ELSEVIER

European Journal of Pharmacology 331 (1997) 193–198

ejp

Protective effects of CD-832 on organ damage in stroke-prone spontaneously hypertensive rats

Teisuke Takahashi *, Satomi Tanikawa, Kenzo Takahashi

1 ST Laboratory, Medical Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403, Yoshino-cho, Ohmiya, Saitama 330, Japan

Received 13 January 1997; revised 14 May 1997; accepted 30 May 1997

Abstract

Effects of a newly developed Ca^{2+} channel antagonist, (4*R*)-(−)-2-(nicotinoylamino)ethyl 3 nitrooxypropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl) 3,5-pyridine-dicarboxylate (CD-832), on hypertensive complications in stroke-prone spontaneously hypertensive rats (SHRSPs) were compared with effects of diltiazem. We examined changes in histological and hematological parameters in SHRSPs given the following treatments at 8 to 20 weeks of age: (a) CD-832; (b) diltiazem; (c) no treatment. CD-832 and diltiazem were added to the diet, in doses of 0.05 and 0.15% (approximately 30 and 100 mg/kg per day), respectively, throughout the experimental period. In untreated control SHRSPs, systolic blood pressure increased and severe renal lesions such as fibrinoid necrosis, smooth muscle proliferation, glomerular and tubular lesions and some cardiac fibrosis were observed at age 20 weeks. 12-week repeated-administration of CD-832 and diltiazem led to a comparable hypotension and decreased heart rate. CD-832 and diltiazem decreased the ratios of weights of kidney and heart to body weight and the concentration of blood urea nitrogen and creatinine in serum, compared to values in controls. In SHRSPs treated with CD-832 and diltiazem, the incidence of renal lesions and myocardial fibrosis was significantly reduced when compared with control SHRSPs. These results suggest that 12-week repeated-administration of CD-832 prevents the development of hypertension and the incidence of organ damage in SHRSPs. CD-832 and diltiazem were equally efficacious in preventing organ damage but this organ-protective effect was obtained at a lower dose for CD-832 (30 mg/kg per day) than that of diltiazem (100 mg/kg per day).

Keywords: CD-832; Ca^{2+} channel antagonist; Stroke-prone spontaneously hypertensive rat (SHRSP); Renal lesion

1. Introduction

Hypertension is aggravated by the incidence of vascular and organ damage such as cardiac hypertrophy, arteriosclerosis and nephrosclerosis. Therefore, the objective of antihypertensive treatment is to normalize BP and to prevent organ damage.

CD-832 {(4*R*)-(−)-2-(nicotinoylamino)ethyl 3 nitrooxypropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)3,5-pyridine-dicarboxylate (Fig. 1) is a dihydropyridine derivative Ca^{2+} channel antagonist newly developed by Taisho Pharmaceutical. CD-832 has a high affinity for the Ca^{2+} channel in rat brain membranes and shows the calcium antagonistic action in the isolated mesenteric arteries of rabbits (Miyata et al., 1993). In the previous study, CD-832 was shown to possess vasorelaxant effects in the vein, an effect which might be related to its nitrate-like action (Yamaura et al., 1994). Moreover, we have found that the vasodilator effect of CD-832 is longer-lasting than that of nifedipine or diltiazem in anesthetized and conscious dogs (Takahashi et al., 1992, 1994). Therefore, we considered that CD-832 may protect against hypertension-induced organ damage.

Stroke-prone spontaneously hypertensive rats (SHRSPs) are regarded as a close model of malignant hypertension (Okamoto et al., 1974). In these animals, hypertension and organ damage is severe in comparison with findings in age-matched Wistar-Kyoto rats. We examined the effects of the oral administration of CD-832 on hypertension and histological changes of kidney and heart of SHRSPs and effects of CD-832 on the lesions were compared with those of diltiazem.

* Corresponding author. Tel.: (81-48) 663-1111; Fax: (81-48) 652-7254.

PII S0014-2999(97)01048-0

2. Materials and methods

2.1. Animals and treatment

Male stroke-prone spontaneously hypertensive rats (SHRSPs) bred in the laboratory of Taisho Pharmaceutical. A standard rat diet and free access to tap water were provided. The room temperature was controlled at 22°C, and a 12 h light/dark cycle (lights on at 07.00 a.m.) was maintained.

At 8 weeks of age, the animals were randomized into three groups. The first group of 10 rats was fed a diet containing CD-832 in a dose of 0.05%. To compare the effects of CD-832 with diltiazem, we gave the diet containing diltiazem in a dose of 0.15% to the second group of 9 rats. The amounts of CD-832 and diltiazem added to the diets were specifically chosen, based on results from pilot studies, to achieve significant and strictly equivalent reductions in systolic blood pressure in the treated SHRSPs compared with control SHRSPs. As controls, the third group of 9 rats was provided the diet but with no drug. Food consumption was estimated every 2 weeks.

2.2. Measurements of systolic blood pressure, heart rate and body weight

Systolic blood pressure and heart rate were measured in the conscious animals using a rat tail manometer–tachometer system (PS-1800, Riken Kagaku) according to the methods of Bunag and Butterfield (1982). Systolic blood pressure and heart rate were measured before starting the treatment (8 weeks age) and then every 2 weeks for 20 weeks. Body weight was also recorded.

2.3. Histopathological and hematological assays

Twelve weeks after initiation CD-832 and diltiazem treatment, all animals were anesthetized with pentobarbital (50 mg/kg, i.p.). After thoracotomy, blood samples were collected from the abdominal aorta for assay of triglyceride, phospholipid, total cholesterol, blood urea nitrogen, creatinine, glutamic–oxaloacetic transaminase (GOT), glutamic–pyruvic transaminase (GPT), Na^+, K^+, Ca^{2+} and phosphorus. Brain, heart, lungs, liver, spleen, kidneys and testis were excised and weighted. Histologic sections from heart, kidney and mesenteric artery were stained with hematoxylin–eosin–safran and examined microscopically. All organ sections were examined under condition in which the examiner was blinded as to the source, etc.

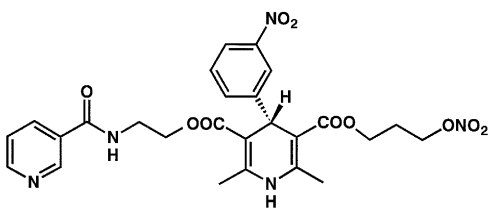

Fig. 1. Chemical structure of CD-832.

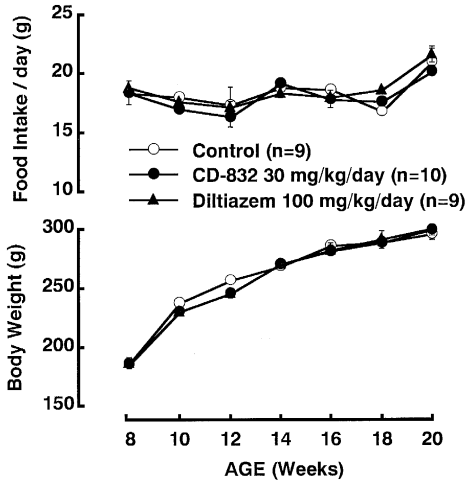

Fig. 2. Development with age of food intake and body weight in control SHRSPs and SHRSPs treated with CD-832 and diltiazem. Values are mean ± S.E.M.

2.4. Drugs and diets

The drugs used in this study included CD-832 {(4*R*)-(−)-2-(nicotinoylamino) ethyl 3-nitrooxypropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl) 3,5-pyridinecarboxylate} (Fig. 1) (Research Center, Taisho Pharmaceutical, Saitama, Japan) and diltiazem (Sigma, St. Louis, MO, USA). The diets used, 0.05% CD-832 diets and 0.15% diltiazem diets, were checked at the Research Center, Taisho Pharmaceutical (Omiya) using the gas chromatographic–mass spectrometric (GC-MS) method.

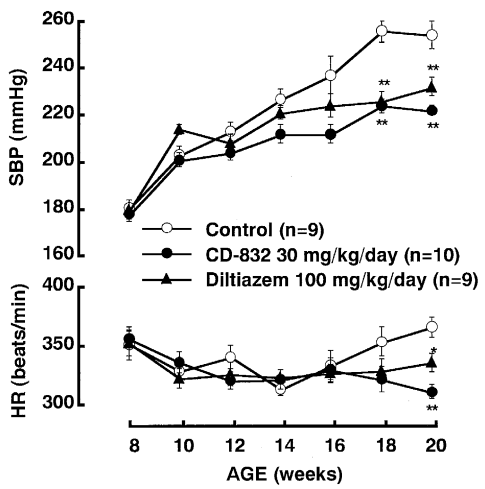

Fig. 3. Development with age of systolic blood pressure and heart rate in control SHRSPs and SHRSPs treated with CD-832 and diltiazem. Values are mean ± S.E.M. * $P < 0.05$, ** $P < 0.01$: significantly different from control SHRSPs.

Table 1
Hematological parameters in control SHRSPs and SHRSPs treated with CD-832 and diltiazem

Parameters	Control ($n=9$)	CD-832 0.05% ($n=10$)	Diltiazem 0.15% ($n=9$)
TG (mg/dl)	37.8±4.5	41.5±2.6	36.7±2.1
PL (mg/dl)	88.2±5.9	86.1±1.2	99.0±11
T-cho (mg/dl)	54.6±4.4	50.9±0.8	64.4±1.0
BUN (mg/dl)	24.9±0.9	19.4±0.3 [b]	20.7±1.2 [a]
Cr (mg/dl)	0.70±0.03	0.55±0.03 [a]	0.54±0.04 [b]
GOT (IU/l)	122.4±2.7	116.8±1.9	118.5±4.3
GPT (IU/l)	57.6±3.4	56.3±1.1	61.5±2.3
Na (mEq/l)	143.4±0.5	144.7±0.3	143.4±0.9
K (mEq/l)	3.9±0.2	4.2±0.1	4.0±0.2
Ca (mEq/l)	10.1±0.1	9.9±0.1	10.1±0.2
P (mEq/l)	7.3±0.8	6.1±0.4	6.1±0.3

TG, triglyceride; PL, phospholipid; T-cho, total cholesterol, BUN, blood urea nitrogen; Cr, creatinine; GOT, glutamic-oxaloacetic transamine; GPT, glutamic–pyruvic transaminase. Values are mean±S.E.M.
[a] $P<0.05$, [b] $P<0.01$: significantly different from control SHRSPs.

Table 2
Ratios of organ weight to body weight (mg/g) in control SHRSPs and SHRSPs treated with CD-832 and diltiazem

Organs	Control ($n=9$)	CD-832 0.05% ($n=10$)	Diltiazem 0.15% ($n=9$)
Brain	6.61±0.34	6.28±0.12	6.08±0.10
Heart	4.92±0.16	4.35±0.09 [a]	4.47±0.12 [a]
Lung	5.07±0.40	4.58±0.16	4.55±0.11
Liver	28.7±0.92	25.9±0.19	29.9±0.51
Spleen	2.07±0.15	1.73±0.06	1.89±0.05
Kidney	7.60±0.23	6.82±0.07 [a]	6.76±0.14 [b]
Testis	9.84±0.45	10.2±0.14	10.3±0.21

Values are mean±S.E.M.
[a] $P<0.05$, [b] $P<0.01$: significantly different from control SHRSPs.

2.5. Statistical analysis

Data are expressed as mean ± S.E.M. Differences between treated and non-treated groups were compared using analysis of variance, followed by Dunnett's *t*-test. In addition, to assess the development of organ damage, scores obtained for each parameter were evaluated using a Mann-Whitney's *U* test. A value of $P<0.05$ was considered significant.

3. Results

3.1. Food intake and body weight

Fig. 2 shows changes with age of food intake and body weight. Animals in these groups showed a similar time-

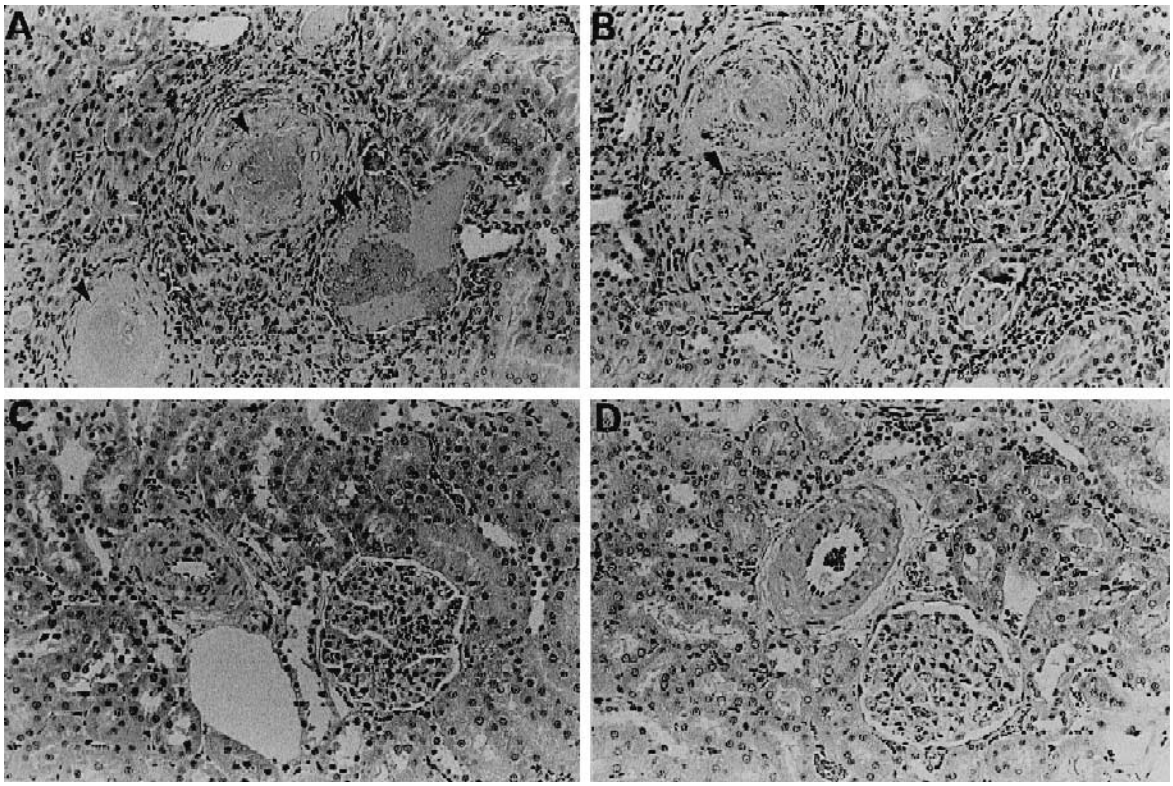

Fig. 4. Typical histologic appearance of kidney in control SHRSPs (A and B) and SHRSPs treated with CD-832 (C) and diltiazem (D) (×60). (A) The central and left lower round structures arteries have a total luminal obliteration due to prominent fibrosis and smooth muscle hyperplasia with fibrinoid necrosis (one arrow). The arteries are surrounded by fibrosis and lymphocytic infiltration. The right central tubule is markedly dilated and contains proteinous casts with hemorrhage (two arrows). (B) The arteriole of the collapsed glomerulus in the left shows total luminal obliteration due to prominent thickening of the wall by fibrosis and smooth muscle hyperplasia on which hemorrhage is superimposed (one arrow). The stroma is fibrotic with lymphocytic infiltration and contains an atrophied uriniferous tubuli. (C and D) In SHRSPs treated with CD-832 (C) and diltiazem (D), no remarkable changes are observed in the artery, glomerulus and tubuli.

courses of gain in daily ingested diets and body weight throughout the experiment.

3.2. Systolic blood pressure and heart rate

Fig. 3 shows changes with age of Systolic blood pressure and heart rate in control SHRSPs and SHRSPs treated with CD-832 and diltiazem. From 8 weeks of age, systolic blood pressure of control SHRSPs rapidly increased, reaching 250 mmHg at age 20 weeks. However, up to age 18 weeks, systolic blood pressure measured in the 2 groups of SHRSPs treated with CD-832 (30 mg/kg per day) or diltiazem (100 mg/kg per day) was significantly lower than in control SHRSPs. In SHRSPs treated with CD-832 and diltiazem, reduction in HR was also observed at 20 weeks.

Table 3
Histopathological findings of kidney in control SHRSPs and SHRSPs treated with CD-832 and diltiazem

	(−)	(±)	(+)	(++)
Fibroid necrosis				
Control (9)	2	3	2	2
CD-832 (10) [b]	9	1	0	0
Diltiazem (9) [a]	7	1	0	1
Smooth muscle proliferation				
Control (9)	0	4	4	1
CD-832 (10) [b]	7	3	0	0
Diltiazem (9) [b]	6	2	0	1
Onion skin lesion				
Control (9)	0	4	4	1
CD-832 (10) [b]	10	0	0	0
Diltiazem (9) [b]	9	0	0	0
Hemorrhage				
Control (9)	3	5	1	0
CD-832 (10) [b]	9	1	0	0
Diltiazem (9)	7	1	1	0
Glomerular proliferation				
Control (9)	4	5	0	0
CD-832 (10) [a]	10	0	0	0
Diltiazem (9)	8	1	0	0
Glomerular fibrin thrombosis				
Control (9)	5	4	0	0
CD-832 (10) [a]	10	0	0	0
Diltiazem (9)	8	1	0	0
Glomerular crescent				
Control (9)	6	3	0	0
CD-832 (10) [a]	10	0	0	0
Diltiazem (9) [a]	9	0	0	0
Proteinous cast in tubuli				
Control (9)	2	3	2	2
CD-832 (10) [b]	10	0	0	0
Diltiazem (9) [b]	8	0	0	1
Lymphocytic infiltration				
Control (9)	2	1	6	0
CD-832 (10) [a]	3	7	0	0
Diltiazem (9) [a]	4	4	1	0

Number of rats is given in parentheses. Values are mean ± S.E.M. Changes: minimum (±), mild (+), moderate (++).
[a] $P < 0.05$, [b] $P < 0.01$: significantly different from control SHRSPs.

Table 4
Histopathological findings of heart and mesenteric artery in control SHRSPs and SHRSPs treated with CD-832 and diltiazem

	(−)	(±)	(+)	(++)
Heart				
Myocardial fibrosis				
Control (9)	6	2	1	0
CD-832 (10) [b]	10	0	0	0
Diltiazem (9) [a]	9	0	0	0
Mesenteric artery				
Control (9)	9	0	0	0
CD-832 (10)	10	0	0	0
Diltiazem (9)	9	0	0	0

Number of rats is given in parentheses. Values are mean ± S.E.M. Changes: minimum (±), mild (+), moderate (++).
[a] $P < 0.05$, [b] $P < 0.01$: significantly different from control SHRSPs.

3.3. Hematological change

Table 1 summarizes changes in the biochemical parameters in the blood. The serum levels of blood urea nitrogen and creatinine, indices of renal function, in SHRSPs treated with CD-832 and diltiazem were significantly lower than those in control SHRSPs. However, no significant changes were observed in levels of triglyceride, phospholipid, total cholesterol, glutamic–oxaloacetic transaminase (GOT), glutamic–pyruvic transaminase (GPT), sodium, potassium, calcium and phosphorus among the three groups.

3.4. Organ weights

Table 2 summarizes the ratios of organ weight to body weight. Ratios of wet weights of heart and kidney to body weight in rats treated with CD-832 and diltiazem were significantly lower than those in control SHRSPs. In other organs, no significant differences in the ratios of wet weight to body weight were observed among the three groups.

3.5. Histopathological changes in organs

Tables 3 and 4 summarize histopathological findings in all SHRSPs at age 20 weeks. The control SHRSPs had vascular, glomerular and tubular lesions in the kidney, and fibrosis in the heart, although there were no notable lesions in the mesenteric artery.

3.5.1. Kidney

Typical histopathologic findings are shown in Fig. 4. The kidney of control SHRSPs showed histologic degradation of arteries, glomeruli and tubules, these changes were characterized by fibrinoid necrosis, smooth muscle prolif-

eration (Fig. 4), onion skin lesion, hemorrhage, glomerular proliferation, glomerular fibrin thrombus, glomerular crescent, proteinous cast in tubuli and lymphocytic infiltration (Table 3). In CD-832-treated SHRSPs, all these renal lesions were significantly reduced when compared with control SHRSPs. Diltiazem also significantly improved renal lesions to an equivalent degree (Table 3).

3.5.2. Heart and mesenteric artery

Slight myocardial fibrosis was seen in 3 of 9 control SHRSPs. However, myocardial fibrosis was nil in SHRSPs treated with CD-832 or diltiazem (Table 4). Notable lesions were nil in the mesenteric artery of all 3 groups (Table 4).

4. Discussion

SHRSPs is a widely used animal model of malignant hypertension (Okamoto et al., 1974). In the present study, control SHRSPs showed a rapid increase in systolic blood pressure and thereafter, followed by a hypertension with blood pressure stabilizing between 250 and 260 mmHg. At age 20 weeks, the control SHRSPs had hypertension-related complications of severe renal lesions, which indicate a malignant phase of hypertension. The pathological changes were characterized by fibrinoid necrosis, smooth muscle proliferation, glomerular and tubular lesions. On the other hand, the oral administration of CD-832 to SHRSPs from their 8th to 20th week of age significantly inhibited the increase in SBP and the development of these renal lesions. Similar types of renal protection by calcium antagonists have been reported in the same rat model (Suzuki et al., 1993; Uehara et al., 1995). The risk of complications of systemic hypertension, such as renal failure and heart disease, is proportional to the level of blood pressure (Roberts, 1990). Although several mechanisms may explain the renal protection by CD-832, these results do indicate that the protective effects of this compound are probably related to its antihypertensive effect. In the present study, the effects of CD-832 were compared with diltiazem, another calcium antagonist in common clinical use. Studies in hypertensive patients have suggested that diltiazem had the potential to improve renal function (Sunderrajan et al., 1986, 1987). In our experimental models, 12-week repeated-administration of diltiazem in doses that led to a similar degree of hypotension also inhibited the development of these renal lesions. These histological findings, suggest that CD-832 could exhibit appreciable and beneficial effects in preventing the incidence of secondary hypertension-related renal lesions.

The ratio of kidney weight/body weight was decreased in CD-832 treated SHRSPs compared with control SHRSPs. Compensatory renal hypertrophy appears to be an important step preceding glomerular injury (Yoshida et al., 1989). Thus, the modulation of renal hypertrophy may contribute to the renal protective effects of CD-832 seen in our study.

The CD-832-treated SHRSPs also showed significantly lower serum levels of blood urea nitrogen and creatinine at 20 weeks, compared to findings in control SHRSPs. Thus, the renal protective effects of CD-832 were suggested by decreased serum levels of blood urea nitrogen and creatinine.

Effects of Ca^{2+} channel antagonists on glomerular capillary pressure in experimental models of hypertension are controversial. It was reported that Ca^{2+} channel antagonists do not reduce glomerular capillary pressure because of a concomitant reduction in afferent arteriolar tone (Loutzenhiser and Epstein, 1985) and impairment of renal autoregulatory responses to changes in renal perfusion pressure (Navar et al., 1986). Thus, it was suggested that these Ca^{2+} channel antagonists would not be effective in protecting against hypertensive glomerular injury. However, in our study, glomerular injury was significantly decreased in CD-832-treated SHRSPs compared with findings in control SHRSPs. Glomerular lesions may be improved by its hypotensive effect.

Myocardial fibrosis was observed in the heart of control SHRSPs. On the other hand, there was no myocardial fibrosis in SHRSPs treated with CD-832 or diltiazem. At the same time, CD-832 and diltiazem also showed lower ratios of heart weight/body weight compared to ratios of control SHRSPs. These observations suggest that the oral administration of CD-832 and diltiazem prevents myocardial fibrosis and cardiac hypertrophy (as assessed by ratios of heart weight/body weight). The hypertrophic response is a means by which the left ventricle can attenuate increases in wall stress and myocardial oxygen consumption per unit mass (Hachamovitch et al., 1988). Because CD-832 and diltiazem inhibited the development of hypertension and reduced HR, the cardiac-protective effects may be due to the reduced myocardial oxygen consumption as a result of a reduction of afterload and negative chronotropism.

In control SHRSPs, slight myocardial fibrosis was observed in 3 out of the 9 hearts. Therefore, histopathologically, renal lesions were more severe than cardiac lesions in our experimental set-up.

In the present study, CD-832 (0.05%) and diltiazem (0.15%) were equally efficacious in preventing the development of hypertension. The doses of drugs were calculated from the daily ingestion of the diets. Because SHRSPs fed 0.05% CD-832 and 0.15% diltiazem diets were given the drugs at average doses of 32.8 ± 0.7 and 103.9 ± 2.7 mg/kg per day, respectively, CD-832 is a more potent antihypertensive for SHRSPs than diltiazem. These data are in accord with our previous reports (Takahashi et al., 1992, 1996).

Mechanisms underlying the antihypertensive effects of CD-832 remain speculative. In a previous study using a whole cell voltage-clamp method, CD-832 blocked the

L-type Ca^{2+} channel in rat aortic smooth muscle cells (Hirakawa et al., 1994). Thus, the antihypertensive effects of CD-832 may be the result of a block of calcium entry through L-type voltage-operated channels.

In conclusion, 12-week repeated-administration of CD-832, a new Ca^{2+} channel antagonist, prevented the development of hypertension and led to a dramatic improvement of renal lesions in SHRSPs. CD-832 and diltiazem were equally efficacious in preventing organ damage but this organ-protective effect was obtained at a lower dose for CD-832 (30 mg/kg per day) than that of diltiazem (100 mg/kg per day). These properties may be advantageous for an agent used for long-term treatment of hypertension.

Acknowledgements

We thank Dr. T. Shibata, Dept. of Pathology, at Tsuchiura-kyodou hospital for morphologic assessment of organ damage in the SHRSPs.

References

Bunag, R.D., Butterfield, J., 1982. Tail-cuff blood pressure measurement without external preheating in awake rats. Hypertension 4, 898–903.

Hachamovitch, R., Sonnenblick, E.H., Strom, J.A., Frishman, W.H., 1988. Left ventricular hypertrophy in hypertension and the effects of antihypertensive drug therapy. Curr. Probl. Cardiol. 13, 371–421.

Hirakawa, Y., Kuga, T., Kanaide, H., Takeshita, A., 1994. Actions of a new Ca^{2+} channel antagonist, CD-832, on two types of Ca^{2+} channels in smooth muscle. Eur. J. Pharmacol. 252, 267–274.

Loutzenhiser, R., Epstein, M., 1985. Effects of calcium antagonists on renal hemodynamics. Am. J. Physiol. 249, F619–F629.

Miyata, N., Yamaura, H., Tanaka, M., Takahashi, K., Tsuchida, K., Otomo, S., 1993. CD-832, a new dihydropyridine derivative with both nitrate-like and calcium channel antagonist vasodilator activities. Eur. J. Pharmacol. 249, 141–149.

Navar, L.G., Champion, W.J., Thomas, C.E., 1986. Effects of calcium channel blockade on renal vascular resistance responses to changes in perfusion pressure and angiotensin-converting enzyme inhibition in dogs. Circ. Res. 58, 874–881.

Okamoto, K., Yamori, Y., Nagaoka, A., 1974. Establishment of the stroke-prone spontaneously hypertensive rat. Circ. Res. 34–35 (Suppl. I), 143–153.

Roberts, W.C., 1990. Frequency of systemic hypertension in various cardiovascular diseases. In: Laragh, H., Brenner, B.M. (Ed.), Hypertension: Pathology, Diagnosis, and Management. Raven Press, New York, NY, pp. 379–387.

Sunderrajan, S., Reams, G., Bauer, J.H., 1986. Renal effects of diltiazem in primary hypertension. Hypertension 8, 238–242.

Sunderrajan, S., Reams, G., Bauer, J.H., 1987. Long-term renal effects of diltiazem in essential hypertension. Am. Heart J. 114, 383–388.

Suzuki, M., Yamakawa, K., Nabata, H., Tachibana, M., 1993. Long term effects of amlodipine on organ damage, stroke and life span in stroke prone spontaneously hypertensive rats. Eur. J. Pharmacol. 228, 269–274.

Takahashi, K., Kishi, S., Miyata, N., Yamaura, H., Tanaka, M., Tsuchida, K., Otomo, S., 1992. Cardiovascular effects of a novel Ca antagonist, CD-832. Jpn. J. Pharmacol. 58 (Suppl. 1), 400.

Takahashi, T., Tomoike, H., Muramatsu, K., Imamura, Y., Narishige, T., Takeshita, A., Nakamura, M., 1994. Effects of a new calcium antagonist, CD-832, on coronary and systemic hemodynamics in conscious dogs. J. Cardiovasc. Pharmacol. 24, 8–12.

Takahashi, T., Takahashi, K., Kishi-Tanikawa, S., Tsuchida, K., Araki, H., Higuchi, S., 1996. Effects of a new calcium antagonist, CD-832, on isoproterenol-induced myocardial ischemia in dogs with partial coronary stenosis. J. Pharmacol. Exp. Ther. 278, 1028–1033.

Uehara, Y., Hirata, N., Takeda, T., Numabe, A., Kawabata, Y., Nagoshi, H., Gomi, T., Ikegami, J., Goto, A., Omata, M., 1995. Possible linkage between renal injury and cardiac remodeling in Dahl salt-sensitive rats treated with the calcium channel antagonist benidipine. Hypertens. Res. 18, 245–253.

Yamaura, H., Miyata, N., Takahashi, K., Tsuchida, K., Otomo, S., 1994. Effects of CD-832, a dihydropyridine derivative with nitrate ester, on rabbit femoral artery and vein. Eur. J. Pharmacol. 260, 269–272.

Yoshida, Y., Fogo, A., Ichikawa, I., 1989. Glomerular hemodynamic changes vs. hypertrophy in experimental glomerular sclerosis. Kidney Int. 35, 654–660.