Renal Protective Effect of Candesartan Cilexetil in Spontaneously Hypercholesterolemic Rats

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ABSTRACT—Spontaneously hypercholesterolemic (SHC) rats exhibit hypercholesterolemia, proteinuria and focal glomerulosclerosis with age, and they finally die as a result of renal failure. In this study, the renoprotective effects of candesartan cilexetil, an angiotensin II type 1 receptor antagonist, and enalapril, an angiotensin I converting enzyme inhibitor, were examined in SHC rats. Candesartan cilexetil (0.1 and 1 mg/kg) and enalapril (10 mg/kg) were administered orally to 10-week-old SHC rats for a 6-week period. Candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) significantly inhibited proteinuria and hypercholesterolemia to a similar extent. In untreated 16-week-old SHC rats, glomerulosclerosis, basophilic change, cast formation and interstitial mononuclear cell infiltration were observed. Candesartan cilexetil (1 mg/kg) inhibited all of these histological changes. Enalapril inhibited glomerulosclerosis and cast formation. These results show that candesartan cilexetil and enalapril have renal protective effects in SHC rats. Thus, angiotensin II might play an important role in renal pathogenesis in a model of focal glomerulosclerosis with hypercholesterolemia.

Keywords: Candesartan cilexetil, Renal protective effect, Spontaneously hypercholesterolemic rat, Angiotensin II, AT₁-receptor antagonist

It has been proposed that focal glomerulosclerosis (FGS) is one of the primary glomerular diseases; it results in nephrotic syndrome, chronic renal failure and end-stage renal disease. Massive albuminuria complicated with hypercholesterolemia is sometimes observed in nephrotic syndrome. It has been reported that puromycin aminonucleoside nephrosis in rats is a useful animal model of FGS complicated with hypercholesterolemia; however, there have been few reports of animal models revealing spontaneous FGS with hypercholesterolemia.

The spontaneously hypercholesterolemic (SHC) rat, an animal model of hypercholesterolemia, was established by repeated selective inbreeding of Sprague-Dawley (SD) rats that have a high plasma total cholesterol (TC) level (1). At the age of 7 weeks, male SHC rats already exhibit higher plasma TC levels than those of age-matched SD rats, even on a normal diet. In addition, SHC rats show massive albuminuria, progressive renal injury with age and finally die as a result of renal insufficiency at the age of about 30 weeks (1, 2). In histopathological studies, it has been reported that SHC rats show severe focal mesangial matrix expansion, deposition of C3, and IgM in glomeruli, which are typical pathological changes that occur in the kidneys of patients with FGS. Thus, SHC rats are thought to be a suitable animal model for the evaluation of agent effects on both hypercholesterolemia and FGS (2).

Many factors are thought to be involved in the progression of renal disease (3–7). One of these factors, angiotensin II, may be crucial in the progression of this disease, not only because it may be a cause of hyperfiltration in the glomeruli, but also because it is involved in the induction of extracellular matrix production (8).

Candesartan cilexetil is a selective and highly potent angiotensin II type 1 receptor antagonist (AT₁ antagonist) that exhibits beneficial renal protective effects in models of both diabetic nephropathy and chronic renal failure in rats (9–14).

In the study described here, the renoprotective effect of candesartan cilexetil was investigated in SHC rats, which
represent a model of FGS with hypercholesterolemia, and was compared with the effect of enalapril, an angiotensin I converting enzyme (ACE) inhibitor.

MATERIALS AND METHODS

Animals and agents
Male 8-week-old SHC rats, originally supplied by Takeda Rabics, Ltd., were used. Male SD rats were purchased from Clea Japan (Osaka). The rats were fed a standard rat chow (CE-2, Clea Japan) and given a tap water ad libitum. Candesartan cilexetil [(±)-1-(cyclo-hexyloxy carbonyloxy)ethyl 2-ethoxy-1-[[2’-(1H-tetrazol-5-yl)biphenyl-4-yl][methyl]-1H-benzimidazole-7-carboxylate] and enalapril maleate were synthesized by Takeda Chemical Industries, Ltd.

Experimental design and measurements
In experiment 1, levels of urinary albumin (UalbV) and total protein (UproV) excretion, and of plasma total cholesterol (TC), systolic blood pressure (SBP), creatinine clearance (Ccr), left kidney weight (LKW), and histopathological changes of the kidney were compared between male SD and SHC rats.

In the experiment 2, the renoprotective effects of candesartan cilexetil and enalapril were evaluated in male SHC rats. In 8-week-old rats, blood samples were obtained via the tail-vein, using heparin as an anticoagulant, and plasma samples were separated by centrifugation. Urine samples were collected over a 24-h period while the animals were kept in metabolic cages with free access to water, but not food. In experiment 2, rats were anesthetized with pentobarbital and their left kidneys were removed. Isolated left kidneys were weighed and fixed in neutral-buffered 10% formalin to allow further histological examination. The fixed kidneys were embedded in paraffin and were sliced into 4-μm-thick sections for light microscopy study. These specimens were stained with periodic acid-methenamine silver (PAM) and hematoxylin-eosin (HE). The extent of the glomerulosclerosis was evaluated in PAM-stained specimens, as the percentage of sclerosed glomeruli of the total number of glomeruli examined. At least 150 glomeruli were examined per kidney specimen. Histological changes in the tubulointerstitium, such as basophilic changes of the tubule, cast formation, and mononuclear cell infiltration into the interstitium, were assessed with HE-stained specimens; and they were graded from 0 to 4 (0, no change; 1, minimal; 2, mild; 3, moderate; 4, marked change). All assessments were performed under blind conditions.

Reagents
The reagents used for the measurement of UalbV and UproV (A/G/B test), plasma TC (Cholesterol-C test), creatinine (Creatinine test) and GPT activity (Transaminase CII test) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka).

Statistical analyses
Data are represented as the mean ± S.E.M. In experiment 1, a comparison between SD rats and SHC rats was carried out by using Student’s t-test for UalbV, UproV, TC, SBP, LKW and glomerulosclerosis, and Wilcoxon’s test was used for tubular lesion. In experiment 2, the effects of 6 weeks of administration of candesartan cilexetil and enalapril on UalbV, UproV and TC were evaluated using repeated-measures analysis of variance (ANOVA), followed by Dunnett’s test for candesartan cilexetil (0.1 and 1 mg/kg), and Student’s t-test was used for enalapril (10 mg/kg). SBP, LKW, glomerulosclerosis and tubular lesion were compared between vehicle-treated and candesartan cilexetil (0.1 and 1 mg/kg)-treated SHC rats using Dunnett’s test. Student’s t-test was used to compare SBP, LKW and glomerulosclerosis between vehicle-treated and enalapril (10 mg/kg)-treated SHC rats, and Wilcoxon’s test was used to compare tubular lesion between the same animals. The level of statistical significance was set at P<0.05.
RESULTS

Comparison between SD rats and SHC rats

Table 1 shows the time course of changes in SBP, UalbV, UproV and TC in SD rats and SHC rats. At the age of 10 weeks, SHC rats already exhibited higher UalbV, UproV and TC levels compared to those of SD rats, and these values increased progressively with age. Table 2 summarizes a comparison of Ccr, LKW, percentage of glomerulosclerosis, tubular basophilic changes and cast formation were observed.

Effects of candesartan cilexetil and enalapril on body weight and SBP in SHC rats

In this experiment, neither agent influenced the body weight of SHC rats (data not shown). SBPs of vehicle-, candesartan cilexetil- and enalapril-treated SHC rats are shown in Fig. 1. At the start of the experiments, the SBP of vehicle-, candesartan cilexetil (0.1 and 1 mg/kg)- and enalapril (10 mg/kg)-treated SHC rats were 146 ± 4, 148 ± 3, 153 ± 4 and 157 ± 5 mmHg, respectively. Five weeks after the commencement of drug or vehicle administration, the SBP of vehicle-, candesartan cilexetil (0.1 and 1 mg/kg)- and enalapril (10 mg/kg)-treated SHC rat was 155 ± 3, 145 ± 3, 131 ± 5 and 126 ± 3 mmHg, respectively. Candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) decreased SBP significantly. The effects of candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) on SBP were comparable.

Effects of candesartan cilexetil and enalapril on UalbV and UproV excretion in SHC rats

Figure 2 shows the time course of changes in UalbV and UproV excretion in vehicle-, candesartan cilexetil (0.1 and 1 mg/kg)- and enalapril (10 mg/kg)-treated SHC rats. In

Table 2. Comparison of creatinine clearance (Ccr), left kidney weight (LKW) and histopathological changes of the kidney glomeruli and tubules between 18-week-old Sprague-Dawley (SD) rats and 18-week-old spontaneously hypercholesterolemic (SHC) rats

| Age (weeks old) | 10  | 12  | 14  | 16  |
|-----------------|-----|-----|-----|-----|
| SBP (mmHg) SD rats | 150.3 ± 2.1 | 137.3 ± 2.3 | 136.8 ± 5.0 | 145.0 ± 2.8 |
| UalbV (mg/day) SD rats | 5.8 ± 0.9 | 4.8 ± 1.2 | 2.6 ± 0.4 | 3.7 ± 0.3 |
| UproV (mg/day) SD rats | 96.9 ± 17.9 | 79.4 ± 24.1 | 203.0 ± 20.1 | 221.4 ± 17.7 |
| TC (mg/dl) SD rats | 53.2 ± 2.7 | 45.0 ± 3.7 | 47.0 ± 2.8 | 51.0 ± 1.7 |

Values are the mean ± S.E.M. (SD rats, n = 4; SHC rats, n = 5). §P<0.05, ††P<0.01 vs SD rats, using Student’s t-test.

Table 1. Time-course changes of systolic blood pressure (SBP), urinary albumin (UalbV) and total protein excretion (UproV) and plasma total cholesterol level (TC) in Sprague-Dawley (SD) rats and spontaneously hypercholesterolemic (SHC) rats

| Age (weeks old) | 10  | 12  | 14  | 16  |
|-----------------|-----|-----|-----|-----|
| SBP (mmHg) SD rats | 221.4 ± 17.7 | 221.4 ± 17.7 | 221.4 ± 17.7 | 221.4 ± 17.7 |
| UalbV (mg/day) SD rats | 146.0 ± 9.0 | 40.3 ± 6.6 | 28.0 ± 1.1 |
| UproV (mg/day) SD rats | 146.2 ± 22.3 | 259.5 ± 33.6 | 280.1 ± 27.0 | 284.9 ± 22.9 |
| TC (mg/dl) SD rats | 53.2 ± 2.7 | 45.0 ± 3.7 | 47.0 ± 2.8 | 51.0 ± 1.7 |

Values are the mean ± S.E.M. (SD rats, n = 4; SHC rats, n = 5). §P<0.05, ††P<0.01 vs SD rats, using Student’s t-test.
Candesartan Cilexetil in SHC Rats

Vehicle-, candesartan cilexetil (0.1 and 1 mg/kg)- and enalapril (10 mg/kg)-treated SHC rats. Values are the mean ± S.E.M. (n = 5). Significant differences (P<0.05) between vehicle-treated and candesartan cilexetil- or enalapril-treated SHC rats were detected using analysis of variance (ANOVA). ††P<0.01 vs vehicle-treated SHC rats (Student’s t-test using the data obtained after 6 weeks of drug or vehicle administration).

Effects of candesartan cilexetil and enalapril on proteinuria in SHC rats

Both UalbV and UproV increased remarkably in the first 2 weeks, and then continued to increase gradually until the end of the experiment. Both candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) inhibited proteinuria in SHC rats. The effects of candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) on proteinuria were comparable, whereas candesartan cilexetil (0.1 mg/kg) tended to inhibit them.

Effects of candesartan cilexetil and enalapril on plasma TC levels in SHC rats

Figure 3 shows the time course of changes in TC in vehicle-, candesartan cilexetil (0.1 and 1 mg/kg)- and enalapril (10 mg/kg)-treated SHC rats. Candesartan cilexetil (1 mg/kg) significantly inhibited the increase in TC, as did enalapril (10 mg/kg). The beneficial effects of these compounds on hypercholesterolemia were comparable with those on proteinuria. Candesartan cilexetil and enalapril had no effect on GPT activity, which is a marker of liver injury, where cholesterol is generated (data not shown).

Effects of candesartan cilexetil and enalapril on Ccr and LKW in SHC rats

At the end of experiment, Ccr of vehicle-, candesartan cilexetil (0.1 and 1 mg/kg)- and enalapril (10 mg/kg)-treated SHC rats was 0.49 ± 0.05, 0.48 ± 0.02, 0.58 ± 0.05 and 0.59 ± 0.03 ml/min per 100 g BW, respectively. Candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) tended to increase the Ccr. Figure 4 shows LKW at the end of the experiment. Candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) significantly inhibited the enlargement of the kidney that usually occurs in SHC rats.

Effects of candesartan cilexetil and enalapril on histopathological changes in SHC rats

At the end of the experiment, in addition to normal glomeruli, glomeruli with focal and segmental mesangial matrix expansion, glomeruli adhered to Bowman’s capsules and
collapses of capillary luminae were frequently observed (data not shown). Figure 5 shows the percentage of the number of glomeruli with injury of the total glomeruli counted with the aid of light microscopy. Both candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) significantly inhibited glomerular injury comparably. Candesartan cilexetil (0.1 mg/kg), however, had no effect. Figure 6 presents photomicrographs of HE-stained tubulointerstitium in the cortex of the kidney of vehicle-, candesartan cilexetil (1 mg/kg)- and enalapril (10 mg/kg)-treated SHC rats. Basophilic changes of the tubules, cast formation and mononuclear cell infiltration into the interstitium were observed in vehicle-treated SHC rats. The effects of candesartan cilexetil and enalapril on the histopathological changes in the tubulointerstitium are summarized in Table 3. Candesartan cilexetil (1 mg/kg) prevented the increase in basophilic changes, cast formation and mononuclear cell infiltration that usually occur in SHC rats. Enalapril (10 mg/kg) prevented the increase in cast formation and tended to prevent the basophilic changes and mononuclear cell infiltration. Candesartan cilexetil (0.1 mg/kg) exerted no significant effects.

DISCUSSION

As summarized in Table 1, male SHC rats exhibited massive albuminuria and hypercholesterolemia at 10 weeks of age, both of which progressed with age; histopathological examinations also revealed FGS. These results indicate that SHC rats may be useful for examining the effects of agents on FGS, especially when complicated with hypercholesterolemia, although it remains to be clarified whether or not renal injury is a primary disorder. The aim of this study was to evaluate the renal protective effect of candesartan cilexetil, an AT1 antagonist, and to compare its effect with that of enalapril, an ACE inhibitor, in a model of FGS.

Candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) inhibited the proteinuria and the glomerulosclerosis that have been shown to occur in SHC rats, suggesting that angiotensin II contributes to the progression of renal disease in SHC rats. It has been reported that angiotensin II may induce intraglomerular hypertension by causing the contraction of efferent arterioles in preference to afferent arterioles in the progressive phase of kidney disease (5). In addition to the effects on hemodynamic changes, angiotensin II facilitates mesangial cell proliferation and the production of extracellular matrix, by releasing cytokines such as interleukin-6, platelet-derived growth factor and transforming growth factor-β, and acts as an albumin permeability factor (7, 8, 16). Therefore, in this study, the renal protective effects of these agents may have been due to the amelioration of renal hemodynamics and inhibition of the direct action of angiotensin II on glomeruli. Candesartan cilexetil (1 mg/kg) and enalapril (10 mg/kg) exhibited the same hypotensive effects in SHC rats. These hypotensive effects might contribute partially to their renal protective effects in SHC rats. It has been reported that candesartan cilexetil exhibits a beneficial renal protective effect in models of renal disease, including deoxycorticosterone acetate-salt hypertensive rats (10), 5/6 nephrectomized rats (11, 12) and Wistar fatty rats, which represent a model of non-insulin dependent diabetic mellitus (13, 14). In the present study, the result that candesartan cilexetil ameliorated the renal injury of SHC rats, a model of FGS, suggests that angiotensin II is a common factor in the progression of various renal diseases that result in renal insufficiency.

Elevated plasma TC levels are frequently observed in human patients and in animal models of chronic renal
failure or nephrotic syndrome. This hypercholesterolemia might be triggered by the enhancement of albumin and TC production in the liver, resulting from hypoalbuminemia (17). Furthermore, it has been reported that hypercholesterolemia is a factor that underlies the progression of renal injury, as well as being a risk factor for atherosclerosis (18), because the deposition and oxidization of plasma cholesterol in glomeruli and tubules induces the expression of transforming growth factor-β1 and thus accelerates renal injury (19, 20). In SHC rats, the abnormality of cholesterol metabolism appeared at the same time as the onset of albuminuria, and this hypercholesterolemia may contribute partially to the pathogenesis and progression of renal injury. Since candesartan cilexetil and enalapril did not affect cholesterol metabolism directly, and did

![Fig. 6. Representative sections of cortex from vehicle-, candesartan cilexetil (1 mg/kg)-, and enalapril (10 mg/kg)-treated SHC rats at the end of the experiment (6 weeks after the first administration) are shown in panels a, b, and c, respectively. Hematoxylin and eosin stain. Bars indicate 200 μm. Asterisks indicate mononuclear cell infiltration.]

**Table 3.** Effects of candesartan cilexetil and enalapril on tubulointerstitial injury in 16-week-old SHC rats

|                  | Basophilic change | Cast formation | MNC infiltration |
|------------------|-------------------|----------------|-----------------|
| Vehicle          | 3.2 ± 0.2         | 2.4 ± 0.2      | 2.2 ± 0.2       |
| Candesartan cilexetil (0.1 mg/kg) | 3.0 ± 0.0         | 2.0 ± 0.0      | 2.0 ± 0.0       |
| Candesartan cilexetil (1 mg/kg)   | 2.2 ± 0.2**       | 1.0 ± 0.3**    | 1.0 ± 0.3**     |
| Enalapril (10 mg/kg)          | 2.6 ± 0.2         | 1.0 ± 0.3³     | 1.8 ± 0.4       |

MNC, mononuclear cell. Values are the mean ± S.E.M. (n = 5). **P<0.01 vs vehicle-treated SHC rats (vehicle), using Dunnett’s test. ³P<0.05 vs vehicle-treated SHC rats (vehicle), using Wilcoxon’s test.
not induce liver toxicity (since it did not affect GTP activity), the suppression of hypercholesterolemia by these agents is thought to be a secondary effect resulting from the inhibition of proteinuria.

In the present study, mononuclear cell infiltration into the interstitium was markedly inhibited by candesartan cilexetil (1 mg/kg) but not by enalapril (10 mg/kg). We have reported that candesartan cilexetil, but not enalapril, significantly ameliorated glomerulosclerosis and interstitial fibrosis in 5/6 nephrectomized rats in a 16-week administration study (12). In SHC rats, the mechanism of the different effect of both drugs on interstitial inflammation remains to be clarified. A long-term administration study of more than 6 weeks may be necessary to define the difference between an AT1 antagonist and an ACE inhibitor in SHC rats.

In conclusion, candesartan cilexetil and enalapril showed beneficial renoprotective effects in SHC rats, which represent a model of FGS with hypercholesterolemia. These results indicate that angiotensin II plays an important role in the progression of FGS complicated with hypercholesterolemia, and that AT1 antagonists and ACE inhibitors might be effective in patients with FGS.

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