Lovastatin But Not Enalapril Reduces Glomerular Injury in Dahl Salt-Sensitive Rats


Dahl salt-sensitive (S) rats fed a high salt diet develop hypertension, hyperlipidemia, and progressive renal disease. Previous studies have suggested that lipids may be important in the pathogenesis of glomerulosclerosis in Dahl S rats. To investigate this possibility, Dahl S rats fed 4% NaCl chow were treated chronically with the cholesterol synthesis inhibitor lovastatin. After 22 weeks, lovastatin-treated rats had a 38% reduction in serum cholesterol, a 76% reduction in urine albumin excretion, and one-sixth the incidence of focal glomerulosclerosis compared with vehicle-treated control rats. Blood pressure in lovastatin-treated rats was significantly (p<0.05) lower than that in vehicle-treated rats both early in the study (4 weeks of treatment) and at the end of the protocol. Lovastatin had no effect on glomerular filtration rate or glomerular ultrafiltration dynamics. The efficacy of angiotensin converting enzyme inhibitors in attenuating proteinuria and experimental glomerular disease may be dependent on sodium intake. Thus, we also investigated the effects of long-term enalapril treatment on glomerular injury in Dahl S rats fed high salt chow. Enalapril treatment (50 or 200 mg/l drinking water) significantly lowered blood pressure in Dahl S rats, but did not significantly affect albuminuria or glomerulosclerosis. Enalapril also had no effect on glomerular hemodynamics. These results suggest that lipids may be important in the development of both glomerular disease and hypertension in Dahl S rats and that angiotensin converting enzyme inhibition may not affect the course of renal disease in a setting of high salt intake. (Hypertension 1992;0:651-658)

KEY WORDS • glomerulosclerosis • lipids • hypertension, sodium sensitive • lovastatin • enalapril • rats, Dahl

The Dahl salt-sensitive (S) rat has been studied as one model of human essential hypertension. Dahl S rats fed a high salt diet develop marked elevations in systemic blood pressure.1-2 Control Dahl salt-resistant (R) rats, on the other hand, remain normotensive despite a high salt intake.1-2 Chronic, progressive glomerular disease is also characteristic of Dahl S rats. One recent study showed that prehypertensive Dahl S rats had increased urine albumin excretion compared with Dahl R rats.3 Marked albuminuria became evident in S rats in association with a high salt intake and the development of hypertension.3-4 Focal glomerulosclerosis (FGS) has been described in Dahl S rats as early as 15-20 weeks of age, and extensive FGS developed in 30-week-old hypertensive S rats.4

The mechanism by which glomerular injury develops in Dahl S rats is unclear. Initial micropuncture studies by Azar and coworkers5 showed that hypertensive S rats had elevated glomerular capillary pressure (Poc) compared with normotensive R rats. Increased Poc has been postulated to be a key factor in the initiation and progression of glomerular disease.5-7 More recent studies, however, have not demonstrated abnormal glomerular pressures in either prehypertensive or mildly hypertensive Dahl S rats, suggesting that other factors may be important for the initiation of glomerular injury in S rats.4,8 In this regard, we have recently shown that prehypertensive S rats have elevated serum triglyceride levels and that serum lipids increase with high salt feeding and the development of hypertension.4 There is substantial evidence that abnormal lipid metabolism plays a role in progressive glomerular disease.9-21 We have hypothesized, therefore, that lipid abnormalities may be important in the development of renal disease in Dahl S rats.4

The present study was designed to further investigate factors responsible for glomerular injury in Dahl S rats. To determine the importance of lipid abnormalities, S rats fed a high salt diet were treated with the cholesterol synthesis inhibitor lovastatin. We also investigated the effects of long-term treatment with the angiotensin converting enzyme (ACE) inhibitor enalapril on the development of glomerular injury in Dahl S rats. Both lovastatin and enalapril have been shown in several experimental models of renal disease to reduce blood pressure, albuminuria, and glomerulosclerosis.6,7,12-19

Received March 4, 1991; accepted in revised form July 2, 1992.
Methods

In all studies, laboratory chow containing 0.3% NaCl was fed to weanling male Dahl S rats (Brookhaven strain) ad libitum. Baseline measurements of systolic blood pressure (BP), fasting serum cholesterol and triglyceride levels, and 24-hour urine albumin excretion (UA/v) were made at 6 weeks of age. Laboratory chow containing 4% NaCl was then fed to all rats ad libitum for the remainder of each study. All procedures were in accordance with guidelines established by the Institutional Animal Care and Use Committee.

Study 1. Effects of Lovastatin and Low Dose Enalapril

Thirty-one Dahl S rats fed 4% NaCl were randomly allocated to three groups. One group (n=10) served as controls and received daily subcutaneous injections of ethanol-propylene glycol (1:1, vol/vol) vehicle. A second group (n=11) received daily injections of lovastatin (4 mg/kg body weight) dissolved in vehicle. The third group (n=10) received enalapril in the drinking water (50 mg/l) and received daily vehicle injections.

Body weights were recorded weekly. Food intakes were measured over a 3-6-day period at 12, 18, and 24 weeks of age. Measurements of BP, serum cholesterol and triglycerides, and UA/v were made at 10, 16, 22, and 28 weeks of age. At 28 weeks, rats were anesthetized with ether, and the left kidneys were removed, blotted, and weighed. Tissue from these kidneys was immersion fixed in Zenker’s solution and processed for histology. The right kidneys were perfusion fixed with glutaraldehyde, and tissue from these kidneys was processed for determination of glomerular areas. In some instances the glutaraldehyde perfusion was not uniform, and tissue from these kidneys was not used for histological evaluation. Blood was also obtained at 28 weeks for determination of plasma renin activity (PRA) and fractionation of plasma lipoproteins.

Study 2. Effects of High Dose Enalapril

A second long-term study was performed to examine the effects of enalapril dose on BP and glomerular injury in Dahl S rats. The dose of enalapril used in study 1, 50 mg/l drinking water, was the same as that previously found to reduce BP and glomerular injury in rats with subtotal renal ablation6,7 and in obese Zucker rats.19 However, in other experimental studies,14,20 higher doses of enalapril have been used in an attempt to modulate the development of glomerular injury. Therefore, the effects of a higher enalapril dose (200 mg/l water) were examined in the present study.

Six-week-old Dahl S rats were fed 4% NaCl chow and were allocated to three groups. One group (n=9) served as untreated controls, a second group (n=9) was treated with low dose enalapril (50 mg/l drinking water), and the third group (n=10) received high dose enalapril (200 mg/l drinking water). Body weights were recorded weekly, and daily food and water intakes were measured over the first 4 weeks of the study. Measurements of BP and UA/v were made at 10 and 16 weeks of age. At 16 weeks, renal tissue was obtained and processed for histology as described above for study 1.

Study 3. Effects of Lovastatin and Enalapril on Glomerular Hemodynamics

Separate groups of 6-week-old Dahl S rats were fed 4% NaCl chow and were treated with vehicle, lovastatin, or enalapril (50 mg/l) as described above. UA/v was measured in all rats at 10 weeks of age. Micropuncture studies of glomerular filtration dynamics were performed in nonfasted, euvoletic rats at 12-16 weeks of age, using techniques previously described.13,14,15

Rats were anesthetized with sodium pentobarbital (50 mg/kg body weight) and placed on a heated table. A tracheostomy was performed, the left femoral vein was cannulated with PE-50 tubing, and a bolus (0.5% body weight) of Ringer’s solution–rat serum (1:1) was administered slowly over 15-20 minutes. The same solution containing 25 µCi/ml [3H]inulin (Dupont New England Nuclear Corp., Boston, Mass.) was then infused at a rate of 0.5 ml/hr per 100 gram body weight for the remainder of the experiment. The femoral artery was cannulated with PE-50 tubing, and mean arterial BP was monitored with a digital display pressure transducer. A PE-50 catheter was placed in the bladder for urine collection. The left kidney was exposed by a subcostal incision, dissected free of perirenal tissue, immobilized in a plastic holder, and continuously bathed with mineral oil at 37°C.

After a 45-minute stabilization period, urine was collected in preweighed tubes for 20-30 minutes. During the period, three timed (3-4 minutes) collections of proximal tubular fluid were obtained from superficial nephrons for determination of single nephron glomerular filtration rate (SNGFR). Arterial blood samples were also collected during this period. Urine volumes were determined gravimetrically. Samples of urine, plasma, and tubular fluid were added to 8 ml scintillation cocktail (SCINT-A; Packard, Downers Grove, Ill.), and radioactivity of the samples was measured in a liquid scintillation spectrometer (model LS 1801, Beckman Instruments, Fullerton, Calif.).

Free flow tubular hydraulic pressures were measured in one group of proximal tubules. Step-flow pressure was measured in the earliest surface convolutions of a different group of proximal tubules after blockage of the tubular lumen with mineral oil. Pressures were also determined in randomly selected efferent vascular well points, or “star” vessels. All pressure measurements were performed with a servonulling micropressure system (model 900, World Precision Instruments, Inc., New Haven, Conn.). During these measurements, an arterial blood sample was obtained for determination of total plasma protein concentration. Plasma colloid osmotic pressure was calculated using the Landis-Pappenheimer equation. POC was estimated as the sum of step-flow pressure and colloid osmotic pressure. Blood samples were obtained from effenter vascular welling points and analyzed, together with an arterial blood sample, for total protein concentration using the micro-Lowry technique.

Measurements of Blood Pressure, Serum Lipids, Urine Albumin Excretion, and Plasma Renin Activity

A tail-cuff system (MK IV, Narco BioSystems, Austin, Tex.) was used to obtain morning BP measurements in conscious rats that had been trained to rest quietly in
warmed restrainers. Serum cholesterol and triglyceride levels were determined colorimetrically using an autoanalyzer (ASTRA, Beckman Instruments, Inc., Brea, Calif.) as previously described.12,21

To determine $U_{\text{out}}$, rats were housed individually in metabolic cages, deprived of food, and allowed free access to water. Urine albumin concentration was measured using a laser nephelometer (Hyland, Inc., Deerfield, Ill.) and a monospecific antibody to rat serum albumin (Cappel Laboratories, West Chester, Pa.) as we have previously described.12,13,21

Blood obtained for PRA determination was mixed immediately with EDTA (1 mg EDTA/1 ml blood) and centrifuged at 4°C for 20 minutes at 1,000g to isolate plasma. PRA was measured using a clinical radioimmunoassay kit (Dupont New England Nuclear) for the measurement of angiotensin I (Ang I) generated from endogenous substrate during a 1-hour incubation period at 37°C and pH 6.0. PRA was expressed as nanograms Ang I per milliliter per hour.

**Plasma Lipoprotein Fractionation**

Plasma lipoproteins were isolated in sequential density fractions by flotation with an ultracentrifuge. Plasma (2.5 ml) obtained from rats at 28 weeks of age was centrifuged at 100,000 rpm for 4 hours at 4°C in a Beckman TL-100 ultracentrifuge with a TLA-100.3 rotor. The very low density lipoprotein layer was removed, and the salt density of the infranate plasma was then adjusted sequentially with KBr and ultracentrifuged as above. The floating layers removed represented the density fractions $d_{1.060}$-$d_{1.006}$ (low density lipoproteins) and $d_{1.006}$-$d_{1.21}$ (high density lipoproteins). Cholesterol in each lipoprotein fraction was determined as described above.

**Histology**

Immersion-fixed tissue was stained with periodic acid-Schiff and examined for the presence of FGS as we have previously described.12,13,21 Each tissue sample was evaluated by two investigators without prior knowledge of the group to which the sample belonged. In each tissue specimen, 100 glomeruli were evaluated, and the percentage of glomeruli with any FGS was determined. FGS was defined as collapse of the glomerular capillary lumens and folding of the glomerular basement membrane with entrapment of amorphous material. Perfusion-fixed tissue was stained with periodic acid-Schiff, and glomerular areas were determined as we have previously described.13,21

**Statistical Analyses**

Results are expressed as mean±SEM. Differences between group means were assessed using one-way analysis of variance with the Duncan multiple range test for comparing multiple group means. Nonparametric data were analyzed using the Kruskal-Wallis method. When group variances were unequal, data were transformed logarithmically before analysis. Differences were considered significant for $p<0.05$.

**Results**

**Study 1**

Baseline body weights at 6 weeks of age were not different among the three groups of Dahl S rats (Figure 1). Thereafter, body weights of lovastatin-treated rats, when compared with vehicle-treated rats, were reduced approximately 10% throughout the 22-week experimental period (Figure 1). Body weights of enalapril-treated rats were not different from those of vehicle-treated rats at any point in the experimental period (Figure 1). Food intakes, measured at 12, 18, and 24 weeks of age, were not different among any of the groups (Table 1). Thus, the slight reduction in body weight in the lovastatin-treated rats was not due to a decrease in calorie intake.

Baseline systolic BP at 6 weeks of age was similar in the three groups (Figure 1). After beginning the high salt diet, BP increased in all groups. BP in the vehicle-treated rats increased 29% between 6 weeks (109±2 mm Hg) and 10 weeks (141±3 mm Hg) of age. Smaller

<table>
<thead>
<tr>
<th>Group</th>
<th>Daily food intake (g/rat)</th>
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<tbody>
<tr>
<td></td>
<td>12 Weeks</td>
</tr>
<tr>
<td>Vehicle</td>
<td>24.2±1.0 (11)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>24.4±1.0 (11)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>25.4±0.9 (10)</td>
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</table>

Results expressed as mean±SEM. Number of rats shown in parentheses. No significant differences were found among the groups at any of the ages.
increments in BP occurred in the other two groups. In the lovastatin-treated rats, BP increased from 111±2 at 6 weeks to 128±3 mm Hg at 10 weeks of age. Similarly, in the enalapril-treated rats BP increased from 105±4 at 6 weeks to 127±4 mm Hg at 10 weeks of age. Thus, at 10 weeks of age BP in the lovastatin-treated and enalapril-treated rats was significantly lower than that in the vehicle-treated rats (Figure 1).

In the vehicle-treated rats, BP rose only slightly between 10 and 16 weeks of age (Figure 1). BP in the enalapril-treated and lovastatin-treated rats also rose over the same time so that, at 16 weeks, BP was not different among the three groups. After 16 weeks, BP increased further in the vehicle-treated rats (Figure 1). In contrast, BP in the lovastatin-treated rats and enalapril-treated rats remained nearly constant after 16 weeks of age. At 22 and 28 weeks, therefore, BP in the lovastatin-treated and enalapril-treated rats was significantly lower than that in the vehicle-treated rats (Figure 1).

There were no significant differences in fasting serum cholesterol among the three groups at either 6 weeks or 10 weeks of age (Figure 2). Thereafter, serum cholesterol rose progressively in both the vehicle-treated rats and the enalapril-treated rats. At 28 weeks, serum cholesterol was increased 64% and 78% in the vehicle-treated and enalapril-treated rats, respectively, compared with baseline values at 6 weeks of age. In contrast, serum cholesterol in the lovastatin-treated rats remained nearly constant at the baseline level throughout the duration of the protocol (Figure 2). Reductions in very low, low, and high density lipoprotein cholesterol occurred in the lovastatin-treated rats when compared with the vehicle-treated rats (Table 2). This was statistically significant only for high density lipoprotein cholesterol. Lipoprotein cholesterol levels were not significantly different between the enalapril-treated and vehicle-treated rats (Table 2).

Qualitatively similar trends were found for fasting serum triglycerides in the three groups of rats (Figure 2). No differences in serum triglycerides were found among the groups at either 6 weeks or 10 weeks of age. Thereafter, serum triglycerides were increased 96% in the vehicle-treated and 194% in the enalapril-treated rats compared with baseline (Figure 2). The rise in triglycerides in the vehicle and enalapril groups, but this did not appear to be due to failure of the rats to thrive. No decrease in body weight between 22 and 28 weeks was seen in either group.

\[ U_{j.b.V} \] at 6 weeks of age was minimal in the three groups of rats and was not different among the groups (Figure 3). In both the vehicle-treated and enalapril-treated rats, \( U_{j.b.V} \) increased more than 10-fold between 6 and 10 weeks of age and was elevated 50-70-fold at 28 weeks compared with baseline (Figure 3). The rise in

### Table 2. Study 1: Characteristics of Dahl Salt-Sensitive Rats at 28 Weeks of Age

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Kidney weight (g)</th>
<th>Glomerular area (μm²)</th>
<th>Plasma renin activity (ng Ang 1•ml⁻¹•hr⁻¹)</th>
<th>Cholesterol (mg/100 ml)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VLDL</td>
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<tr>
<td>Vehicle</td>
<td>456±12</td>
<td>1.98±0.07</td>
<td>11,472±452</td>
<td>1.65±0.23</td>
<td>9.8±1.7</td>
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<tr>
<td></td>
<td>(9)</td>
<td>(7)</td>
<td>(9)</td>
<td></td>
<td>(9)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>417±11*</td>
<td>1.75±0.07</td>
<td>11,748±362</td>
<td>2.09±0.56</td>
<td>5.5±1.4</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td>(7)</td>
<td>(9)</td>
<td></td>
<td>(7)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>451±12</td>
<td>1.88±0.15</td>
<td>11,806±372</td>
<td>3.82±0.85*</td>
<td>14.1±5.7</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(6)</td>
<td>(9)</td>
<td></td>
<td>(6)</td>
</tr>
</tbody>
</table>

Ang 1, angiotensin I; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein. Results expressed as mean±SEM. Number of observations shown in parentheses.

* p<0.05 vs. other two groups.
† p<0.05 vs. enalapril group.
Glomerular Disease in Dahl Rats

U\textsubscript{aV}, urine albumin excretion; FGS, focal glomerulosclerosis. Results expressed as mean±SEM.

*p<0.05 vs. other two groups.

20–25% in the enalapril-treated rats (Table 3). There was no difference in BP between Dahl S rats receiving either low dose or high dose enalapril. As found in study 1, U\textsubscript{aV} was not reduced by enalapril treatment (Table 3). Indeed, U\textsubscript{aV} in the high dose enalapril-treated rats was significantly greater than in the other two groups. Moreover, as found in study 1, there was a trend for less FGS in the enalapril-treated rats, but this was not statistically significant (Table 3). Importantly, the incidence of FGS was very similar in the low dose and high dose enalapril-treated rats.

Study 3

Vehicle-treated, enalapril-treated, and lovastatin-treated Dahl S rats that underwent micropuncture at 12–16 weeks of age were representative of comparably treated S rats in study 1 at the same age. Body weight of lovastatin-treated rats that underwent micropuncture was reduced 8% compared with vehicle-treated rats (Table 4). BPs in rats during micropuncture were similar to those in rats in study 1 at the same age (Table 4). In addition, values of U\textsubscript{aV} at 10 weeks of age in the rats that underwent micropuncture were similar to those of 10-week-old rats in study 1 (Table 4).

There were no differences in glomerular filtration rate among the three groups of rats that underwent micropuncture studies (Table 4). SNGFR was also not different among the three groups (Table 4). There were no significant differences in single nephron plasma flow among the groups, although there was a trend for single nephron plasma flow to be reduced in the lovastatin-treated rats (Table 4). Both afferent arteriolar resistance and efferent arteriolar resistance were increased in the lovastatin-treated rats compared with resistances in the vehicle-treated rats. No alterations in renal arteriolar resistances occurred in the enalapril-treated rats.

There were no significant differences in either P\textsubscript{oc} or the mean transcapillary hydraulic pressure difference among the groups (Table 4). Compared with the vehicle-treated rats, colloid osmotic pressure was not altered in either the enalapril-treated or the lovastatin-treated rats (Table 4). There were no significant differences in glomerular ultrafiltration coefficient (K\textsubscript{f}) among the three groups (Table 4).

Discussion

The present results support our previous studies that suggested that lipids are important in the pathogenesis of glomerular disease.
of progressive glomerular disease. In those studies, lovastatin reduced albuminuria and FGS in subtotally nephrectomized rats and obese Zucker rats without altering glomerular hemodynamics.12,13 Qualitatively similar results were obtained in Dahl S rats of the present study that were treated with lovastatin, suggesting that lipids also play an important role in the development of glomerular injury in this experimental model of hypertension and renal disease.

The mechanism by which lovastatin ameliorated glomerular injury in Dahl S rats was not specifically addressed by these studies, but may have involved the ability of lovastatin to lower serum lipid and lipoprotein levels. Recent studies have suggested that lipid-mediated glomerular injury might result in part from actions of lipoproteins on the glomerulus. Lipoprotein binding and uptake by mesangial cells and glomerular epithelial cells has been demonstrated.22-24 Moreover, mesangial cells have been shown to oxidize lipoproteins, and these oxidized lipoproteins can be cytotoxic.25,26 Lipoprotein accumulation in the glomerulus could also promote macrophage infiltration, formation of foam cells, and release of factors such as reactive oxygen molecules and cytokines that could influence mesangial cell proliferation and matrix production.9 Thus, it is possible that lovastatin exerted its beneficial effects in Dahl S rats by lowering serum lipoprotein levels and reducing cholesterol delivery to, and uptake by, the glomerulus. Specifically, there was a trend for lower low density lipoprotein cholesterol in the lovastatin-treated rats. Moreover, high density lipoprotein cholesterol, the principal form of cholesterol transport in the rat,27 was significantly reduced in the lovastatin-treated rats. A trend for lower neprhon plasma flow in the lovastatin-treated Dahl S rats may also have been important in attenuating cholesterol delivery to the glomerulus.

Because body weight was slightly reduced in the lovastatin-treated Dahl S rats, it might be argued that lovastatin exerted its beneficial actions, in part, by restricting caloric and protein intake. Measurements of daily food intakes at three different intervals during the experimental period indicated that lovastatin did not affect food intake. It is possible, however, that lovastatin affected nutrient absorption, and we have no data to substantiate or refute that possibility. Interestingly, in our previous studies, lovastatin at the same dose also slightly reduced body weight in rats with subtotal renal ablation as well as in obese Zucker rats.12,13 Thus, lovastatin may have an effect of slightly restricting body growth, although the mechanism of such an effect remains to be established.

Initial micropuncture studies in Dahl S and R rats demonstrated increased Poc in hypertensive S rats.5 It was, therefore, postulated that elevated glomerular pressures might be responsible for the development of glomerular structural injury in Dahl S rats.32-34 More recent micropuncture studies in our laboratory and others, however, demonstrated that Poc was not abnormal in either prehypertensive Dahl S rats or moderately hypertensive S rats in which some glomerular disease was already evident.35-38 Those studies suggested that nonhemodynamic factors might be important in at least the initiation of glomerular injury in Dahl S rats, while not ruling out the possibility that elevated Poc occurs in Dahl S rats with severe hypertension and extensive glomerular injury and contributes to the progression of glomerulosclerosis.

The micropuncture results of the present study support our previous conclusion4 that alterations in glomerular pressures are not necessary for the initiation of glomerular injury in Dahl S rats. At 12–16 weeks of age, Poc was similar in all three groups of S rats, whereas the lovastatin-treated S rats had less glomerular injury as assessed by the magnitude of albuminuria. It is possible that Poc in the vehicle-treated S rats rose after 16 weeks of age, in association with a further rise in systemic BP, and contributed to the progression of glomerular disease.

Interestingly, enalapril did not significantly reduce glomerular injury in Dahl S rats, even when administered at a high dose. This is in contrast to findings in several other experimental models of glomerular disease, in which ACE inhibitors were remarkably effective in reducing albuminuria and glomerulosclerosis.5,7,14-19 Moreover, there are many reports that ACE inhibitors reduce proteinuria in human renal disease.20-23 The mechanism by which ACE inhibitors such as enalapril reduce glomerular injury is unclear. It has been proposed that inhibition of intrarenal angiotensin II production by ACE inhibitors protects the glomerulus by reducing Poc, independent of any effects on systemic BP.6 More recently, it has been demonstrated that ACE inhibition can ameliorate glomerular injury by a nonhemodynamic mechanism, perhaps by attenuating glomerular growth.32-34 Glomerular hypertrophy has been implicated as an important factor in the pathogenesis of glomerulosclerosis.32-34 Thus, the lack of a significant effect of enalapril on glomerular injury in Dahl S rats may have been due to either the inability of enalapril to lower Poc or to a lack of effect of enalapril on glomerular growth.

**Table 4. Glomerular Ultrafiltration Dynamics in 12–16-Week-Old Dahl Sati-Sensitive Rats**

<table>
<thead>
<tr>
<th>Group</th>
<th>BW (g)</th>
<th>LKW (g)</th>
<th>MAP (mm Hg)</th>
<th>UaV (mg/g/24 hr)</th>
<th>GFR (ml/min)</th>
<th>SNGFR (nl/min)</th>
<th>SNPF (nl/min)</th>
<th>Poc (mm Hg)</th>
<th>ΔP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (n=7)</td>
<td>416±6</td>
<td>1.78±0.06</td>
<td>138±4</td>
<td>33.6±7.9</td>
<td>1.77±0.16</td>
<td>48.0±5.9</td>
<td>55.6±2.1</td>
<td>44.1±1.1</td>
<td></td>
</tr>
<tr>
<td>Lovastatin (n=6)</td>
<td>375±11*</td>
<td>1.48±0.04*</td>
<td>131±3</td>
<td>14.2±5.1</td>
<td>1.60±0.13</td>
<td>45.6±4.7</td>
<td>52.0±1.0</td>
<td>41.5±0.9</td>
<td></td>
</tr>
<tr>
<td>Enalapril (n=6)</td>
<td>400±7</td>
<td>1.56±0.03*</td>
<td>137±2</td>
<td>35.2±6.7</td>
<td>1.85±0.13</td>
<td>48.9±3.9</td>
<td>53.8±2.6</td>
<td>41.8±2.3</td>
<td></td>
</tr>
</tbody>
</table>

BW, body weight; LKW, left kidney weight; MAP, mean arterial blood pressure; UaV, urine albumin excretion; GFR, glomerular filtration rate; SNGFR, single nephron GFR; SNPF, single nephron plasma flow; Poc, glomerular capillary hydraulic pressure; ΔP, mean transcapillary hydraulic pressure difference; COP, arterial plasma colloid osmotic pressure; Rk, afferent arteriolar resistance; Re, efferent arteriolar resistance. *p<0.05 vs. vehicle group.
Our enalapril results are similar to observations in another experimental model of glomerular disease associated with high salt intake. Dworkin et al.20 recently demonstrated that enalapril did not reduce proteinuria or glomerulosclerosis in rats with deoxycorticosterone acetate–salt hypertension. Thus, in a setting of high salt intake, ACE inhibitors may be ineffective in ameliorating glomerular disease. Some data in patients with renal disease support this suggestion. When sodium intake in patients receiving lisinopril was increased from 50 to 200 mmol/day, proteinuria increased to levels present before lisinopril treatment was begun.25

Despite no effect on glomerular disease, enalapril lowered BP in Dahl S rats. That enalapril was effective in lowering BP in this experimental low-renin setting is consistent with clinical observations in patients with low-renin essential hypertension.26 The mechanism by which enalapril lowered BP in Dahl S rats is unknown, although enalapril did not lower BP by reducing glomerular injury. At 28 weeks of age, enalapril-treated Dahl S rats had lower BPs than vehicle-treated S rats, even though glomerular injury, as assessed by albuminuria and the incidence of FGS, was comparable in both groups.

Results of the first long-term study indicated low PRA values in Dahl S rats. Others have also reported low PRA levels in Dahl S rats.37,38 Indeed, PRA levels in the vehicle-treated and lovastatin-treated Dahl S rats were very similar to PRA previously found in S rats.38 Dahl S rats also appear to demonstrate a blunted response to stimuli that elevate PRA. In a previous report, S rats placed on a sodium-restricted diet (0.01% sodium) only doubled PRA,29 which is comparable to the present finding that enalapril (50 mg/l) doubled PRA in S rats.

Perhaps the most unique finding of the present study was that lovastatin reduced BP in Dahl S rats. One could argue that this was due primarily to less glomerular structural injury in the lovastatin-treated S rats. Indeed, this may have been the case in the latter part of the study when extensive glomerular disease in the vehicle-treated Dahl S rats likely contributed to the progressive BP rise in that group. However, lovastatin-treated Dahl S rats also had lower blood pressures in the early part of the study, at 10 weeks of age, when glomerular structural injury in the vehicle-treated Dahl S rats presumably was minimal. These results suggest that lipids, in particular cholesterol, may directly influence BP in Dahl S rats. Further studies are warranted to investigate the mechanism by which lipid abnormalities might play a role in the pathogenesis of hypertension in Dahl S rats.


daniels and thank ellen davis for assistance in preparation of the manuscript.

**Acknowledgments**

We acknowledge the expert technical assistance of Frank Daniels and thank Ellen Davis for assistance in preparation of the manuscript.

**Table 4.** Continued

<table>
<thead>
<tr>
<th>COP (mm Hg)</th>
<th>$R_A$ (dyne • sec • cm$^{-2}$ • 10$^4$)</th>
<th>$R_B$ (nl • sec$^{-1}$ • mm Hg$^{-1}$)</th>
<th>$K_T$ (nl • sec$^{-1}$ • mm Hg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.1 ± 0.4</td>
<td>1.84 ± 0.24</td>
<td>0.99 ± 0.12</td>
<td>0.033 ± 0.004</td>
</tr>
<tr>
<td>17.1 ± 0.3</td>
<td>2.57 ± 0.24</td>
<td>1.41 ± 0.14</td>
<td>0.035 ± 0.003</td>
</tr>
<tr>
<td>18.8 ± 0.5</td>
<td>1.92 ± 0.20</td>
<td>1.01 ± 0.07</td>
<td>0.038 ± 0.002</td>
</tr>
</tbody>
</table>

**References**

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Hypertension. 1992;20:651-658  
doi: 10.1161/01.HYP.20.5.651

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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