Effects of Lipid-Lowering Agents in the Dahl Salt-Sensitive Rat

Thomas W Wilson, Magdalena Alonso-Gahcla, Richard J. Roman

Abstract—Inducing renal cytochrome P4504A (P4504A) activity with clofibrate prevents the development of hypertension in Dahl salt-sensitive (Dahl S) rats. To determine if this also occurs with other antihypertensive agents, we compared the effects of a related drug, fenofibrate, with those of an unrelated agent, pravastatin, on blood pressure, renal histology, and P4504A activity. Dahl S rats were pretreated with fenofibrate (95 mg/kg per day), pravastatin (70 mg/kg per day), or vehicle for 7 days before and after being switched from a low-salt (0.1% NaCl) to a high-salt (8% NaCl) diet. After 3 weeks on the high-salt diet, mean arterial pressures averaged 183±13 (n=9), 126±10 (n=9), and 148±11 mm Hg (n=8), respectively, in vehicle-, fenofibrate-, and pravastatin-treated animals. Both drugs reduced the degree of proteinuria and glomerular injury. P4504A protein levels and the synthesis of 20-hydroxyecos-5,8,11,14-tetraenolic acid (20-HETE) were increased in the liver and kidney of fenofibrate-treated, but not pravastatin-treated rats. We also administered these agents to Dahl S rats in which hypertension had previously been induced by a high-salt diet. Mean arterial pressures averaged 164±10, 113±23, and 160±15 mm Hg in rats treated with vehicle, fenofibrate, or pravastatin for 3 weeks. Fenofibrate-treated rats exhibited a natriuresis. Proteinuria and glomerular injury were reduced by pravastatin but not by fenofibrate. These results indicate that fenofibrate prevented the development of hypertension and reduced subsequent glomerular injury in Dahl S rats, probably secondary to increased renal production of 20-HETE. Although pravastatin did not induce renal P4504A activity in these animals, it reduced the severity of hypertension and renal damage through some other mechanism (Hypertension. 1998;31[part 2]:225-231.)

Key Words: salt sensitivity • cytochrome P450 • hydroxyecosatetraenolic acids • glomerulosclerosis • antihypertensive drugs • pravastatin • fenofibrate

The Dahl S rat is the most widely studied genetic model of salt-sensitive hypertension. When these animals are fed a high-salt diet, mean arterial pressure typically increases by 20 mm Hg within 24 hours and continues to rise to a plateau of 170 mm Hg or higher, around 2 weeks. The initial rise in arterial pressure appears to be triggered by sodium retention. The animals gain about 7% in body weight; plasma volume and cardiac output increase significantly. Later, cardiac output returns toward control values, and the hypertension is maintained by increased peripheral vascular resistance.

Previous studies have indicated that the pressure-natriuretic relation is reset to a higher level of renal perfusion pressure in Dahl S rats. This resetting is largely due to a marked elevation in sodium reabsorption in the thick ascending limb of the loop of Henle and is associated with a deficiency of the production of 20-HETE, which is a potent inhibitor of Na⁺,K⁺,2Cl⁻ cotransport in this segment of the nephron. Indeed, exogenous administration of 20-HETE has been reported to normalize chloride transport in the loop of Henle of Dahl S rats, and inhibitors of 20-HETE formation increase chloride transport in Dahl salt-resistant rats. Moreover, blockade of renal medullary 20-HETE synthesis by chronic renal medullary interstitial infusion of 17-octadecynolic acid induces hypertension in normotensive Lewis rats. Clofibrate belongs to the class of lipid-lowering agents often called "fibrates," which stimulate the peroxisome proliferator-activated receptor and induce genes coding for P4504A enzymes in the liver and kidney. Administration of clofibrate to Dahl S rats increases the synthesis of 20-HETE in the kidney and prevents the development of hypertension. However, the mechanism by which clofibrate lowers arterial pressure has not been determined, and it remains to be seen whether the antihypertensive effect is restricted to agents that induce the formation of 20-HETE or is a general property of antihypertensive agents. The present study examined this question by studying the effects of the peroxisome proliferator-activated receptor agonist, fenofibrate, and an unrelated antihypertensive agent, pravastatin, on blood pressure, renal P4504A activity, renal histology, and proteinuria in Dahl S rats before and after exposure to a high-salt diet.

Methods
Experiments were performed in male and female Dahl S/Jr/Hsd/MCW rats, which were obtained from a colony maintained at the Medical College of Wisconsin. They were weaned at 3 weeks of age.
Selected Abbreviations and Acronyms

Dahl S rat = Dahl salt-sensitive rat
HDLC = high-density lipoprotein
20-HETE = 20-hydroxyeicosatetraenoic acid
LDL = low-density lipoprotein
P4504A = cytochrome P4504A
PAS = periodic acid-Schiff

and then maintained on a low-sodium (0.1% NaCl) diet until 8 weeks of age when they entered the study. Rats were housed individually in stainless steel cages in an animal care facility that is accredited by the American Association for the Accreditation of Laboratory Animal Care, and all protocols were approved by the Animal Care Committee of the Medical College of Wisconsin.

Equal numbers of rats of both sexes were assigned to either the prevention study, in which drug therapy was begun before the switch from a low-salt to a high-salt diet or a treatment study, in which the drugs were started after 2 weeks of a high-salt diet.

Prevention Study

The animals were divided into three groups. One group was given vehicle, consisting of 

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TABLE 1. Weight, Plasma Lipid, and Creatinine Concentrations

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Body Weight at 9 Weeks, g</th>
<th>Weight Gain, g</th>
<th>Chol, mmol/L</th>
<th>Trig, mmol/L</th>
<th>Creat, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle (9)</td>
<td>242 ± 18</td>
<td>25 ± 16</td>
<td>3.5 ± 0.5</td>
<td>0.5 ± 0.2</td>
<td>60 ± 7</td>
</tr>
<tr>
<td>Fenofibrate (9)</td>
<td>215 ± 12</td>
<td>19 ± 13</td>
<td>3.0 ± 0.8</td>
<td>0.4 ± 0.1</td>
<td>45 ± 7</td>
</tr>
<tr>
<td>Pravastatin (8)</td>
<td>207 ± 7</td>
<td>19 ± 11</td>
<td>2.1 ± 1.0</td>
<td>0.4 ± 0.2</td>
<td>44 ± 7</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle (5)</td>
<td>207 ± 24</td>
<td>37 ± 9</td>
<td>4.6 ± 1.1</td>
<td>0.6 ± 0.2</td>
<td>54 ± 6</td>
</tr>
<tr>
<td>Fenofibrate (4)</td>
<td>207 ± 14</td>
<td>11 ± 16*</td>
<td>5.3 ± 0.8</td>
<td>1.0 ± 0.4</td>
<td>62 ± 4</td>
</tr>
<tr>
<td>Pravastatin (5)</td>
<td>224 ± 18</td>
<td>35 ± 16</td>
<td>4.7 ± 0.7</td>
<td>0.7 ± 0.2</td>
<td>70 ± 10</td>
</tr>
</tbody>
</table>

Numbers in parentheses are numbers of rats in each group. Prevention and treatment refer to animals entered in the prevention and treatment studies (see text). Chol indicates total serum cholesterol; Trig, serum triglycerides; and Creat, creatinine.

*P < .05 compared with the value for the corresponding vehicle-treated group.

the urinary excretion of protein are summarized in Fig 1. Mean arterial pressure was significantly lower in the rats treated with either fenofibrate or pravastatin than in control animals (Fig 1, top panel). All rats developed proteinuria within 2 weeks of the switch to the high-salt diet. However, urinary excretion of protein was significantly lower in the rats treated with either fenofibrate or pravastatin compared with control group values.

Prevention Study Histology

The histological assessment of the liver appeared normal in all groups of rats. There was no necrosis nor evidence of abnormal growth. Kidney weight also was not significantly different among the groups (Table 2). Fig 2 shows representative photomicrographs of the renal cortex for the three groups of animals in the prevention study; a summary of the semi quantitative analysis of the degree of glomerular injury is presented in Table 2. About 15% of the glomeruli of vehicle-treated rats exhibited glomerulosclerosis. PAS-positive material was found in the mesangium and occlusion and filling in of about 50% of the capillary loops in abnormal glomeruli. Treatment with fenofibrate or pravastatin significantly reduced the number of abnormal glomeruli, the degree of mesangial expansion, and glomerulosclerosis (Table 2). Glomeruli were slightly larger in fenofibrate-treated rats than in control animals, while those of pravastatin-treated rats were significantly smaller than those seen in the control animals (Table 2).

Prevention Study

Treatment Study

Figure 1. Effects of pravastatin and fenofibrate on blood pressure and urinary protein excretion in Dahl S rats. Mean values ± SEM of each treatment group are presented. *P < .05 compared with the value in the corresponding vehicle-treated group. MAP indicates mean arterial pressure.
TABLE 2. Renal Histology: Semiquantitative Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Kidney Weight, g</th>
<th>Glomerular Sclerosis, % Glomeruli</th>
<th>Mesangial Wall/Lumen Expansion, U</th>
<th>Glomerulosclerosis, U</th>
<th>Wall/Lumen Ratio Size, μm²/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>1.53±0.16</td>
<td>15±3</td>
<td>1.25±0.08</td>
<td>0.42±0.06</td>
<td>8.1±1.3</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>1.66±0.18</td>
<td>6±1</td>
<td>0.85±0.08*</td>
<td>0.18±0.04*</td>
<td>7.4±1.4</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1.43±0.07</td>
<td>3±1</td>
<td>0.96±0.08*</td>
<td>0.56±0.04*</td>
<td>4.9±0.7*</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>1.33±0.21</td>
<td>32±4</td>
<td>2.08±0.08*</td>
<td>1.80±0.07*</td>
<td>14.8±2.1*</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>1.51±0.06</td>
<td>29±4</td>
<td>1.97±0.07*</td>
<td>1.50±0.07*</td>
<td>10.6±2.5*</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1.67±0.19</td>
<td>17±1</td>
<td>1.11±0.10*</td>
<td>0.82±0.07*</td>
<td>7.9±0.9*</td>
</tr>
</tbody>
</table>

n=4 animals (2 male and 2 female) from each treatment group.
*P<.05 compared with the value in the prevention study vehicle-treated group.
†P<.05 compared with the value in the treatment study vehicle-treated group.

Pravastatin and fenofibrate also had significant effects on the structure of preglomerular arterioles (Fig 3). Interlobular and afferent arterioles of pravastatin-treated rats had thinner walls than those from rats in the other two groups. Wall/lumen area ratios were lower in pravastatin-treated animals (Table 2).

CYP4504A Protein Expression and Activity

In preliminary studies, we found that pravastatin and fenofibrate treatment produced similar changes in CYP4504A protein concentration and enzyme activity in rats in the treatment and prevention protocols. Therefore, the results from both groups were combined and are presented together in Fig 4. Representative immunoblots of protein extracted from the liver and kidney of vehicle and drug-treated animals are presented in Fig 4a and 4b. CYP4504A protein levels were markedly induced in the renal cortex and liver of fenofibrate-treated rats (Fig 4a, 4c, and 4e), but were not significantly different from control in rats treated with pravastatin (Fig 4b, 4c, and 4e). CYP4504A protein levels also tended to be higher in the outer medulla of fenofibrate-treated than vehicle-treated rats, but this difference did not reach statistical significance (4d).

CYP4504A enzyme activity was assessed by measuring 20-HETE production in renal and hepatic microsomes incubated with arachidonic acid and is shown in Fig 5. The production of 20-HETE was significantly greater in the renal cortex and liver of rats treated with fenofibrate than in control animals or pravastatin-treated rats. Mean renal medullary 20-HETE production was greater in fenofibrate-treated rats than in the other two groups, but this difference was not statistically significant. Pravastatin had no effect on 20-HETE synthesis in either the liver or the kidney.
Treatment Study
Food, sodium, and water intakes were similar in the three groups of rats throughout the drug treatment period and averaged approximately 20 g, 20 mmol/d, and 80 mL/d, respectively. The rats consumed on average 68 mg/kg per day of fenofibrate and 61 mg/kg per day of pravastatin during the study. All animals gained weight during the study. However fenofibrate-treated rats gained about 20 g less weight than pravastatin-treated or control animals (Table 1). Plasma cholesterol and triglyceride levels were higher in the treatment protocol rats than in those in the prevention protocol, but it should be noted that the treatment protocol was longer and the rats were 2 weeks older (14 versus 12 weeks of age) at the time of the study. Neither fenofibrate nor pravastatin had any significant effect on plasma cholesterol, triglyceride, or creatinine concentrations (Table 1). A summary of the effects of pravastatin and fenofibrate on blood pressure and urinary excretion of protein in Dahl S rats with established hypertension is presented in Fig 1. Mean arterial pressures were normalized in the rats treated with fenofibrate, whereas pravastatin had no significant effect on blood pressure (top panel). Despite the reduction in arterial pressure, urinary excretion of protein was significantly greater in fenofibrate-treated than in control rats (bottom panel). In contrast, urinary excretion of protein was reduced in pravastatin-treated rats.

Treatment Study Histology
The histological assessment of the kidney was abnormal in all vehicle- and drug-treated rats. Many glomeruli exhibited various stages of damage and juxtamedullary glomeruli appeared to be more affected. There were areas of tubular necrosis and fibrosis throughout the renal cortex and medulla. Preglomerular arterioles exhibited medial thickening of the wall. In the control group, some vessel walls were infiltrated with plasma and red cells.

The degree of glomerular damage and mesangial expansion was similar in control and fenofibrate-treated rats and the wall/lumen ratios of pregglomerular arterioles were similar (Table 2). Pravastatin seemed to offer some degree of renoprotection. The extents of glomerulosclerosis and mesangial expansion were significantly lower in the pravastatin-treated rats (Table 2). Pravastatin also reduced the wall/lumen ratio of pregglomerular arterioles.

Discussion
Although a previous study indicated that clofibrate can prevent the development of hypertension in Dahl S rats, it remained to be determined whether the antihypertensive action is a common property of antilipemic therapy. Also, the mechanism of the antihypertensive action was unknown. To address these questions, we examined the effects of fenofibrate, a related drug that induces P4504A activity, and another antilipemic agent, pravastatin, that has no known actions on this enzyme system. We found that both drugs attenuated the development of hypertension in Dahl S rats. Immunoblotting studies confirmed that only fenofibrate enhanced...
CYP4504A protein levels in the liver and renal cortex. Furthermore, the activity of CYP4504A enzyme, as measured by the conversion of arachidonic acid to 20-HETE was also increased in microsomes prepared from the liver and the kidney of the fenofibrate-treated rats. 20-HETE inhibits Na-K-ATPase activity and sodium reabsorption in the proximal tubule. Elevations in 20-HETE formation have recently been suggested to mediate the natriuretic effects of angiotensin II, parathyroid hormone, and dopamine in this segment of the nephron. 20-HETE also inhibits chloride transport in the thick ascending loop of Henle by blocking a 70 pS potassium channel required for the recycling of potassium and the operation of the Na+,K+,2Cl− cotransporter. Thus, an explanation for the present findings is that fenofibrate increases the renal production of 20-HETE, which, in turn, inhibits sodium reabsorption. Our recent finding that sodium excretion and the pressure-natriuretic response is normalized by clofibrate is consistent with this notion. Treatment study rats receiving fenofibrate gained less weight over the course of the study as than did the vehicle- and pravastatin-treated rats and also exhibited a natriuresis. Nevertheless, more carefully controlled balance studies will have to be performed before one can conclude that the antihypertensive action of fenofibrate in Dahl S rats with established hypertension is related to a diuretic action.

The effect of pravastatin to reduce blood pressure in Dahl S rats in the prevention study was unexpected. Unlike fenofibrate, pravastatin did not increase CYP4504A expression or activity in either the liver or the kidney. Moreover, rats receiving pravastatin gained amounts of weight equivalent to the control rats. We considered the possibility that the antihypertensive effect of pravastatin could be explained by its antilipidemic action even though total plasma cholesterol and triglyceride concentrations were not reduced. Oxidized LDLs have been shown to impair endothelial function and alter vascular reactivity. Reducing LDL cholesterol concentration in hyperlipidemic humans can improve endothelial function. However, it is unlikely that changes in the ratio of HDL to LDL cholesterol could contribute to the changes in blood pressure seen in the present study since total cholesterol concentration was relatively low and, in our preliminary work, we found that >85% of cholesterol is in the form of HDL cholesterol in our strain of Dahl S rats. Our findings confirm a previous report by O'Donnell et al. that lovastatin prevented the development of hypertension in Dahl S rats in the absence of any effect on total, LDL, very low density lipoprotein, or HDL cholesterol levels.

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors such as pravastatin not only reduce the synthesis of cholesterol but also inhibit the formation of ubiquinones, heme A, dolichol pyrophosphate, and isoprenoids. It is possible that reduced amounts of the latter compounds might contribute to the antihypertensive effect of pravastatin. Isoprenoids such as farnesol and geranylgeranylated combine with many types of proteins involved in signal transduction. Among the many proteins undergoing isoprenylation are ras and ras-like small G-proteins. In particular, ras can increase smooth muscle responsiveness to increased intracellular calcium and, perhaps more importantly, it is a key player in the tyrosine kinase-mediated growth-signaling pathway involved in the proliferation of vascular smooth muscle and other cell types. Indeed, a consistent finding throughout the present study is that pravastatin markedly reduced the wall/lumen ratio of preglomerular renal arterioles. The antiproliferative effects of pravastatin may ameliorate some of the further rise in blood pressure associated with changes in renal vascular resistance that accompany hypertrophy of resistance vessels. The recent report by Jiang and Roman from our laboratory, indicating that chronic treatment with lovastatin markedly reduced hypertrophy of preglomerular arterioles, improved the pressure natriuresis response, and prevented the development of hypertension in spontaneously hypertensive rats, is consistent with this formulation.

Regardless of the mechanism of action, the important new finding in the present study is that pravastatin did partially ameliorate the development of hypertension in Dahl S rats and reduced the degree of glomerular damage. In the treatment studies of Dahl S rats with preexisting hypertension, pravastatin had no effect on blood pressure, although we cannot rule out a small antihypertensive effect. Despite the fact that pravastatin...
did not lower arterial pressure, it reduced proteinuria and improved the histological appearance of the kidney. The wall/lumen ratio of renal resistance blood vessels and the glomerulosclerotic and mesangial expansion indices were significantly reduced in pravastatin-treated animals. We suspect that pravastatin did not reverse glomerulosclerotic in hypertrophied and badly damaged glomeruli, but rather arrested the tendency of unaffected glomeruli to enter a proliferative, hypertrophic growth phase. Thus, damaged glomeruli might continue to hypertrophy, but normal glomeruli would not. This presumably explains why the average glomerular size was not reduced in the pravastatin-treated treatment study animals. Ultimately, this would reduce proteinuria, as the damaged glomeruli undergo sclerosis and stop filtering. Only damaged but filtering glomeruli are thought to contribute to protein excreted in the urine.20 Fenofibrate given to rats with established hypertension seemed to have little effect on glomerular histological changes and may have actually increased proteinuria. This observation should be confirmed, currently its mechanism is unknown. A direct toxic effect of fenofibrate on the kidney is unlikely as animals in the prevention study given the drug had less proteinuria and renal damage. In summary, the present results indicate that fenofibrate prevents the development of hypertension in Dahl S rats, probably secondary to induction of the renal production of 20-HETE and the promotion of sodium excretion. Pravastatin did not induce the renal formation of 20-HETE, but it still partially prevented the hypertension. In established hypertension, pravastatin had no measurable effect on blood pressure in anesthetized animals. Even though an antihypertensive effect was minimal or absent in these rats, pravastatin exhibited renoprotective effects on glomeruli and small renal arteries. Whether antihyperlipidemic agents will exhibit any antihypertensive or renoprotective actions in human hypertension is unknown, but seems to be worth exploring.

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