Histopathological Investigation on Salt-Loaded Stroke-Prone Spontaneously Hypertensive Rats, Whose Biochemical Parameters of Renal Dysfunction Were Ameliorated by Administration of Imidapril

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Received December 3, 1993 Accepted July 7, 1994

ABSTRACT--Our previous studies showed that imidapril prevented the occurrence of cerebral stroke and ameliorated biochemical parameter changes of renal dysfunction at a dose that did not inhibit the progression of hypertension in salt-loaded stroke-prone spontaneously hypertensive rats (SHRSP). To confirm these findings, a histopathological investigation was conducted on the kidney of salt-loaded (from 11 to 16 weeks of age) SHRSP, which was the subject of the preceding study. Their brains and hearts were also examined. Histopathologically, renal lesions such as fibrinoid necrosis and proliferative arteritis of small calibration arteries, necrotizing glomerulitis and tubular degeneration, and cerebral hemorrhage and slight cardial hypertrophy were observed in salt-loaded control SHRSP. The occurrence of these lesions were prevented in a dose-dependent manner by the administration of imidapril (1 and 2 mg/kg/day). Especially, the preventive effects on the renal lesions were apparently noted. Enalapril also prevented these renal lesions, but its preventive effects were weaker than those of imidapril at the same dose (2 mg/kg/day). It became evident from the results of the present and previous studies that imidapril reduced renal biochemical and histopathological injuries.

Keywords: Salt-loaded SHRSP, Histopathology, Kidney, Imidapril

Imidapril hydrochloride (imidapril) is a "prodrug" type of ACE inhibitor whose pharmacological effects are derived from its active metabolite (imidaprilat). The antihypertensive effect of imidapril is due to the inhibition by imidaprilat of the production of angiotensin II. The antihypertensive action of imidapril is equipotent with that of enalapril, which is also an ACE inhibitor, and is 5 to 10 times more potent than that of captopril. The ACE inhibiting action of imidapril is 6 to 18 times (inhibition constant on the swine kidney and human serum ACEs) more potent than either of the latter two (1, 2).

It has been reported that ACE inhibitors show prophylactic effects on cerebral stroke (3-6), ameliorating effects on renal dysfunction (4, 7, 8), and protective effects on myocardium (9-12) along with its antihypertensive (depressor) effects. ACE inhibitors are currently used in the prevention and treatment of diseases that have hypertension as a complication.

Recently, we reported that imidapril reduced the incidence of cerebral stroke, the increased excretion of proteinuria and urinary *N*-acetyl-β-glucosaminase (NAG) activity at a dose (0.5-2.0 mg/kg/day, p.o.) that did not inhibit the progression of hypertension in salt-loaded stroke prone spontaneously hypertensive rats (SHRSP) (7, 13). Moreover, we showed that the abnormal fluctuations in the biochemical parameters of renal functions such as increases of blood urea nitrogen (BUN) and creatinine (CRNN) and a decrease of potassium were ameliorated by the administration of imidapril.

In this report, we histopathologically investigated the effect of imidapril on the kidney, brain and heart in salt-loaded SHRSP in which we have already confirmed the amelioration in renal function by this drug (7). In addition, the effects of imidapril on the lesions were compared with those of enalapril.

MATERIALS AND METHODS

Animals and experimental groups

Thirty-nine male SHRSP were used. These SHRSP were obtained from Dr. Okamoto at Kinki University and bred at Tanabe Seiyaku Co., Ltd. The rats were main-

tained under the following conditions: room temperature of 23±1℃, relative humidity of 55±5% and 12-hr light-dark cycle.

The SHRSP were divided into the following 5 groups: non-salt-loaded control group (Group I, n=8); salt-loaded control group (group II, n=7); imidapril, 1 mg/kg group (group III, n=8); imidapril, 2 mg/kg group (group IV, n=8); and enalapril, 2 mg/kg (group V, n=8). All rats were maintained on a normal diet (CRF-1; Oriental Yeast Co., Ltd., Tokyo) and tap water until 10 weeks of age. Salt-loaded rats (groups II, III, IV and V) were maintained on 1% NaCl solution and a special diet (high NaCl and low protein content; Funabashi SP, Funabashi Farm Co., Ltd., Funabashi) and non salt-loaded rats (group I) were maintained on tap water and the special diet from 11 to 16 weeks of age.

Drugs

Imidapril ((4*S*)-1-methyl-3-{(2*S*)-2-[*N*-((1*S*)-1-ethoxycarbonyl-3-phenylpropyl)amino]propionyl}-2-oxo-imidazolidine-4-carboxylic acid) hydrochloride (Lot No. 403010) and enalapril maleate (Lot No. 1030082A) were both synthesized at the Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd. (Osaka). The agents were dissolved in distilled water and administered daily to the rats by gavage at a volume of 5 ml/kg for 5 weeks from 11 weeks of age.

Pathological evaluation

Measurement of organ weight and specimen preparation: Autopsy was carried out 24 hr after the last administration (16 weeks of age); arterial blood was collected from the abdominal aorta (Results of hematology and blood biochemical examination were shown in the previous study (7)) under deep ether anesthesia; and the kidney, brain and heart were removed and weighed. Relative weights (organ weight with respect to body weight) were calculated. After the measurement of organ weight, the organs were fixed with Lillie's 10% neutral buffered solution and embedded in paraffin. The paraffin blocks were cut into 2- to 4-μm-thick slices and stained with hematoxylin-eosin (HE). Kidney tissues were also stained with periodic acid Schiff (PAS), Masson's trichrome, and phosphotungustic acid hematoxylin (PTAH).

Histopathological observations and quantitative analysis of the lesions: Cross-sectional area of the kidney including the reniportal were examined microscopically. The number of degenerated glomeruli (necrotizing glomerulitis) and the total number of glomeruli was counted in PAS- and Masson's trichrome-stained sections. The number of arteries showing fibrinoid necrosis and proliferative arteritis were counted in HE-, PAS- and PTAH-stained sections.

The diameter and vascular wall thickness of the basilar artery were measured in sections that included the hippocampus, thalamus and hypothalamus. The ratio of vascular wall thickness to diameter of the basilar artery was also determined. Hemorrhagic foci in the brain were examined microscopically.

The heart was transversely sectioned about 5 mm below the coronary sulcus at a location where both left and right ventricles could be seen.

Statistical analyses

Data were analyzed by dispersion analysis as proposed by Bartlett. When the distribution was uniform, the data were analyzed by one-way dispersion. Otherwise, they were analyzed by Kruskal-Wallis analysis. When there were intergroup differences, a multiple comparison was made by Scheffe's parametric method or non-parametric method.

RESULTS

Organ weight

Absolute and relative weight of the kidneys, brains and hearts are shown in Table 1.

By comparison with group I, group II showed increases in the absolute weights of the kidneys and the relative weights of the kidneys, brains and hearts. The weights of these organs in groups III and IV were significantly lower than those in group II, in a dose-dependent manner; and the weights of these organs in group IV were similar to those of the organs in group I. The weights of the same organs in group V were almost similar to those in group III.

Histopathological findings

One rat in group II died during the experiment. As extensive hemorrhage was observed in the cerebral cortex and medulla of the dead rat, it is likely that the rat died of stroke. The pathological findings of the kidneys and heart seen in the dead rat were similar to those observed in other group II rats autopsied at the end of the experimental period.

Histological findings observed in the kidneys, brains and hearts are summarized in Table 2.

Kidney: Fibrinoid necrosis and proliferative arteritis were seen in small calibration arteries, particularly in arterioles smaller than arcuate arteries in group II rats (Fig. 1a). In advanced cases, the concentric proliferation of the vascular smooth muscle cells with fibrinoid necrosis and hemorrhage was also seen (Fig. 1b). These vascular lesions were frequently observed in the juxtaglomerular efferent and afferent arterioles (Fig. 1c). Glomeruli were found to be swelling and necrotizing; moreover, fibrinoid necrosis and fibrin thrombi were seen in the glomeruli

Table 1. Absolute and relative organ weights of the kidneys, brains and hearts in SHRSP treated with imidapril and enalapril

Experimental group	N	Body weight (g)	Absolute weight			Relative weight		
			kidney (g)	brain (g)	heart (g)	kidney (g/100 g B.W.)	brain (g/100 g B.W.)	heart (g/100 g B.W.)
I (Non-salt-loaded control)	8	295.3 ±13.7	2.34 ±0.16	1.82 ±0.06	1.46 ±0.08	0.79 ±0.04	0.62 ±0.03	0.50 ±0.02
II (Salt-loaded control)	6[1)]	245.8 ±32.8	2.65$^{\#\#}$ ±0.13	1.85 ±0.07	1.49 ±0.18	1.09$^{\#\#}$ ±0.16	0.76$^{\#}$ ±0.09	0.61$^{\#\#}$ ±0.05
III (Imidapril 1 mg/kg)	8	289.4* ±24.8	2.45 ±0.27	1.80 ±0.05	1.50 ±0.15	0.85* ±0.04	0.62** ±0.04	0.52** ±0.02
IV (Imidapril 2 mg/kg)	8	300.1** ±28.5	2.47 ±0.28	1.81 ±0.09	1.50 ±0.19	0.82** ±0.03	0.61** ±0.03	0.50** ±0.04
V (Enalapril 2 mg/kg)	8	288.8 ±25.9	2.49 ±0.13	1.83 ±0.04	1.54 ±0.07	0.86** ±0.05	0.64** ±0.05	0.54** ±0.05

Salt-loaded rats were maintained on 1% NaCl solution and a special diet (Funabashi SP) and non-salt-loaded rats were maintained on tap water and the special diet from 11 to 16 weeks of age. They were given the drugs orally once a day. Values are means with standard deviation. $^{\#}$: $P<0.05$, $^{\#\#}$: $P<0.01$ vs. non-salt-loaded SHRSP and *: $P<0.05$, **: $P<0.01$ vs. salt-loaded SHRSP by Scheffe's multiple comparison. [1)]: One rat died at the 13th week.

Table 2. Histopathological findings of the kidneys, brains and hearts in SHRSP treated with imidapril and enalapril

Organ	Microscopic findings	Groups	I Non-salt-loaded control (n=8)	II Salt-loaded control (n=7)	III Imidapril 1 mg/kg (n=8)	IV Imidapril 2 mg/kg (n=8)	V Enarapril 2 mg/kg (n=8)
Kidney	Fibrinoid necrosis of arterial walls		7	7	8	5	7
	Proliferation of vascular smooth muscle cells		3	7	8	3	7
	Lesion combined with fibrinoid necrosis and proliferation of vascular smooth muscle cells		1	7	3	1	4
	Necrotizing glomerules		2	7	5	0	5
	Dilation and basophilic change of tubules		0	7	1	0	2
Brain	Hemorrhage		0	4	0	0	0
Heart	Slight cardiac fibrosis		1	3	3	2	0
	Hypertrophy of myocardiums		1	3	0	0	0

Salt-loaded rats were maintained on 1% NaCl solution and a special diet (Funabashi SP) and non-salt-loaded rats were maintained on tap water and the special diet from 11 to 16 weeks of age. They were given the drugs orally once a day. Necropsy was carried out 24 hr after the last administration under deep anesthesia of ether, and the kidney, brain and heart were removed. These organs were fixed in Lillie's 10% neutral buffered formalin and embedded in paraffin. The paraffin blocks were cut into 2- to 4-μm-thick slices and staind with hematoxylin-eosin.

(necrotizing glomerulitis, Fig. 1c). The basement membrane of renal tubules was thickened, and epithelial cells appeared basophilic in areas where the most marked glomerular changes were seen (tubular regeneration). The lumina of the renal tubules were abnormally dilated in some instances. In the interstitium around degeneratic glomeruli and tubuli, small round cell infiltration was noted.

Figure 2 shows the renal lesions of rats in groups I, III, IV and V.

In group I rats, renal small calibration arteries and glomeruli exhibited similar but mild pathological changes as seen in group II rats, and no tubular changes were noted (Fig. 2a).

In rats of groups III and IV (imidapril at the dose of 1 and 2 mg/kg, respectively), marked renal lesions, as seen in group II rats, were prevented in a dose-dependent manner (Fig. 2, b and c). Particularly, renal vascular lesions in group IV rats were as mild as those in group I rats, and glomerular lesions were not observed in this group (Fig. 2c). In the rats of group V (enalapril, 2 mg/kg), these lesions were moderately reduced (Fig. 2d). When imidapril and enalapril were given at the same dose (2 mg/kg), imidapril was more potent than enalapril in preventive

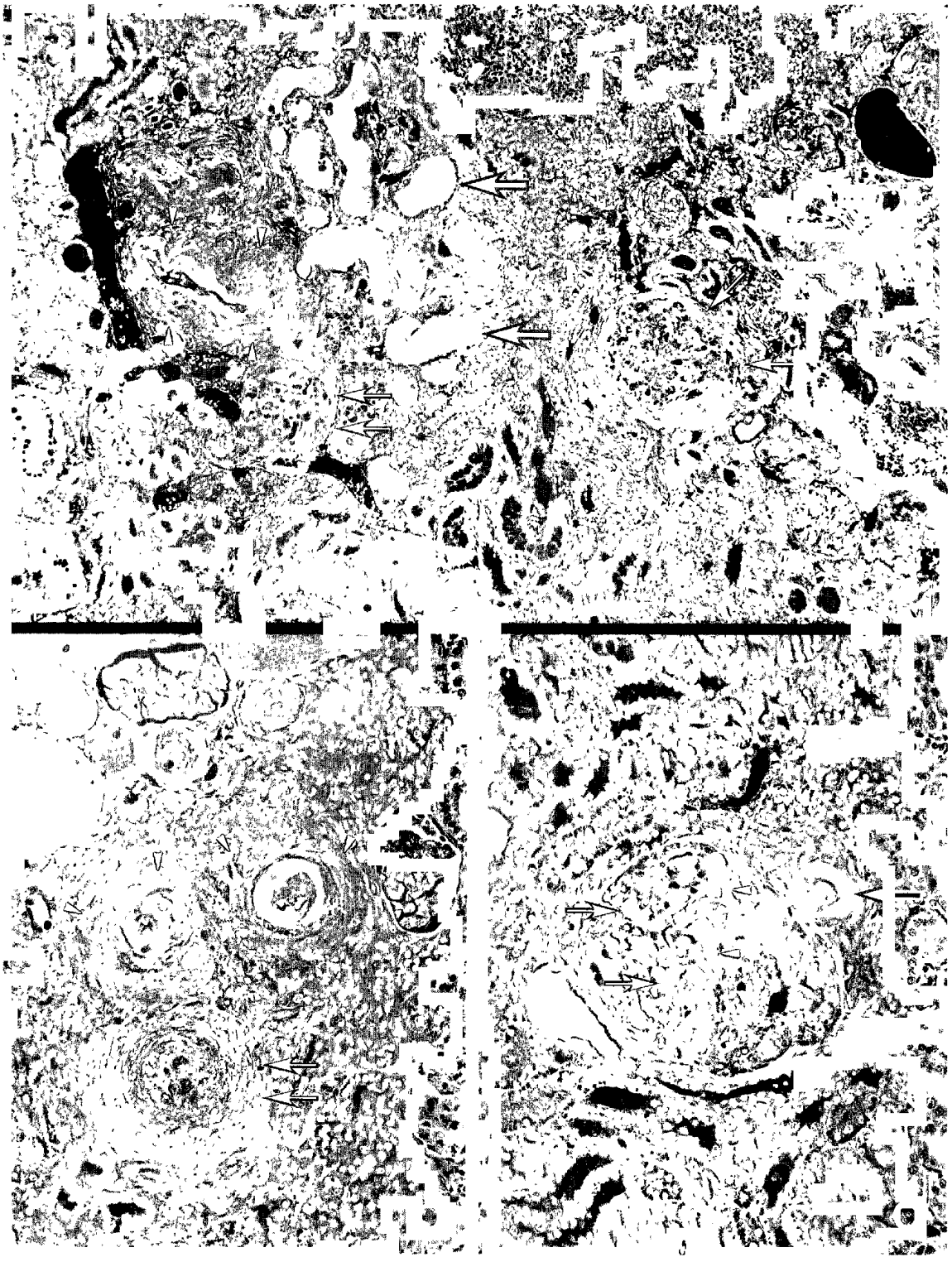

Fig. 1. Renal lesions in salt-loaded control SHRSP (group II). Salt-loaded rats were maintained on 1% NaCl solution and a special diet (Funabashi SP) and non salt-loaded rats were maintained on tap water and the special diet from 11 to 16 weeks of age. They were given the drug orally once a day. a: Fibrinoid necrosis with proliferative endoarteritis (arrowheads), necrotizing glomerulitis (small arrows) and dilation of tubules (large arrows) in the kidney (H.E. stain, ×130). b: Renal vascular lesions showing fibrinoid necrosis with proliferative endoarteritis (arrowheads), concentric proliferative endoarteritis with fibrinoid necrosis and hemorrhage (arrows) (H.E. stain, ×250). c: Necrotizing glomerulitis showing fibrinoid necrosis in glomerular capillaries and mesangial cells (arrowheads) and fibrin thrombi (small arrows). Jaxtaglomerular efferent and afferent arterioles also showed fibrinoid necrosis (large arrow) (H.E. stain, ×250).

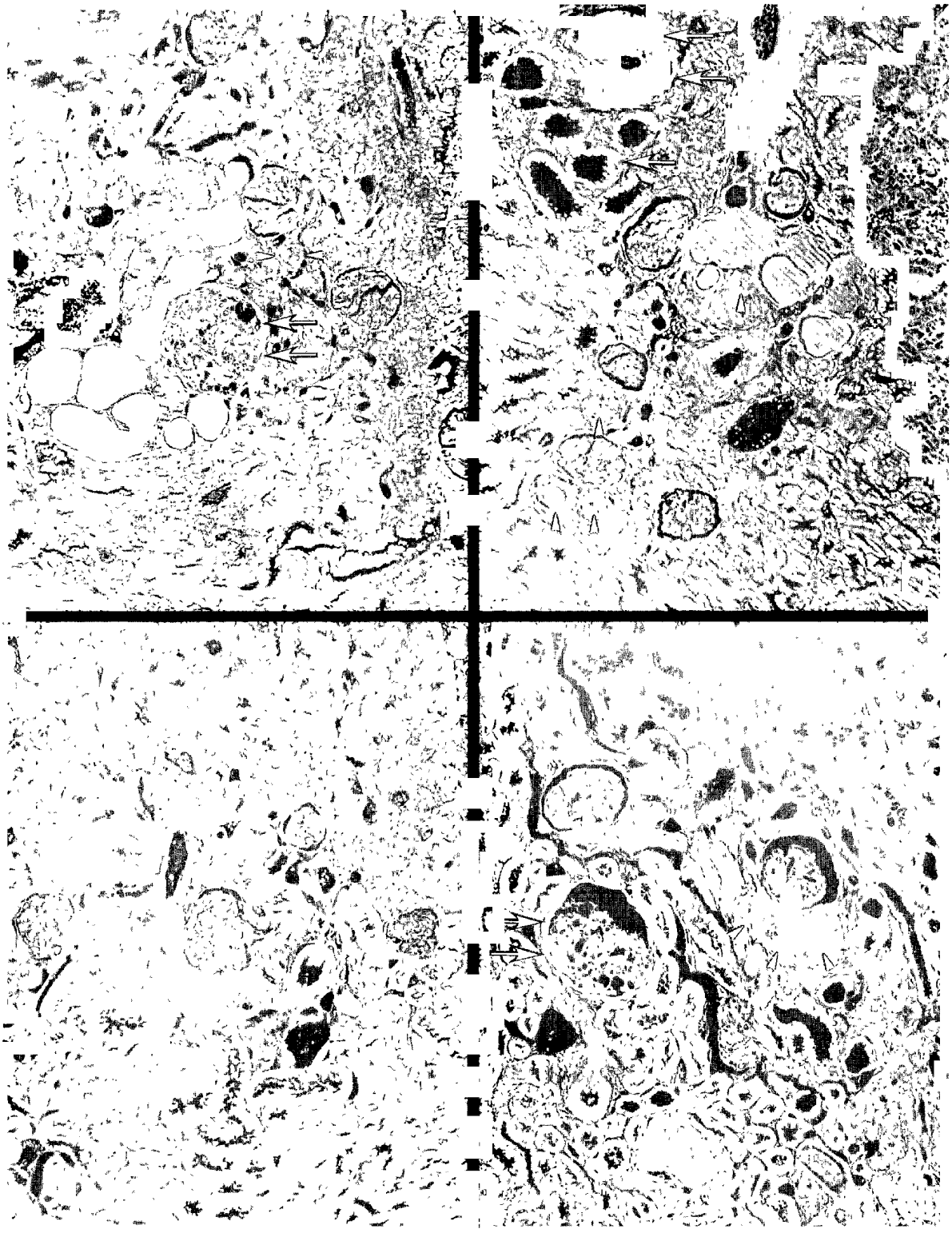

Fig. 2. The comparison of renal lesions in each group (H.E. stain, ×100). Salt-loaded rats were maintained on 1% NaCl solution and a special diet (Funabashi SP) and non salt-loaded rats were maintained on tap water and the special diet from 11 to 16 weeks of age. They were given the drugs orally once a day. a: Non-salt-loaded control (group I). The proliferative endoarteritis of small calibration arteries (arrowheads), necrotizing glomerulitis (arrows) and dilation of tubules are seen. b: Imidapril, 1 mg/kg (group III). Slight fibrinoid necrosis of vascular wall (arrowheads) and regeneratic tubules (arrows) are seen. c: Imidapril, 2 mg/kg (group IV). Significant lesions are not seen. d: Enalapril, 2 mg/kg (group V). The fibrinoid necrosis of juxtaglomerular efferent and afferent arterioles (arrowheads) and necrotizing glomerulitis (arrows) are seen.

effects on the occurrence of the renal lesions, particularly glomerular and tubular changes (Fig. 2, c and d).

Brain: There were no significant lesions in the basilar artery or its branches of group II rats, but hemorrhage per rexis was seen in the cerebrum in 4 out of 7 rats. The hemorrhage per rexis was not seen in rats in groups I, III, IV and V.

Heart: Both slight myocardial fibrosis and hypertrophy were seen in 3 out of 7 rats in group II and in 1 out of 8 rats in group I. The myocardial fibrosis alone was seen in 3 out of 8 rats in group III and 2 out of 8 rats in group IV. There were no myocardial changes in group V.

Quantitative analysis of pathological lesions in the kidneys and cerebral basilar arteries

Analysis of glomerular lesions: The ratio of glomeruli with necrotizing glomerulitis to normal glomeruli in one microscopic section in kidneys is shown in Fig. 3. Necrotizing glomerulitis was seen in all rats in group II; the ratio of necrotizing glomerulitis was 19.1±3.1% (mean±S.E.). The ratio was significantly higher than that of group I rats (0.4±0.3%). Imidapril significantly reduced the number of glomeruli exhibiting necrotizing glomerulitis. The ratio was 1.9±2.4% in group III rats. There were no glomerular lesions seen in group IV rats. The ratio was 2.1±3.0% in group V rats.

Analysis of renal vascular lesions: The number of renal vascular lesions in one microscopic section of each rat is shown in Fig. 4.

In group II rats, the average of 12.0±2.3 (mean±S.E.) lesions showing fibrinoid necrosis were seen. The average number of lesions showing proliferative arteritis was 31.1±6.4 and the average number of 13.3±2.2 for mixed lesions (The proliferative arteritis with fibrinoid necrosis and hemorrhage) was observed. Corresponding values in group I rats were 1.8±0.9, 3.3±3.3, and 0.1±0.2, respec-

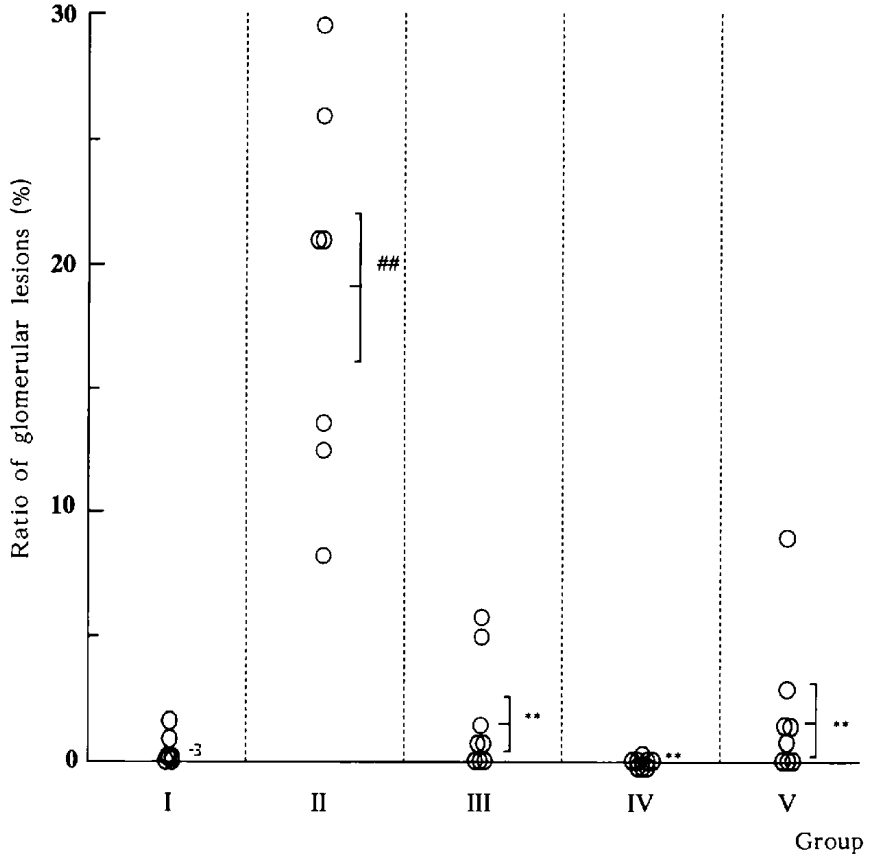

Fig. 3. The ratio of renal glomerular lesions in one microscopic section of a kidney in salt-loaded SHRSP treated with imidapril and enalapril. The degeneration of the glomerulus was noted as necrotizing glomerulitis. Salt-loaded rats were maintained on 1% NaCl solution and a special diet (Funabashi SP) and non-salt-loaded rats were maintained on tap water and the special diet from 11 to 16 weeks of age. They were given the drugs orally once a day. I: Non-salt-loaded control group (n=8), II: Salt-loaded control group (n=7), III: Imidapril (1 mg/kg) group (n=8), IV: Imidapril (2 mg/kg) group (n=8), V: Enalapril (2 mg/kg) group (n=8). ##: $P<0.01$ vs. non-salt-loaded control group (I) and **$P<0.01$ vs. salt-loaded control group (II) by Scheffe's multiple comparison.

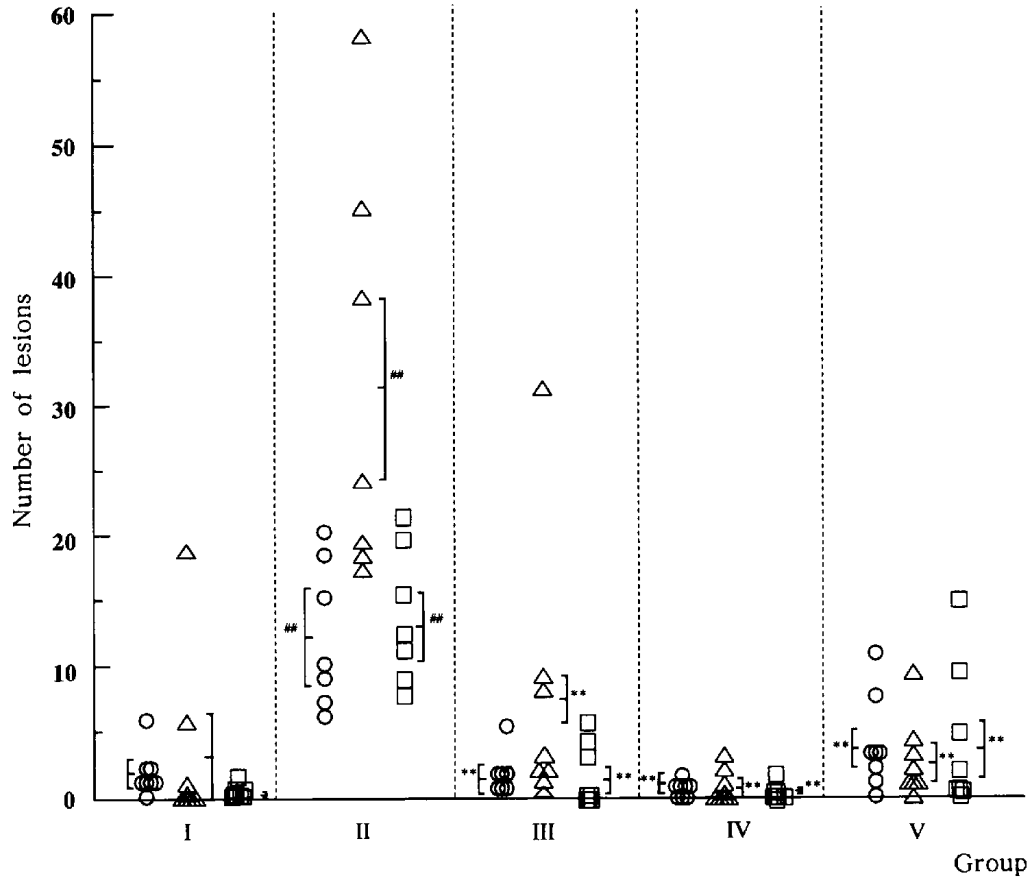

Fig. 4. The number of renal arterial lesions in one microscopic section of a kidney in salt-loaded SHRSP treated with imidapril and enalapril. The appearance of fibrinoid necrosis (○), proliferative endoarteritis (△) and the lesion showing a combination of both changes (□) are shown. Salt-loaded rats were maintained on 1% NaCl solution and a special diet (Funabash SP) and non-salt-loaded rats were maintained on tap water and the special diet from 11 to 16 weeks of age. They were given the drugs orally once a day. I: Non-salt-loaded control group (n=8), II: Salt-loaded control group (n=7), III: Imidapril (1 mg/kg) group (n=8), IV: Imidapril (2 mg/kg) group (n=8), V: Enalapril (2 mg/kg) group (n=8). ##: $P<0.01$ vs. non-salt-loaded control group (I) and **$P<0.01$ vs. salt-loaded control group (II) by Scheffe's multiple comparison.

Table 3. The ratio of arterial wall thickness to diameter of the artery in SHRSP treated with imidapril and enlapril

Experimental group	N	Thick of arterial wall / Diameter
I (Non-salt-loaded control)	8	48.8±3.7
II (Salt-loaded control)	5	48.6±3.6
III (Imidapril 1 mg/kg)	7	47.9±7.4
VI (Imidapril 2 mg/kg)	5	45.2±4.4
V (Enalapril 2 mg/kg)	5	48.8±5.3

Salt-loaded rats were maintained on 1% NaCl solution and a special diet (Funabashi SP) and non-salt-loaded rats were maintained on tap water and the special diet from 11 to 16 weeks of age. They were given the drugs orally once a day. Values are means with standard errors.

tively.

The number of renal vascular lesions also decreased in the imidapril-treated rats in a dose-dependent manner. In the group III rats, the number of lesions due to fibrinoid necrosis in the vascular walls was 2.0±0.7; that of lesions showing proliferative artetitis was 4.0±2.0. The number of mixed lesions was 1.9±1.3. The corresponding incidences for the group IV rats were 0.9±0.5, 0.8±0.6 and 0.1±0.2, respectively. In the group V rats, the number of renal vascular lesions also decreased. However, enalapril was much less potent than imidapril at the same dose (2 mg/kg) in the prevention of the renal lesions. The number of renal vascular lesions in the group V rats was 3.8±1.8, 2.6±1.4 and 3.6±2.8, respectively.

Analysis of the basilar artery: The ratio of the diameter of a basilar artery to the wall thickness of the basilar artery was determined, but there were no significant differences among the groups (Table 3).

DISCUSSION

In SHRSP, the blood pressure increases early after birth. When the mean systolic pressure exceeds 200 mmHg at the age of about 15 weeks, stroke occurs, and lesions showing fibrinoid necrosis and proliferative arteritis are formed in the renal as well as systemic blood vessels (14, 15). The increase in the blood pressure, the occurrences of stroke, and the systemic vascular lesions can be induced earlier by loading SHRSP with salt (14, 16, 17).

Ogiku et al. (7, 13) reported that imidapril alleviated the increases in urinary protein excretion and urinary NAG activity and the changes in biochemical parameters suggesting renal dysfunction such as increases in BUN, CRNN and a decrease of potassium. Imidapril also prevented stroke in salt-loaded SHRSP at doses (0.5−2.0 mg/kg, p.o.) that did not inhibit the progression of hypertension. They speculated that renal dysfunction might be closely related to the occurrence of stroke, because stroke was observed after the elevation of urinary protein excretion and NAG activity and because the onset of stroke could be delayed by ameliorating these changes.

In this study, kidneys of salt-loaded SHRSP, in which changes in the above parameters were ameliorated by imidapril, were histopathologically evaluated with simultaneous examination of the brain and heart. In addition, the effects of imidapril were compared with those of enalapril to study differences between these agents with respect to their effects on the occurrence of the renal lesions.

In SHRSP, salt loading resulted in a marked increase in the kidney weight and histopathologic changes such as fibrinoid necrosis and proliferative arteritis in arteries smaller than arcuate arteries, especially afferent and efferent arterioles. In the glomeruli, fibrin thrombi and fibrinoid necrosis implicating necrotizing glomerulitis were noted. These lesions were in agreement with those characteristics of SHRSP reported by Ogata et al. (15). In the groups administered imidapril, the appearance of such necrotizing glomerulitis was reduced in a dose-dependent manner, and no lesions were noted at 2 mg/kg. When the occurrence of these vascular and glomerular lesions was expressed quantitatively and compared among the groups, it was the most notably prevented in the group administered imidapril at 2 mg/kg. The renal lesions were also prevented in the group administered enalapril at 2 mg/kg, but the effect of enalapril was weaker than that of the same dose of imidapril (2 mg/kg).

This prevention of renal lesions by the administration of imidapril and enalapril is considered to be closely related to the improvement in the lesions of small calibration arteries. Angiotensin II contracts efferent arterioles more markedly than afferent arterioles and increases blood pressure (18). Sustained stimulation by angiotensin II promotes the proliferation of vascular smooth muscle cells and injures blood vessels (19, 20). Imidapril inhibits the conversion of angiotensin I to angiotensin II in blood and vascular walls and prevents injuries of renal afferent and efferent arterioles. Imidapril may ameliorate renal dysfunction by dilating efferent arterioles and reducing pressure load on the kidneys (21).

In the salt-loaded control group, the insufficient regulation of the renal blood flow due to the degeneration of small calibration arteries is considered to induce a reduction in glomerular blood flow. The reduction of the blood flow and the proliferation of mesangial cells promoted by angiotensin II may cause primary glomerular degeneration followed by the secondary change of renal tubules (22, 23). The glomerular and tubular changes following the vascular lesions might be prevented by reversing the vascular lesions and inhibiting the direct damage of angiotensin II to the glomeruli by the administration of imidapril and enalapril. The development of these lesions was markedly inhibited in the group administered imidapril at 2 mg/kg, probably due to the reduction of the vascular lesions. Furthermore, the increase in the kidney weight caused by salt loading was reduced to the same level as the non salt-loaded control group by the suppression of the renal lesions and improvements in the renal functions.

Recently, many studies suggested the participation of the kallikrein-kinin-prostaglandin system in the antihypertensive effect of ACE inhibitors. Okamura et al. (24) reported that imidapril and enalapril significantly suppressed the contraction caused by angiotensin I and potentiated the relaxations by bradykinin in a concentration-dependent manner in isolated dog arteries; they found that the potency of imidaprilat, which is the active metabolite of imidapril, to potentiate the bradykinin action was relatively lower than that of enalaprilat, which is the active metabolite of enalapril, at the same dose. The inhibitory activity for ACE of imidapril in arteries is more potent than that of enalapril (1). Thus, it is suggested that the potentiation of bradykinin activity does not participate in the improvement of renal arterial lesions by administration of imidapril in this paper.

Concerning the cerebral lesions, hemorrhage was observed in 4 out of the 7 animals in the salt-loaded control group, but changes such as the thickening and degeneration of cerebral vessels were not seen. Usually, the thickening and degeneration of vascular walls are found in the basilar arteries and penetrating arteries of cerebral parenchyma on the long-term breeding of SHRSP. In this study, however, only hypertension occurred, and secondary morphological changes did not become evident, possibly because hypertension was induced early by salt loading. However, the rupture of cerebral vessels suggests that

the cerebral pressure regulating mechanism was impaired and that sustained pressure overload led to the rupture of the vessels.

Shibota et al. (16) suggested that the activation of the renin-angiotensin system was involved in the malignant hypertension of salt-loaded SHRSP. The activation of the renin-angiotensin system is considered to shift the range of autoregulation of cerebral blood flow to higher blood pressure and induce the thickening and remodeling of cerebral vessels (25). ACE inhibitors suppress the activation of the renin-angiotensin system and exert protective effects on the cerebral circulation by shifting the range of autoregulation of the cerebral blood flow to lower blood pressure (26, 27).

Nagaoka et al. (28) reported that the development of stroke in SHRSP was associated with changes in hemodynamics due to the thickening of afferent arterioles. They also reported the suppression of the thickening of the afferent arterioles was preventive of stroke and that the occurrence of stroke was delayed by protecting the kidney from hypertension. The reduction of the occurrence of cerebral hemorrhage by imidapril and enalapril at doses that did not inhibit the progression of hypertension in salt-loaded SHRSP suggests that hemorrhage is closely related to the renal vascular lesions and that the renin-angiotensin system in cerebral vessels is involved in the pathogenesis of hemorrhage.

In the heart of the salt-loaded control group, fibrosis and hypertrophy of the myocardium were observed, but the SHRSP used in this study were young, and all these changes were mild. The occurrence of the myocardial hypertrophy was prevented by the administration of imidapril and enalapril, and the fibrosis was also prevented by enalapril. The development and progression of myocardial hypertrophy is thought to involve the local renin-angiotensin system (9, 10, 29, 30). In addition, there is a report demonstrating that angiotensin II directly stimulates myocardial protein synthesis (31). Imidapril may prevent the development of the lesions by inhibiting the production of angiotensin II, which induces the myocardial hypertrophy.

From the above histopathological findings, which are in agreement with the results of the hematology and blood chemical examination in the previous study (7), imidapril reduced the occurrence of cerebral hemorrhage in salt-loaded SHRSP and more potently ameliorated renal dysfunctions and the renal lesions preceding cerebral hemorrhage than the same dose of enalapril. These differences in the ability to alleviate histological lesions and to improve renal functions between these two drugs may be related to the higher inhibitory activity for ACE and the greater tissue affinity of imidapril than enalapril shown in the in vitro comparative study of the inhibitory effects of the two drugs against ACE derived from rat tissue (1).

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