Cataracts and Hypertension in Salt-Sensitive Rats
A Possible Ion Transport Defect

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SUMMARY In previous unrelated studies, we observed a 35 to 50% incidence of cataract formation in several groups of Dahl salt-sensitive hypertensive rats (DS) over a 4-year period. In the present study we evaluated longitudinal changes in blood pressure in DS in which cataracts eventually developed and those in which cataracts did not develop when all animals were maintained on a high sodium diet. Lenses were evaluated by slit-lamp microscopy to determine if cataractous lesions were similar among rats, to classify lesion types, and to define the age at which cataracts were detectable in DS. The possible participation of several cataractogenic risk factors as major influences on cataract formation also was evaluated. Finally, aqueous humor concentrations and lenticular content of sodium and potassium were determined to evaluate the possibility that a defect in ion transport at the lens epithelium and ciliary body might play a role in cataractogenesis in DS, since ion transport defects have been shown to lead to lens opacification in other models of genetic and experimental cataracts. Parallel studies were performed in Dahl salt-resistant control rats (DR). A high incidence of cataract formation was found in DS. Although systolic blood pressure was not consistently greater in adult DS with cataracts compared with values in age-matched DS without cataracts, the initial pressor response to a high salt diet was greatest in weanling DS in which cataractous lesions later developed. Slit-lamp analysis revealed that cataracts in this genetic model were cortical, with one mixed cortical, nuclear lesion. Posterior subcapsular lesions were not observed, suggesting that lesions were not steroid-induced. Serum ultrafiltrable calcium concentration was similar among DS with and without cataracts and normotensive DR, indicating that hypocalcemia was not involved in cataractogenesis. Analysis of aqueous humor showed high potassium concentration and low sodium concentration in DS with cataracts, suggesting a possible ion transport defect in the ciliary processes or lens epithelium (or both). In addition, increased lenticular water and sodium content, as well as decreased potassium content, indicated that mature cataracts in DS were associated with altered sodium and potassium transport. Although aqueous humor sodium concentration and lenticular sodium content were not altered in DS without cataracts, lenticular potassium content was decreased while aqueous humor potassium concentration was increased compared with values in control DR. These data suggesting a decreased transmembrane potassium gradient in DS without cataracts also suggest that a specific defect in potassium transport may precede the development of cataracts in this genetic model. The finding of a potential genetic model of cataracts in which cataractogenesis is associated with hypertension suggests a possible link between hypertension and cataract formation.

KEY WORDS • hypertension • cataracts • lens • aqueous humor • sodium

We have noticed a high incidence of cataract formation in Dahl salt-sensitive rats (DS), a finding that, to our knowledge, has not been reported previously. Hypertension in DS apparently is associated with altered ionic transport in several tissues and altered adrenal steroidogenesis, as indicated by the excessive production of 18-OH deoxycorticosterone. Either of these factors might contribute to the development of cataracts in DS. Decreased lenticular ionic transport resulting from a specific decrease in Na+,K+-adenosine triphosphatase

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(ATPase) activity at the lens epithelium leads to cataract formation in the Nakano mouse. In this genetic model, the only identified defect is the cataract. Furthermore, in vitro incubation of lenses with the Na+,K+-ATPase inhibitor ouabain also results in lens opacification. Low Na+,K+-ATPase activity has been described in renal microsomal preparations from hypertensive DS compared with values in control Dahl salt-resistant rats (DR), and if decreased activity of this transport enzyme is a generalized epithelial defect, the formation of a metabolic cataract analogous to that observed in the Nakano mouse might occur. Alternatively, since chronic steroid therapy has been shown to result in an increased incidence of cataract formation secondary to the development of glaucoma, the altered steroidogenesis described in hypertensive DS could be responsible for cataract formation.

In the present study, we evaluated the incidence of cataract formation in DS and DR. Slit-lamp analysis was performed to verify the presence of cataracts as well as to determine whether opacities were cortical, nuclear, or posterior subcapsular. In addition, aqueous humor electrolyte composition was determined, and lenticular sodium and potassium content and state of hydration were evaluated to further characterize cataractous lesions. Some factors that might contribute to cataract formation were also studied. Serum ultrafiltrable calcium concentration was measured, for example, since hypocalcemic states are associated with a high incidence of cataract formation and since hypocalcemia has been proposed to contribute to the development of hypertension. Finally, because of the high incidence of cataract formation during diabetes mellitus, fasting serum glucose concentration was measured.

Materials and Methods

The study included 40 female DS and 40 female DR (Brookhaven National Laboratory, Upton, NY, USA). All rats were maintained on a high sodium diet (0.9% saline in place of drinking water) beginning at the age of 4 weeks. Systolic blood pressure was measured before and after the first 2 weeks on a high salt diet, and additional measurements were made weekly in each rat. Each measurement was based on 10 consecutive determinations in conscious, restrained rats by tail cuff plethysmography. Cataract formation was assessed by visual inspection. At the age of 20 weeks, the rats were divided into three groups: DS in which moderate to severe cataracts had developed (DSC), DS in which cataracts had not developed (DSnc), and DR. DS in which mild cataractous lesions developed were not evaluated. A total of 12 rats from each group were selected at random for further study. Slit-lamp evaluation was performed in half of the rats from each group. The animals then were subjected to an overnight fast. The following morning, the rats were decapitated and blood samples (2.0 ml) were collected for the determination of fasting serum glucose concentration and serum ultrafiltrable calcium concentration. Blood urea nitrogen was measured in samples obtained from separate groups of DSC, DSnc, and DR that were similarly studied to evaluate the possibility of chronic renal failure in DSC. This measurement was performed in a total of six rats selected at random from each group.

Immediately upon decapitation, hand-drawn glass pipettes were quickly inserted tangentially into the anterior chamber of the eye for collection of aqueous humor. The lenses were then dissected from the eyeballs, blotted with filter paper that had been moistened with a sodium-free buffer solution, and transferred to tared weighing vials. The vials were placed in an oven at 100°C, and lenses were dried to constant weight (72 hours). Water content was expressed as the difference between wet and dry weights and was corrected for dry weight. Lenses were then digested by addition of 50 µl of concentrated hydrochloric acid to each vial and again placed in the oven for 24 hours.

At this time, 200 µl of concentrated sulfuric acid was added to each vial and the lenses were maintained at room temperature (25°C) for 12 hours to complete digestion of lenticular tissue. Samples were diluted for electrolyte analysis. Sodium and potassium concentrations in lenticular preparations and aqueous humor samples were measured by flame photometry. Serum ultrafiltrates for the measurement of calcium were obtained by filtration using a micropartition system (MPS-1; Amicon Corp, Lexington, MA, USA). Calcium concentration was determined colorimetrically, and glucose concentration was measured with a glucose analyzer (Beckman Instruments, Palo Alto, CA, USA). Blood urea nitrogen was measured by autoanalyzer technique (Technicon; Tarrytown, NY, USA).

Statistical analysis of the data was done using Student’s t test between groups, paired t evaluation within groups, and analysis of variance among the three groups. A p value less than 0.05 was considered significant. Values were expressed as the arithmetic mean ± SEM. All experimental procedures were approved by the local institutional review board for animal care and use, and procedures were performed in accordance with the guidelines of the National Institutes of Health and the American Physiological Society.

Results

A 35% incidence of cataract formation was observed among 20-week-old DS maintained on a high sodium diet. Slit-lamp analysis confirmed cataracts in DSC and lens transparency in DSnc and DR. All cataracts studied were anterior cortical, and nuclear opacification was also present in one severe cataract. Fasting serum glucose concentration was similar among DS (96 ± 3 mg/dl), DSnc (102 ± 5 mg/dl), DR (90 ± 4 mg/dl). Serum ultrafiltrable calcium concentration was also similar among the three groups (DSC: 4.1 ± 0.2; DSnc: 4.4 ± 0.5; DR: 3.7 ± 0.2 mg/dl). In addition, no differences in blood urea nitrogen (DSC: 33 ± 1; DSnc: 31 ± 2; DR: 31 ± 2 mg/dl) were observed among the three groups.

Under these conditions, aqueous humor sodium
TABLE 1. Concentration of Sodium and Potassium in Aqueous Humor

<table>
<thead>
<tr>
<th>Group</th>
<th>Na⁺ (mEq/L)</th>
<th>K⁺ (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With cataracts</td>
<td>139 ± 1*†</td>
<td>13.6 ± 1.7*†</td>
</tr>
<tr>
<td>Without cataracts</td>
<td>149 ± 2</td>
<td>10.2 ± 0.4*</td>
</tr>
<tr>
<td>DR</td>
<td>148 ± 4</td>
<td>8.4 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Significant variations in aqueous humor sodium concentration (p < 0.05) and potassium concentration (p < 0.001) were observed among the three groups. *p < 0.05, compared with corresponding values in DR. †p < 0.05, compared with corresponding values in DS without cataracts.

concentration was lower in DSc than in DSnc and DR (Table 1). Potassium concentration in the same sample was higher in DSc than in DSnc and DR (see Table 1). In addition, the aqueous humor potassium concentration was greater in DSnc than in DR, despite similar sodium concentrations in these two groups.

Lenticular water content was increased in DSc as compared with values in DSnc and DR (Figure 1). No difference was observed between the lens water content in DSnc and DR. Increased water content in DSc was associated with a marked rise in lens sodium content (Figure 2) and a decrease in lens potassium content (Figure 3) as compared with values in DSnc and DR.

Although lenticular sodium content was similar in DSnc and DR, a modest but significant decrease in lens potassium content was observed in DSnc as compared with values in DR. Systolic blood pressure was elevated in all DS between the ages of 18 and 21 weeks independently of the presence of cataracts, as compared with values in DR (Table 2). At this age systolic blood pressure was greater in DSc than in DSnc, although the difference between the two groups was not consistently significant from week to week. In weanling rats, however, the rise in systolic blood pressure in response to the first 2 weeks on a high sodium diet was greater in DS in which cataracts later developed (152 ± 4 mm Hg) than in DSnc in which cataracts did not develop (133 ± 4 mm Hg; p < 0.01) and in DR (107 ± 2 mm Hg; p < 0.01).

Discussion

Diabetes mellitus, hypoparathyroidism, renal failure, and hypocalcemic states are associated with an increased incidence of cataract formation. Hypertensive disease, however, has not been evaluated as a cataractogenic risk factor in either experimental or clinical studies. Although several models of cataract formation have been described previously in mice, blood pressure has not been reported in these models. Yet, early clinical studies of cataract formation in diabetes mellitus noted a high prevalence of arterial hypertension in those diabetic subjects in whom cataractous lesions developed. In the present study we found a high incidence of cataract formation in genetically hypertensive rats. Although cataractogenesis in DS may be a genetic defect resulting from successive inbreeding of rats from this strain, the increased pressor response to the first 2 weeks on a high salt diet in DS in which cataracts later developed suggests a possible link with hypertension. The possibility...
of a relationship between sodium intake and cataractogenesis cannot be evaluated on the basis of the present data. Nevertheless, the accelerated development of hypertension in DSc supports our hypothesis that cataract formation is related to the degree of salt-sensitivity in this model.

The precise mechanism of cataractogenesis in DSc cannot be defined from the data presented here. Hypertonic saline loading has been reported to induce cataracts as a consequence of lenticular dehydration resulting from high extracellular fluid osmolality. Although the administration of isotonic saline in addition to sodium in standard rat chow (0.45% sodium) constitutes mildly hypertonic sodium loading, the increased lenticular water content in DSc is clear evidence that cataracts did not result from lens dehydration. It is also unlikely that cataract formation in DSc was the consequence of altered steroidogenesis, since steroids induce posterior subcapsular cataracts, which were not observed in DSc. This finding, however, does not rule out a possible contributing role of high adrenocortical steroid levels to cataractogenesis in DSc.

Other factors that could have resulted in cataract formation were also considered in the present study. Hypocalcemia does not appear to be the cause of lens opacification, since the presence of cataracts in DSc was not associated with low serum ultrafilterable calcium concentration. Neither was cataract formation associated with renal failure, since blood urea nitrogen was similar among DSc, DSnc, and DR. Equally unlikely is the possibility that cataracts resulted from hyperglycemia, since fasting serum glucose levels were similar among DSc, DSnc, and DR. In addition, diabetes is not a factor in DS or DR.

The most plausible explanation for our findings of altered aqueous humor and lenticular electrolyte composition is that cataractogenesis in DSc may have resulted from altered ionic transport at the lens epithelium or ciliary body (or both). In the epithelium lining the anterior lenticular surface, Na⁺,K⁺-ATPase transports potassium from aqueous humor into the lens in exchange for sodium. In this manner, Na⁺,K⁺-ATPase counterbalances the passive leak of sodium and potassium across the posterior lens surface, as proposed in the classic pump-leak hypothesis. Thus, inhibition of the enzyme in the lens epithelium would result in decreased lenticular chemical gradients of sodium and potassium, which could explain the results of the present study. Since aqueous humor formation is regulated largely by transport processes at the ciliary ridge epithelium, inhibition of Na⁺,K⁺-ATPase activity exclusively at the anterior lens surface may not be sufficient to explain altered aqueous humor electrolyte composition in DS. Decreased Na⁺,K⁺-ATPase activity at the ciliary ridge epithelium, on the other hand, might partially account for our observations. At the ciliary processes where aqueous humor is secreted, Na⁺,K⁺-ATPase moves potassium from aqueous humor across basolateral membranes of the nonpigmented epithelial cell layer in exchange for sodium. Although sodium movement from blood to aqueous humor appears to be mediated largely by transport mechanisms other than Na⁺,K⁺-ATPase, selective inhibition of Na⁺,K⁺-ATPase activity might lead to measurable changes in aqueous humor electrolyte composition. Thus, inhibition of Na⁺,K⁺-ATPase at the lens epithelium or ciliary ridges (or both) might account for our findings.

**Table 2. Systolic Blood Pressure in DS With and Without Cataracts and in DR Between 18 and 21 Weeks of Age**

<table>
<thead>
<tr>
<th>Group</th>
<th>Systolic blood pressure (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>18 wk</td>
</tr>
<tr>
<td>DS With cataracts</td>
<td>198±2*†</td>
</tr>
<tr>
<td>DS Without cataracts</td>
<td>151±13*</td>
</tr>
<tr>
<td>DR</td>
<td>98±2</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

* p < 0.001, compared with corresponding values in DR.
† p < 0.05, compared with corresponding values in DS without cataracts.
Nevertheless, on the basis of the data presented here, alternative explanations for the aqueous and lenticular electrolyte imbalance in DS and DSnc cannot be ruled out. The transport disturbance might result from changes in membrane ionic permeabilities, for example, rather than inhibition of Na\(^+\),K\(^+\)-ATPase activity. Furthermore, data in DS without cataracts suggest a decreased transmembrane potassium gradient with no change in the sodium gradient, raising the possibility that a specific potassium transport defect may precede cataract formation in this genetic model. Whatever the case, our data may reflect a generalized disturbance in passive or active ion transport in DS. The increased aqueous humor potassium concentration and the decreased lenticular potassium content observed in DS without cataracts suggest that altered ionic transport may be a characteristic of this genetic model but that cataract formation may result only when the transport defect is severe.

In conclusion, we have described a potential genetic model of cataracts in which cataractogenesis is associated with hypertension. This observation raises the question of a possible link between hypertension and cataract formation.

Acknowledgments

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