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Involvement of angiotensin II in development of spontaneous nephrosis in Dahl salt-sensitive rats

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Abstract

We investigated the effect of angiotensin-converting enzyme inhibition on spontaneous nephrosis in Dahl salt-sensitive (Dahl/S) rats. Dahl/S rats fed on a normal sodium diet spontaneously developed nephrosis and mild hypertension from a young age. In young Dahl/S rats, an angiotensin-converting enzyme inhibitor, imidapril, attenuated the development of proteinuria accompanied by a decrease in blood pressure. Methylprednisolone, a potent therapeutic agent for proteinuria, did not affect the development of nephrosis. An angiotensin AT_1 receptor antagonist, losartan, but not a Ca^{2+} channel blocker, verapamil, inhibited the development of nephrosis while both agents decreased blood pressure to a similar extent as imidapril. In mature Dahl/S rats, imidapril suppressed not only the development of proteinuria but also the glomerular lesions. It is concluded that the development of spontaneous nephrosis in Dahl/S rats is mediated by angiotensin II.

Keywords: Angiotensin-converting enzyme inhibitor; Dahl salt-sensitive rat; Nephrosis; Proteinuria

1. Introduction

Dahl salt-sensitive (Dahl/S) rats are genetically predisposed to develop hypertension when fed on a high salt diet (Dahl et al., 1962). Dahl/S rats have been used as a model of salt-sensitive hypertension. Salt-induced hypertension in Dahl/S rats leads to renal damage (Jaffe et al., 1970), and there are slight morphological changes in Dahl/S rats fed on a normal sodium diet. Other investigators have demonstrated that the kidneys of Dahl/S rats are abnormal. Sterzel et al. (1988) demonstrated that young Dahl/S rats had proteinuria which was not prevented by a low sodium diet. O'Donnell et al. (1989) demonstrated that Dahl/S rats fed on standard laboratory chow had proteinuria and hyperlipidemia, and developed focal and segmental glomerulosclerosis. Abnormalities of lipid metabolism in Dahl/S rats also have been reported (Reaven et al., 1991; Mondon et al., 1993; Donnelly et al., 1994; Hirano et al., 1994). Although Dahl/S rats develop nephrosis spontaneously, there are few studies about nephrosis in Dahl/S rats fed on a normal sodium diet. The present study was undertaken to clarify the role of angiotensin II in the development of spontaneous nephrosis in Dahl/S rats.

2. Materials and methods

2.1. Animals

Male Dahl salt-resistance (Dahl/R) rats and Dahl/S rats were purchased from SEAC Yoshitomi (Fukuoka, Japan). These strains of Dahl rats originated in Møllegaards Avlslaboratorium (Ejby, Denmark). The rats were given standard laboratory chow containing 0.39% (w/w) of sodium (CE-2, CLEA, Tokyo, Japan) and tap water was available ad libitum throughout the experiments. Four rats were housed in one cage except during the periods of urine collection. All the experiments were undertaken under observance of the 'Guideline Principles for the Care and Use of Laboratory Animals' approved by The Japanese Pharmacological Society.

2.2. Drugs

Imidapril and losartan were synthesized by Tanabe Seiyaku (Osaka, Japan). Methylprednisolone and vera-

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pamil were purchased from Sigma (St. Louis, MO, USA). Each compound was dissolved in purified water and administered p.o. once a day at noon.

2.3. Experimental procedure

2.3.1. Effects of imidapril and methylprednisolone on nephrosis in young Dahl / S rats

A total of 32 Dahl/S rats aged 4 weeks were divided into four groups. Animals in each group were daily given either vehicle, imidapril (0.5 or 2 mg/kg) or methylprednisolone (2 mg/kg) for 15 days from the age of 5 weeks. Eight age-matched Dahl/R rats were given vehicle and served as a reference. The 24-h urine collection was performed 5 days before and 1, 8 and 15 days after the start of drug administration. Urinary protein excretion (UproV) was calculated from the urinary protein concentration and urine volume. Systolic blood pressure was measured by the tail-cuff method (UR-5000, Ueda, Tokyo, Japan) 3 days before and 4 and 11 days after the start of drug administration. Blood pressure was measured in the morning just before drug administration. On the day of last urine collection, animals were anesthetized with sodium pentobarbital (50 mg/kg) by an i.p. injection, and then blood samples were collected via the abdominal aorta. Plasma levels of total cholesterol, triglyceride, albumin, total protein, and plasma and urine levels of creatinine were measured, and the creatinine clearance was calculated.

2.3.2. Effects of losartan and verapamil on nephrosis in young Dahl / S rats

A total of 24 Dahl/S rats aged 4 weeks were divided into three groups and were daily given either vehicle, losartan (10 mg/kg), or verapamil (60 mg/kg) for 15 days from the age of 5 weeks. Urine and blood collection, and measurements of systolic blood pressure were performed following the same procedure as in Section 2.3.1.

2.3.3. Effect of imidapril on nephrosis in mature Dahl / S rats

A total of 16 Dahl/S rats aged 12 weeks were divided into two groups and were daily given either vehicle or imidapril (2 mg/kg) for 22 days from the age of 13 weeks. Eight age-matched Dahl/R rats were given vehicle and served as a reference group. The 24-h urine collection was performed 5 days before and 1, 8, 15 and 22 days after the start of drug administration. Systolic blood pressure was measured 3 days before and 4 and 11 days after the start of drug administration. On the day of last urine collection, animals were anesthetized, and then blood samples were collected as described above. Then the left kidney was removed for the histological examination.

2.4. Measurements

Blood samples were placed in heparin-containing tubes on ice, and plasma samples were obtained by centrifuga-

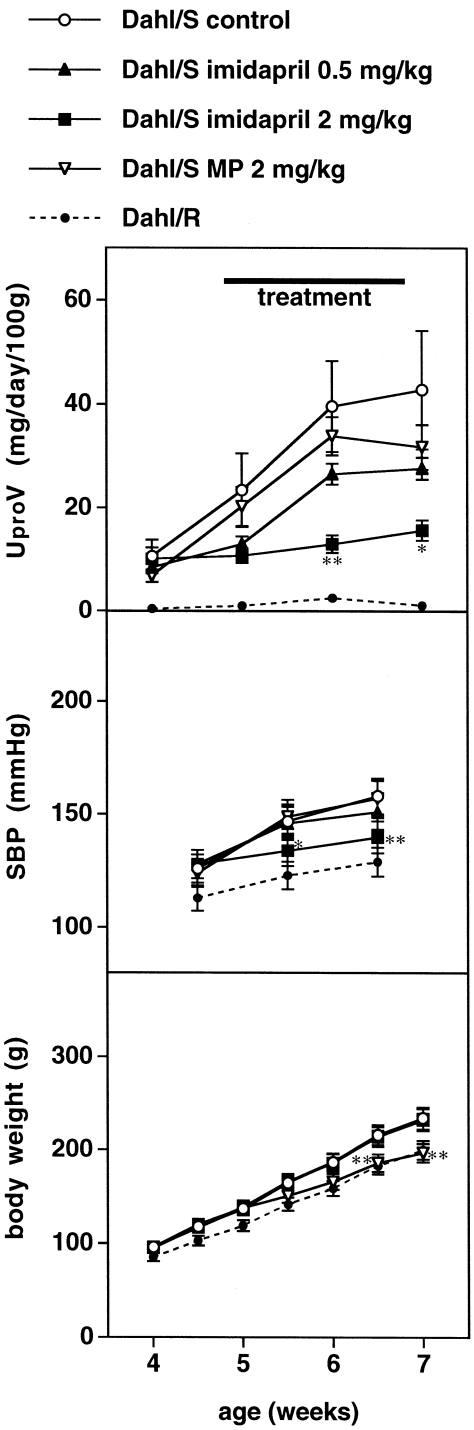

Fig. 1. Effects of imidapril and methylprednisolone (MP) on UproV, systolic blood pressure (SBP), and body weight in young Dahl/S rats. Data are expressed as the means ± S.E.M. for eight animals. * $P < 0.05$ and ** $P < 0.01$ as compared with corresponding Dahl/S control values by Dunnett's test. Dahl/R: Dahl salt-resistant rats.

tion (2500 rpm, 15 min, 4°C). The creatinine concentration in plasma and urine was measured by an enzymatic method (Creatinizyme, Eiken, Tokyo, Japan), using an automatic analyzer (Hitachi705, Hitachi, Tokyo, Japan). Urinary protein concentration was determined by the pyrogallol red method (Micro TP-AR, Wako, Osaka, Japan), using an automatic analyzer. Plasma levels of total cholesterol, triglyceride, albumin and total protein were measured by routine methods, using an analyzer.

2.5. Histological examination

Each kidney specimen was fixed in phosphate-buffered 10% formalin and dehydrated with ethanol. The tissues were then embedded in paraffin and sectioned. The sections were stained with the periodic acid–Schiff reagent for light microscopic examination. The percentage of glomeruli with lesions was determined by blind observation.

2.6. Data analysis

Data are expressed as the means ± S.E.M. Analysis of variance followed by Dunnett's test was used for comparisons between data for the control Dahl/S rats in the experiments with young Dahl/S rats. Unpaired *t*-test was used for data obtained for mature Dahl/S rats. Differences with *P*-values less than 0.05 were considered to be statistically significant. The values for Dahl/R rats are shown as a reference, but were not included in the statistical analysis.

3. Results

3.1. Effects of imidapril and methylprednisolone on nephrosis in young Dahl / S rats

The time courses of changes in body weight, UproV, and systolic blood pressure are shown in Fig. 1. Control Dahl/S rats developed mild hypertension and marked proteinuria during the experimental periods. Imidapril inhibited both the hypertension and the increase in UproV in a dose-dependent manner. Methylprednisolone did not affect the development of proteinuria or hypertension, but significantly inhibited the increase in body weight.

Plasma chemistry values and creatinine clearance are shown in Table 1. Control Dahl/S rats had high levels of total cholesterol and triglyceride and low levels of albumin and total protein. Treatment with imidapril at a dose of 2 mg/kg significantly lowered the concentration of total cholesterol and triglyceride, and elevated the level of total protein and albumin. Methylprednisolone suppressed the plasma level of total cholesterol but increased the triglyceride level. Creatinine clearance was not affected by these drugs.

3.2. Effects of losartan and verapamil on nephrosis in young Dahl / S rats

The time courses of changes in body weight, UproV, and systolic blood pressure are shown in Fig. 2. Losartan and verapamil similarly suppressed the increase in systolic blood pressure. Losartan inhibited the development of proteinuria. In contrast, verapamil inhibited UproV only on the 1st day, but not on the 8th and 15th days after the start of administration. Verapamil caused a slight but significant suppression of the increase in body weight.

Plasma chemistry values and creatinine clearance are shown in Table 2. Losartan significantly elevated the plasma albumin level. Verapamil significantly elevated the plasma total cholesterol level and creatinine clearance. Creatinine clearance was not affected by losartan.

3.3. Effect of imidapril on nephrosis in mature Dahl / S rats

The time courses of changes in body weight, UproV, and systolic blood pressure are shown in Fig. 3. Imidapril decreased UproV and systolic blood pressure. Plasma chemistry values and creatinine clearance were not affected by imidapril (Table 3). Hyaline droplets and hypertrophy of podocytes were frequently seen in some glomeruli, and adhesion of the glomerulus to Bowman's capsule was less frequently observed in control Dahl/S rats (Fig. 4). Imidapril significantly decreased the inci-

Table 1
Effects of imidapril and methylpredonisolone on plasma concentration of total cholesterol (CHO), triglyceride (TG), total protein (TP) and albumin (ALB), and creatinine clearance (Ccr) in 7-week old Dahl/S rats

Strain	Drug	Dose (μg/kg)	CHO (mg/dl)	TG (mg/dl)	TP (g/dl)	ALB (g/dl)	Ccr (ml/day/100 g)
Dahl/S	–	–	96 ± 9	153 ± 2	5.10 ± 0.07	3.07 ± 0.10	1015 ± 44
Dahl/S	imidapril	0.5	85 ± 2	132 ± 8	5.30 ± 0.04	3.26 ± 0.04	1056 ± 44
Dahl/S	imidapril	2.0	79 ± 2[a]	109 ± 8[b]	5.35 ± 0.06[a]	3.41 ± 0.03[b]	1046 ± 60
Dahl/S	MP[d]	2.0	71 ± 2[b]	329 ± 31[b]	4.98 ± 0.08	3.12 ± 0.06	1118 ± 51
Dahl/R[c]	–	–	62 ± 1	118 ± 12	4.87 ± 0.07	3.34 ± 0.04	1047 ± 28

Values are the means ± S.E.M. for eight animals. [a]$P < 0.05$ and [b]$P < 0.01$ as compared with corresponding Dahl/S control values by Dunnett's test. [c]Dahl salt-resistant rats and [d]methylpredonisolone.

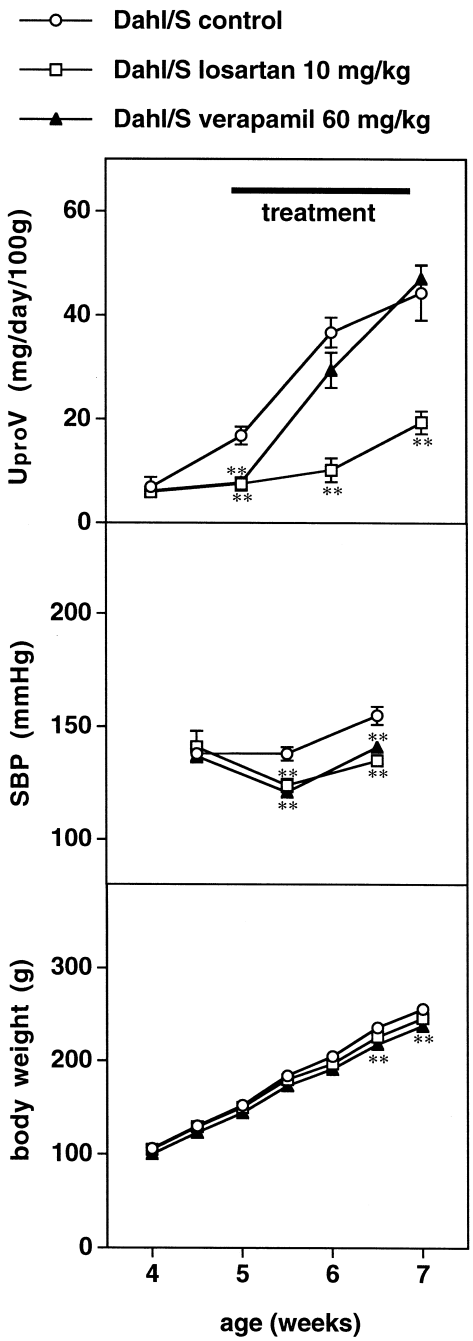

Fig. 2. Effects of losartan and verapamil on UproV, systolic blood pressure (SBP), and body weight in young Dahl/S rats. Data are expressed as the means ± S.E.M. for eight animals. ∗∗ $P < 0.01$ as compared with corresponding Dahl/S control values by Dunnett's test.

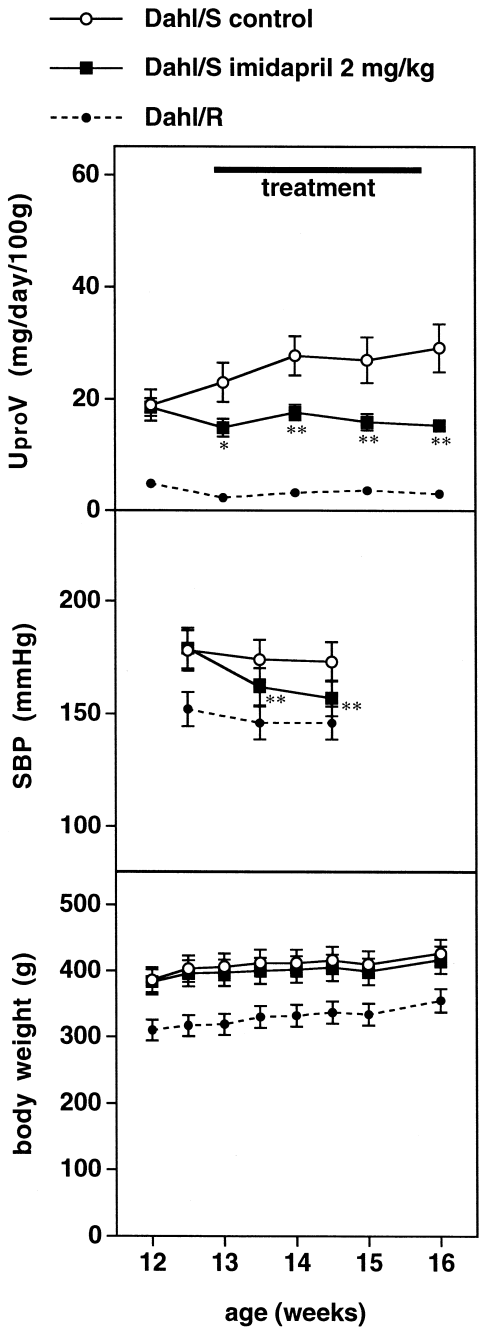

Fig. 3. Effects of imidapril on UproV, systolic blood pressure (SBP), and body weight in mature Dahl/S rats. Data are expressed as the means ± S.E.M. for eight animals. ∗ $P < 0.05$ and ∗∗ $P < 0.01$ as compared with corresponding Dahl/S control values by unpaired *t*-test. Dahl/R: Dahl salt-resistant rats.

Table 2
Effects of losartan and verapamil on plasma concentration of total cholesterol (CHO), triglyceride (TG), total protein (TP) and albumin (ALB), and creatinine clearance (Ccr) in 7-week old Dahl/S rats

Strain	Drug	Dose (μg/kg)	CHO (mg/dl)	TG (mg/dl)	TP (g/dl)	ALB (g/dl)	Ccr (ml/day/100 g)
Dahl/S	–	–	82 ± 2	167 ± 13	5.16 ± 0.07	3.27 ± 0.06	1021 ± 123
Dahl/S	losartan	10	75 ± 2	114 ± 7[b]	5.18 ± 0.01	3.43 ± 0.03	1093 ± 42
Dahl/S	verapamil	60	93 ± 2[b]	162 ± 10	5.16 ± 0.08	3.21 ± 0.04	1373 ± 66[a]

Values are the means ± S.E.M. for eight animals. [a] $P < 0.05$ and [b] $P < 0.01$ as compared with corresponding Dahl/S control values by Dunnett's test.

Table 3
Effects of imidapril on plasma concentration of total cholesterol (CHO), triglyceride (TG), total protein (TP) and albumin (ALB), and creatinine clearance (Ccr) in 16-week old Dahl/S rats

Strain	Drug	Dose (μg/kg)	CHO (mg/dl)	TG (mg/dl)	TP (g/dl)	ALB (g/dl)	Ccr (ml/day/100 g)
Dahl/S	–	–	70 ± 3	127 ± 13	5.47 ± 0.50	2.84 ± 0.30	736 ± 60
Dahl/S	imidapril	2	67 ± 2	147 ± 24	5.46 ± 0.03	2.93 ± 0.05	751 ± 41
Dahl/R[a]	–	–	49 ± 5	111 ± 15	5.20 ± 0.03	3.05 ± 0.07	820 ± 89

Values are the means ± S.E.M. for eight animals.
[a]Dahl salt-resistant rats.

dence of these glomerular lesions (Fig. 5A). The percentage of disordered glomeruli was significantly correlated with the values of UproV in Dahl/S rats (Fig. 5B).

4. Discussion

This is the first report that drug treatment attenuates the development of spontaneous nephrosis in Dahl/S rats fed on a normal salt diet. There was marked proteinuria in 4-week old Dahl/S rats. Other investigators demonstrated that Dahl/S rats showed proteinuria at the same age (Sterzel et al., 1988). The average absolute daily urinary excretion of protein at 4, 7, 12 and 16 weeks of age in control Dahl/S rats was 10, 89, 78 and 125 mg/day, respectively. Proteinuria in Dahl/S rats became steady after 7 weeks of ages. The 7-week old Dahl/S rats had abnormal plasma chemistry values, including high levels of total cholesterol and triglyceride, and low levels of albumin and total protein. Furthermore, we observed glomerular lesions in 16-week old Dahl/S rats. These changes were mild, but similar to those in patients with nephrosis. Thus, Dahl/S rats spontaneously develop nephrosis from a young age.

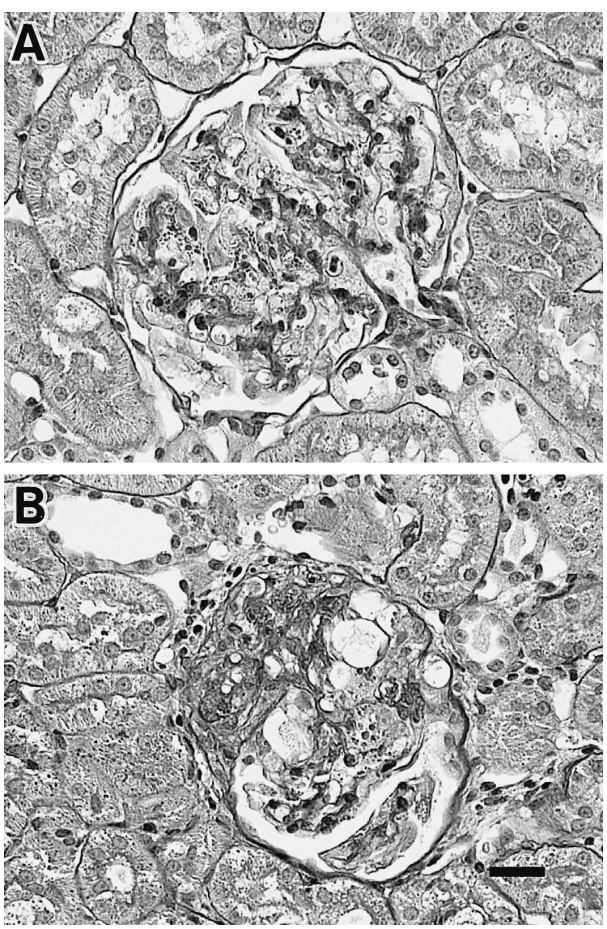

Fig. 4. Light micrographs of typical glomerular lesions in 16-week old Dahl/S rats (periodic acid–Schiff reagent stain, bar: 25 μm). (A) There are numerous hyaline droplets and hypertrophic podocytes in the glomerular tuft. (B) The glomerulus is partially adhered to the Bowman's capsule, causing a segmental sclerosis.

An angiotensin-converting enzyme inhibitor, imidapril, decreased proteinuria and normalized plasma chemistry variables in young Dahl/S rats. An angiotensin AT_1 receptor antagonist, losartan, also inhibited the development of nephrosis in Dahl/S rats, like imidapril. The data suggest that angiotensin II is one of the causes and/or malignant factors in spontaneous nephrosis in Dahl/S rats. We did not measure plasma angiotensin II levels in this study. There is a report that serum angiotensin II levels of Dahl/S rats without sodium loading are the same as those of Dahl/R rats, but glomerular angiotensin II receptor density in Dahl/S rats is higher than that in Dahl/R rats (Sahlgren, 1989). Bouhnik et al. (1992) reported that plasma renin activity and plasma angiotensin II concentration in Dahl/S rats tended to be lower than those in Dahl/R rats. Further studies on glomerular angiotensin II receptors are required to make clear the relationship between spontaneous nephrosis in Dahl/S rats and angiotensin II.

Verapamil, a Ca^{2+} channel blocker, prevented the development of mild systemic hypertension but not proteinuria. These results suggest that imidapril and losartan attenuate the development of nephrosis by mechanisms other than systemic hypotension. In patients with proteinuria, angiotensin-converting enzyme inhibition decreases proteinuria independently of the decrease in systemic blood pressure (Gansevoort et al., 1993). In remnant kidney rats, a Ca^{2+} channel blocker that decreased blood pressure to the same extent as an angiotensin-converting enzyme inhibitor failed to suppress proteinuria (Tolins and Raij, 1990). Dahl/S rats fed on a high salt diet develop severe

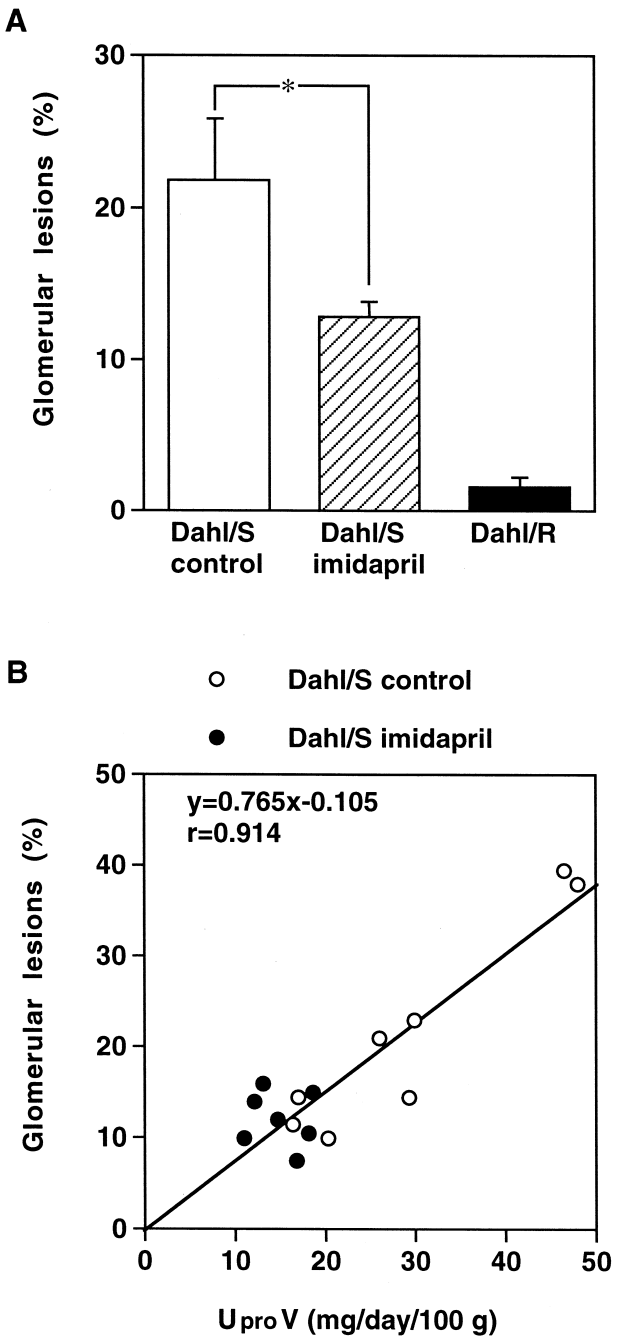

Fig. 5. Effect of imidapril on glomerular lesions (A) and correlation between UproV and glomerular lesions (B) in 16-week old Dahl/S rats. Data are expressed as the means + S.E.M. for eight animals. $* P < 0.05$ as compared with corresponding Dahl/S control values by unpaired *t*-test. Dahl/R: Dahl salt-resistant rats.

hypertension and renal damage (Jaffe et al., 1970). Prevention of the hypertension by nifedipine in salt-loaded Dahl/S rats reduces renal morphological changes (Luckhaus et al., 1982). However, spontaneous nephrosis in Dahl/S rats is different from hypertension-induced renal damage because we could not observe any morphological changes typical of hypertensive renal impairment, such as arteriolosclerosis, in this study.

On the day after the start of drug administration, verapamil decreased proteinuria temporarily (Fig. 2). There is a report that a decrease in blood pressure initiates the antiproteinuric effect of angiotensin-converting enzyme inhibition in patients with renal disease (Hemmelder et al., 1996). The transient reduction of proteinuria produced by imidapril or verapamil may result in part from the fall in blood pressure. A sustained attenuation of proteinuria requires inhibition of the renin–angiotensin system.

The increase in creatinine clearance elicited by verapamil suggests the possibility that this compound causes hyperfiltration in the glomeruli (Table 2). We did not determine single nephron hemodynamics. Angiotensin-converting enzyme inhibition, however, may not affect glomerular filtration in Dahl/S rats adversely. It has been reported that an angiotensin converting-enzyme inhibitor reduces glomerular filtration pressure but that a Ca^{2+} channel blocker dose not (Remuzzi et al., 1994).

In mature Dahl/S rats, imidapril suppressed mild hypertension and proteinuria, but failed to normalize plasma chemistry variables. The reason was that Dahl/S rats treated with imidapril still leaked a certain amount of protein into the urine. Imidapril, however, did ameliorate glomerular lesions. To evaluate glomerular damages, scoring methods have often been used (Raij et al., 1984). In this study, 60–85% of glomeruli in control Dahl/S rats did not have significant histological changes: typical glomerular lesions were the accumulation of hyaline droplets in podocytes (Fig. 4). The changes in podocytes indicate that there was an increase in the glomerular filtration of protein. Glomerular damage, such as increase in mesangial matrix material or glomerulosclerosis, which are well-known changes in Dahl/S rat fed on a high-salt diet (Raij et al., 1984), was not frequently observed in this study. We, therefore, used the incidence of disordered glomeruli to determine glomerular lesions. There was a positive correlation between UproV and the incidence of glomerular lesions in mature Dahl/S rats. Proteinuria and glomerular lesions are closely associated in Dahl/S rats. It has been reported that the prevention of proteinuria by an angiotensin-converting enzyme inhibitor is important to renal protection in the adriamycin nephrosis rat (Wapstra et al., 1996).

Abnormalities of lipid metabolism in Dahl/S rats have been demonstrated (Reaven et al., 1991; Mondon et al., 1993; Donnelly et al., 1994; Hirano et al., 1994). Hirano et al. (1994) reported abnormal properties of lipoprotein in Dahl/S rats. Probucol treatment in Dahl/S rats fed on a normal sodium diet decreased high-density lipoprotein cholesterol levels, but it could not correct proteinuria and hypoalbuminemia (Naito and Hirano, 1994). In this study, imidapril treatment resulted in the suppression of proteinuria and in a reduction of hypercholesterolemia and hypertriglycemia in young Dahl/S rats. The findings indicate the possibility that the abnormal lipid metabolism in Dahl/S rats is primarily caused by spontaneous nephrosis.

The development of nephrosis in Dahl/S rats was resistant to methylprednisolone, which is widely used in patients with proteinuria. We think that the dosage of methylprednisolone was enough because methylprednisolone increased the plasma level of triglyceride and suppressed the gain in body weight, which are common side effects of glucocorticoids (Schimmer and Parker, 1996). Nephrosis in Dahl/S rats is different from immune-mediated glomerulonephritis. An angiotensin-converting enzyme inhibitor can be used to treat some aspects of steroid-resistant nephrosis.

In summary, Dahl/S rats developed nephrosis without sodium loading. Imidapril attenuated the development of nephrosis and renal glomerular lesions in Dahl/S rats. Angiotensin II may play an important role in the development of spontaneous nephrosis in Dahl/S rats.

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