values significantly different (P < 0.05) from corresponding values in DS.

present, rather than reversed, as in the previous experiment. Six DSc with mild cataractous lesions showed increased lens sodium content (106 ± 4 mEq/kg lens dry weight) and decreased potassium content (45 ± 2.0 mEq/kg lens dry weight) compared to values in acutely sodium-restricted DR (Table 2). Lens water content (14.65 ± 0.4 mg/10 mg lens dry weight) and dry weight (21.19 ± 0.3 mg) in these DSc were similar to values in DR. Although no difference was observed between lens sodium content in DSc with mild cataractous lesions and DSc following reversal of mild cataractous lesions by acute sodium restriction, lens potassium content was markedly different between the two groups of rats, further indicating normalization of this parameter in DSc in which mild cataractous lesions were reversed.

Discussion

Chronic dietary sodium restriction completely prevented the development of cataractous lesions in DS. This prevention of cataractogenesis was associated with a marked attenuation of the rise in systolic blood pressure known to occur in DS that are maintained on a high sodium diet beginning at weanling age. This finding suggests either that cataract formation in DS is dependent on elevated blood pressure, or that mechanisms that contribute to the hypertensive process also participate in the development of cataractous lesions in this genetic model. In rats previously maintained on a high sodium diet, however, the reversal of pinpoint opacities in hypertensive DSc in response to acute volume contraction through sodium restriction indicates that cataractogenesis in DSc is probably not related to elevated blood pressure. This conclusion is based upon the observation that acute sodium restriction in adult hypertensive DSc and DS did not alter blood pressure, but consistently reversed early cataractous changes. Therefore it seems likely that extracellular fluid volume contraction during both chronic and acute sodium restriction may have played a role in the prevention and reversal of cataracts in this genetic model. Although neither extracellular fluid volumes nor blood volumes were measured in the present study, earlier reports have shown that sodium restriction effectively lowers plasma volume in DS. In addition, we have

Table 2. Aqueous humor electrolyte concentrations and lenticular contents in adult salt-sensitive and salt-resistant rats during acute dietary sodium restriction

<table>
<thead>
<tr>
<th>Group</th>
<th>Na⁺ content (mEq/kg dry weight)</th>
<th>K⁺ content (mEq/kg dry weight)</th>
<th>H₂O content (mg/10 mg dry weight)</th>
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<tr>
<td>DSc*</td>
<td>149 ± 4</td>
<td>51.1 ± 22</td>
<td>13.91 ± 0.20</td>
</tr>
<tr>
<td>DR</td>
<td>157 ± 12</td>
<td>27.0 ± 8</td>
<td>14.10 ± 0.40</td>
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</table>

*Values obtained after reversal of early cataractous lesions.

For all values measured, there is no statistically significant difference between corresponding values in DSc and DR.
shown that the decrease in plasma volume in response to acute sodium restriction is reportedly greater in adult hypertensive DS than in control DR. 

Although it is attractive to postulate that cataractogenesis was prevented though prevention of fluid volume expansion during chronic dietary sodium restriction, other possible explanations for our findings cannot be excluded on the basis of these data alone. The effects of chronic dietary sodium restriction on growth and development, for example, could contribute to prevention of cataractogenesis in DS. Sodium is essential for normal growth not only of bone, but of other tissues as well. In the present study, chronic sodium restriction beginning at weaning age not only resulted in decreased body weight in both DS and DR, but also resulted in decreased lenticular dry weight and increased lenticular electrolyte content compared to values previously observed after chronic sodium loading or during normal sodium intake in this strain of rats. Consequently, sodium restriction initiated at weaning age may have influenced lenticular development, which in turn could have altered the course of cataractogenesis in DS. The reversibility of cataracts in adult hypertensive DS through acute sodium restriction, however, argues against altered lens development as a major factor in the prevention of cataracts in chronically sodium-restricted DS. The most likely explanation for the prevention and reversibility of cataractous lesions in DS in the present study is that fluid volume state plays a role in cataractogenesis. If this proves correct, one might postulate that the difference between hypertensive DS and DS control is the degree of extracellular fluid volume expansion in response to chronic administration of a high sodium diet. This concept is consistent with the heterogeneity of hypertensive disease among Brookhaven DS, and is also consistent with our hypothesis that the hypertensive rats that develop cataracts are more salt-sensitive than those that fail to develop cataracts. The increased pressor response to a high sodium diet observed in DS that eventually developed cataracts, compared to that observed in DS that did not develop cataracts, is also consistent with this hypothesis.

The manner in which fluid-volume state influences cataractogenesis in DS is not altogether clear. Both acute and chronic sodium restriction might influence humoral and hormonal factors that in turn act at the lenticular or ciliary ridge epithelia. In addition, sodium restriction might alter lens extracellular space and extracellular fluid composition. These factors influence lens electrical properties and membrane ionic permeabilities and consequently, might partially mediate the observed effects of dietary sodium restriction on cataractogenesis in DS. It is also possible that hemodynamic effects of volume contraction on aqueous humor dynamics might contribute to the observed prevention and reversal of cataracts in DS through sodium restriction. Whatever the case, prevention of cataracts through chronic sodium restriction might be explained through prevention of extracellular fluid volume expansion and of the subsequent mechanisms that give rise to hypertension in DS. The striking reversal of cataracts in DS through acute sodium restriction, however, suggests that mechanisms responsible for the maintenance of hypertension are not the same as the mechanisms that lead to cataract formation. It is possible, however, that the volume-related mechanisms that trigger the initiation of the hypertensive process in DS may also play a pivotal role in cataractogenesis. Taken together, these studies suggest that extracellular fluid volume may be an important factor linking the hypertensive process and cataractogenesis in this genetic model.

Key words: hypertension, cataracts, sodium, crystalline lens

References