Original Article

Effects of Exercise Training on Glomerular Structure in Fructose-Fed Spontaneously Hypertensive Rats

Kazunori YOSHIDA, Takayuki KAWAMURA, Hong-Lan XU, Lina JI,
Nobuyoshi MORI, and Masahiro KOHZUKI

A high-fructose diet (HFD) has been shown to elevate blood pressure (BP) and to decrease insulin sensitivity in rats. Although running exercise can attenuate these phenomena, its effect on target organ protection is not clear. We investigated whether exercise training has renal protective effects in this model. Nine-week-old spontaneously hypertensive rats were allocated to groups that received HFD or a control diet (control group) for 15 weeks. At the age of 10 weeks, fructose-fed rats were allocated to groups that were given vehicle (FRU group), temocapril, an angiotensin converting enzyme inhibitor (TEM group), exercise training (EX group; treadmill running), or temocapril plus exercise training (TEM + EX group). BP was higher in the FRU group than in the control group. Exercise training tended to decrease BP and temocapril treatment decreased BP significantly. Proteinuria was similar in the five groups. Plasma leptin concentration and epididymal fat weight were lower in the EX and TEM + EX groups than in the FRU group. In the soleus muscle of the FRU group, the composite ratio of type I fiber was decreased and that of type IIa fiber was increased compared with those in the control group. Both temocapril and exercise training restored these ratios. The glomerular sclerosis index (GSI) was higher in the FRU group than in the control group. GSI was decreased equally in the TEM, EX, and TEM + EX groups and was positively correlated with plasma leptin concentration. The results suggest that exercise training ameliorates glomerular sclerosis through mechanisms other than a reduction in BP. (*Hypertens Res* 2003; 26: 907–914)

Key Words: fructose, spontaneously hypertensive rats, exercise, kidney, temocapril

Introduction

Rats maintained on a diet rich in fructose or sucrose have been reported to develop insulin resistance (1–3). Previous studies have shown prominent glomerular injury in rats maintained on a high-fructose diet (HFD) (4). Cohen *et al.* suggested that this injury resembles diabetic glomerulopathy and postulated that it was caused by insulin resistance (4). On the other hand, another study showed only a slight increase in glomerular sclerosis in Sprague-Dawley rats fed fructose for 12 months (5). Insulin-stimulated glucose uptake is enhanced in exercise-trained rats, and the hyperinsuline-

mia associated with HFD is attenuated if rats are allowed to run spontaneously (6, 7). Furthermore, exercise training has been shown to attenuate fructose-induced hypertension in rats (7). In humans, exercise has long been considered an important component in the treatment of diabetes (8) and has been shown to lower blood pressure in patients with hypertension (9). Little is known, however, about the effects of exercise on renal disease in humans. Strenuous acute exercise may increase albumin excretion in subjects with diabetes (10). Since regular exercise is often prescribed for patients with diabetes or hypertension, the effects of exercise training on renal structure in such patients should be determined.

Although excess ingestion of fructose or sucrose causes

From the Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan.

This study was supported by a grant from the Miyagi Kidney Foundation, Sendai, Japan.

Address for Reprints: Kazunori Yoshida M.D., Ph.D., Department of Medicine, Furukawa City Hospital, Furukawa 989–6183, Japan. E-mail: kazunori@gakushikai.jp

Received March 10, 2003; Accepted in revised form July 23, 2003.

elevation in blood pressure, the degree of elevation varies among rat strains (2, 11). Reaven *et al.* reported that the magnitude of fructose-induced increases in blood pressure and in plasma insulin and triglyceride concentrations was significantly greater in spontaneously hypertensive rats (SHR) than in normotensive Wistar-Kyoto rats (11). Furthermore, it is well known that hypertension accelerates nephropathy in various models of experimental renal disease (12–14). However, data on the long-term effects of fructose or sucrose in SHR are scarce, and the effects of exercise training on renal structure in this model remain to be determined. Therefore, the present study was undertaken to determine the effects of chronic exercise training using a treadmill on the function and structure of the kidneys in SHR maintained on HFD.

Methods

Animals and Treatment

Eight-week-old male SHR (Charles River Japan, Atsugi, Japan) were used for this study. This animal study was approved by the Committee of Animal Care and Use of Tohoku University School of Medicine. All rats were maintained in a humidity- and temperature-controlled room with a 12-h light-dark cycle (07:00 on and 19:00 off) during the study. The rats were fed a standard rat chow (Funabashi F2: 0.19% sodium, 0.75% potassium, 20.8% protein by weight; Funabashi Farm, Chiba, Japan) and had free access to tap water. At the age of 8 weeks, baseline measurements of body weight, systolic blood pressure (SBP), urine volume and urinary protein excretion (UprotV) were performed. At the age of 9 weeks, the rats were divided into two groups. Thirty-eight rats were placed on an HFD (53% of calories from fructose, 0.19% sodium, 0.75% potassium by weight; Funabashi Farm), and 8 rats were placed on a control diet (Funabashi Farm) in which fructose was replaced with cornstarch (control group) (15). At the age of 10 weeks, fructose-fed rats were randomly allocated to groups that were given an angiotensin converting enzyme (ACE) inhibitor, temocapril (Sankyo Co., Tokyo, Japan), at a dose of 10 mg/kg/day (TEM group, $n = 10$), treadmill exercise training (EX group, $n = 8$), temocapril (10 mg/kg/day) plus treadmill exercise training (TEM + EX group, $n = 10$), or vehicle alone as an untreated group (FRU group, $n = 10$). Temocapril was suspended in 0.5% carboxymethylcellulose (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and administered for 14 weeks by daily gavage between 09:00 and 10:00. In the EX and TEM + EX groups, rats were subjected to exercise training using a treadmill (KN-73 Tread-Mill; Natsume Industries Co., Tokyo, Japan) operated at a speed of 20 m/min and zero-degree incline for 60 min a day, 5 days a week between 10:00 and 12:00 (15, 16). Based on a previous report (17), this intensity of exercise corresponds to 65% of maximal oxygen uptake. For metabolic study, each rat was placed in a

metabolic cage designed to prevent feces-urine contact (METABOLICA model ST; Sugiyamagen, Tokyo, Japan) at the age of 8 weeks, after which 24-h urine samples were collected, and water and food intakes were measured every 2 weeks up to 24 weeks of age (12–14). Conscious SBP was measured by the indirect tail-cuff method (UEDA UR 5000; Ueda Industries Co., Tokyo, Japan) with heating beforehand (15 min at 37°C) between 14:00 and 15:00 (12–16). Three measurements were made per session, and the average value was used for analysis.

Blood and Tissue Preparation

At the age of 24 weeks, the rats were decapitated and the blood, kidneys, hearts, soleus muscles and epididymal fat pads were collected. The rats were left without exercise and/or drug administration for 24 h and the chow was removed from the cages 5 h before decapitation. The organs were then removed and weighed. The plasma and serum were obtained by centrifugation and stored at -20°C , the soleus muscles snap-frozen on dry ice and stored at -80°C until use, and the kidneys fixed in 10% buffered formalin and embedded in paraffin for histological analysis.

Biochemical Measurements

Blood chemistry and urinary chemistry were measured by a standard autoanalyzer technique (SYNCHRON Clinical System CX7; Beckman Coulter Inc., Fullerton, USA). Creatinine clearance was calculated at the age of 24 weeks. Glycosylated hemoglobin (HbA_{1c}) was determined by affinity chromatography (Isolab Inc., Akron, USA) (13). Plasma insulin and leptin levels were measured by radioimmunoassay kits (Amersham Pharmacia Biotech Inc., Piscataway, USA and Linco Research Inc., St. Charles, USA, respectively) (13, 15).

Histological Examination

Transverse sections of the soleus muscle were cut at a thickness of $10\ \mu\text{m}$ in a cryostat maintained at -24°C and air-dried. Muscle fiber types were determined by myofibrillar adenosine triphosphatase (mATPase) staining (18, 19). Images were captured at 10-fold magnification using a video camera connected to a light microscope. To calculate the proportions of each fiber type (type I, type IIa, or type IIb), 300–400 fibers from each section that had been stained with mATPase were examined (18, 19). Midcoronal sections of the kidney were cut at a thickness of $3\ \mu\text{m}$ and stained with periodic acid-Schiff (PAS). A semiquantitative score was used to evaluate the degree of renal injury. High-power fields were used to seek evidence of focal sclerosis and to determine glomerular volume. To calculate the glomerular sclerosis index (GSI), 150–200 glomeruli from each section that had been stained with PAS were examined (13, 14, 16).

Fig. 1. Line graph showing sequential values of body weights in the five groups. Symbols are (○) control, (□) FRU, (△) TEM, (●) EX, and (■) TEM + EX groups. Each group was treated as shown in Table 1. Body weight was significantly greater in the control group ($p < 0.05$), and significantly lower in the TEM group ($p < 0.01$) than in the FRU group (repeated measures ANOVA).

The degree of sclerosis in each glomerulus was subjectively graded on a scale of 0 (no change) to 4 (global sclerosis). Then the average of the degrees was calculated and registered as the GSI. Glomerular volume was calculated by using the formula for a sphere ($4\pi r^3/3$) (13, 14), where r is the mean glomerular radius calculated from > 100 glomeruli in each section according to the method of van Damme and Koudstaal (20). The renal interstitial volume was estimated by the point counting technique (13, 14) according to the method of Bennett *et al.* (21) with some modifications. Eight portions of renal cortex were randomly selected, and 968 (121×8) points were analyzed in each section. Relative interstitial volume (RIV) was expressed as the percentage of points on the interstitium to the total number of points.

Statistical Analysis

Values are expressed as the means $\pm$ SEM. Intergroup comparisons for biochemical measurements and histological examination were carried out using analysis of variance (ANOVA) with Fisher's probability least significant difference (PLSD) test for *post hoc* comparisons. For water and food intakes, body weight, SBP, urine volume and UprotV, intergroup comparisons over the study period were made by repeated measures ANOVA with Fisher's PLSD test. Correlations were analyzed by simple regression. A Macintosh statistical package software, StatView 4.5 (Abacus Concepts Inc., Berkeley, USA), was used. Values of $p < 0.05$ were considered statistically significant.

Fig. 2. Line graphs showing sequential values of systolic blood pressure (SBP) and urinary protein excretion (UprotV) in the five groups. Symbols are (○) control, (□) FRU, (△) TEM, (●) EX, and (■) TEM + EX groups. Each group was treated as shown in Table 1. (A) SBP was significantly lower in the control ($p < 0.001$), TEM ($p < 0.001$), and TEM + EX groups ($p < 0.001$) than in the FRU group (repeated measures ANOVA). SBP tended to decrease in the EX group compared with that in FRU ($0.1 < p < 0.05$). (B) There was no significant difference in the values of UprotV among the five groups. For simplicity, data obtained every 4 weeks are presented.

Results

Among the five groups of rats, there were no significant differences in body weight, SBP, or UprotV before the treatments. Over the 16-week study period, the weight gain in the control group was greater and that in the TEM group was smaller than that in the FRU group (Fig. 1). There was no

Table 1. Biochemical Measurements in the Spontaneously Hypertensive Rats at the Age of 24 Weeks

	Control (<i>n</i> = 8)	FRU (<i>n</i> = 10)	TEM (<i>n</i> = 10)	EX (<i>n</i> = 8)	TEM + EX (<i>n</i> = 10)
Glucose (mg/dl)	95.9 ± 2.5	94.6 ± 1.6	89.2 ± 2.6	108.4 ± 2.6 [‡]	108.7 ± 2.3 [‡]
Plasma insulin (ng/ml)	2.30 ± 0.17	2.52 ± 0.29	2.17 ± 0.25	2.59 ± 0.17	2.77 ± 0.35
Glucose/insulin ratio	43.5 ± 3.5	41.1 ± 3.8	45.9 ± 5.0	43.0 ± 2.8	45.5 ± 5.8
HbA _{1c} (%)	3.18 ± 0.05	3.15 ± 0.04	3.28 ± 0.04	3.24 ± 0.05	3.20 ± 0.05
Triglyceride (mg/dl)	42.4 ± 5.0	55.3 ± 10.5	55.3 ± 8.1	56.4 ± 10.4	33.1 ± 3.3
Total cholesterol (mg/dl)	31.6 ± 1.3	32.2 ± 0.9	30.8 ± 1.6	32.9 ± 2.1	31.5 ± 1.2
BUN (mg/dl)	18.5 ± 1.0	21.6 ± 0.9	36.1 ± 3.5 [‡]	17.9 ± 0.7	30.7 ± 3.1 [†]
Serum creatinine (mg/dl)	0.41 ± 0.04	0.46 ± 0.05	0.49 ± 0.03	0.41 ± 0.05	0.44 ± 0.04
C _{cr} (ml/min/100g BW)	0.59 ± 0.08	0.57 ± 0.14	0.40 ± 0.05	0.56 ± 0.10	0.52 ± 0.05
Plasma leptin (ng/ml)	3.39 ± 0.46 [*]	2.53 ± 0.23	1.90 ± 0.20	1.44 ± 0.16 [†]	1.07 ± 0.12 [‡]

HbA_{1c}, glycosylated hemoglobin; BUN, blood urea nitrogen; C_{cr}, creatinine clearance; BW, body weight. Control, rats that received a control diet (cornstarch diet); FRU, rats that received a high fructose diet (HFD) alone; TEM, rats that received HFD in combination with temocapril (10 mg/kg/day); EX, rats that received HFD in combination with running exercise; TEM + EX, rats that received HFD in combination with temocapril (10 mg/kg/day) and running exercise. ^{*}*p* < 0.05, [†]*p* < 0.01, [‡]*p* < 0.001 compared with the FRU group.

Table 2. Organ Weights in the Spontaneously Hypertensive Rats Measured at the Age of 24 Weeks

	Control (<i>n</i> = 8)	FRU (<i>n</i> = 10)	TEM (<i>n</i> = 10)	EX (<i>n</i> = 8)	TEM + EX (<i>n</i> = 10)
Heart (mg/g BW)	3.95 ± 0.07	3.94 ± 0.05	3.35 ± 0.09 [‡]	4.09 ± 0.06	3.32 ± 0.09 [‡]
Kidney (mg/g BW)	6.12 ± 0.04	6.79 ± 0.09	7.05 ± 0.09 [*]	6.68 ± 0.07	7.41 ± 0.06 [‡]
Epididymal fat (mg/g BW)	12.94 ± 0.84	12.66 ± 0.39	11.66 ± 0.30	9.23 ± 0.52 [‡]	8.15 ± 0.36 [‡]
Soleus muscle (mg/g BW)	0.446 ± 0.015	0.426 ± 0.011	0.446 ± 0.014	0.416 ± 0.012	0.425 ± 0.009

Each group was treated as shown in Table 1. ^{*}*p* < 0.05, [‡]*p* < 0.001 compared with the FRU group. Abbreviations are the same as Table 1.

Fig. 3. The ratio of muscle fiber to total soleus muscle in the five groups. Symbols are (□) control, (▨) FRU, (▩) TEM, (▤) EX, and (■) TEM + EX groups. Each group was treated as shown in Table 1. [‡]*p* < 0.001 compared with the FRU group.

significant difference between food intakes in the control, FRU, and TEM groups. Rats in the EX and TEM + EX groups consumed more food than those in the FRU group (19% and 17% more, respectively, *p* < 0.01 for both, data not shown). Over the study period, SBP in the FRU group was significantly higher than that in the control group (Fig. 2A), and effects of fructose feeding on SBP were evident at the age of 10 weeks (*p* < 0.001, ANOVA). SBP tended to decrease in the EX group compared with that in the FRU group. Heart rate was decreased significantly in the EX group compared with that in the FRU group (*p* < 0.05, repeated measures ANOVA, data not shown). There were no significant differences in the levels of UprotV among the five groups over the study period (Fig. 2B).

The results of biochemical measurements in the five groups of rats are shown in Table 1. Although plasma glucose levels were higher in the EX and TEM + EX groups, there were no significant differences in plasma insulin, glucose/insulin ratio, index of insulin sensitivity, or glycosylated hemoglobin among the five groups. The blood urea nitrogen level was significantly higher in the TEM and TEM + EX groups than in the FRU group. There were, however, no statistically significant differences in serum creatinine or creatinine clearance among the five groups. Plasma leptin concentration was lower in the FRU group than in the control

Fig. 4. Glomerular sclerosis indices and glomerular volumes in the five groups. Each group was treated as shown in Table 1. (A) Glomerular sclerosis indices were significantly lower in the control, TEM, EX, and TEM + EX groups than in the FRU group. $^{\dagger} p < 0.01$, $^{\ddagger} p < 0.001$ compared with the FRU group. (B) There was no significant difference in glomerular volumes among the five groups.

group. Plasma leptin concentration tended to decrease in the TEM group and was significantly lower in the EX and TEM + EX groups than in the FRU group. Heart weight was decreased and kidney weight was increased in the TEM and TEM + EX groups (Table 2). Epididymal fat weight was decreased in the EX and TEM + EX groups (Table 2). A significant correlation of epididymal fat weight with plasma leptin level was found using regression analysis among the individual rats pooled from all groups ($r = 0.786$, $p < 0.001$, data not shown).

In the FRU group, the composite ratio of type I fiber was significantly decreased and the composition ratio of type IIa fiber was significantly increased in the soleus muscle compared with those in the control group (Fig. 3). Both temocapril and exercise training restored the composition ratios of type I and type IIa fibers to the same levels as those of the control group (Fig. 3).

Morphological analysis of the kidney revealed that GSI

Fig. 5. Correlation between plasma leptin concentration and glomerular sclerosis index (GSI) in SHR on HFD. Symbols are () FRU, () TEM, () EX, and () TEM + EX groups. A correlation of plasma leptin concentration with GSI was evident ($r = 0.513$, $p < 0.001$).

was slightly but significantly increased in the FRU group compared with that in the control group (Fig. 4A). GSI was significantly decreased not only in the TEM group but also in the EX group compared with that in the FRU group. There were no significant differences in GSI among the control, TEM, EX and TEM + EX groups. Glomerular volume was not changed significantly by any treatment (Fig. 4B). In SHR on HFD, a significant correlation of plasma leptin concentration with GSI was found using a regression analysis (Fig. 5). There was no significant difference in RIV among the five groups (data not shown).

Discussion

In the present study, the effects of aerobic exercise using a treadmill on the function and structure of the kidneys in SHR on HFD were investigated. Chronic fructose feeding elevated blood pressure and induced modest glomerular sclerosis in the SHR. Temocapril, an ACE inhibitor, reduced blood pressure distinctly and ameliorated glomerular sclerosis in this model. On the other hand, exercise training tended to reduce blood pressure and ameliorated glomerular sclerosis to the same extent as did temocapril.

Although beneficial effects of 2-week exercise training have been demonstrated in rats on HFD (7), there are no available data on the organ-protective effects of exercise training in this model. We have demonstrated for the first time that chronic exercise training prevents renal morphological changes in SHR on HFD. Beneficial effects of exercise training on the kidneys have been demonstrated in other experimental models. In obese Zucker rats, a model of non-in-

sulin-dependent diabetes mellitus (22), and in Sprague-Dawley rats made diabetic by streptozotocin, an insulin-dependent diabetes model (23), exercise training significantly reduced the increase in fractional volume of mesangium. We and another group previously reported that exercise training significantly improved renal function and morphology in rats with subtotal nephrectomy (16, 24). Conversely, strenuous exercise superimposed on immune complex-mediated glomerulonephritis resulted in worsening of the renal function and structure in rabbits (25). Therefore, exercise may affect the function of the kidney in different ways depending on the nature of the renal injury.

Cohen and coworkers reported that lesions characteristic of diabetic nephropathy were observed in rats fed fructose and sucrose (4, 26). Such lesions, however, were not observed in the present study. The reason for the discrepancy between our results and those of the study by Cohen and coworkers is not clear. One possible reason is that they used genetically selected albino rats (4, 26), whereas we used SHR. Most experimental studies on diabetic renal disease have been performed in rats with insulin-dependent diabetes. In those studies, diabetes was induced by administration of streptozotocin (12, 23, 27). ACE inhibitors prevent the progression of diabetic nephropathy in both animal models and humans (12, 27, 28).

There are few data on the renal histology in other strains of rats fed fructose or sucrose. Park and Meyer reported that only modest renal injury was observed in Sprague-Dawley rats fed fructose for 12 months (5). Another group reported that fructose feeding for 27 weeks in SHR was not associated with increased proteinuria, decreased renal function, or prominent renal pathological changes (29). In that study, renal histological changes were minor, as in our results. In spite of the increased GSI in the FRU group, there were no significant differences in UprotV among the five groups. Urinary protein may not have been sensitive enough to reflect the modest glomerular changes in the present study. One factor that could have contributed to the modest increase in glomerular sclerosis in SHR on HFD is elevation of blood pressure. SHR, however, have a relatively low susceptibility to developing glomerular damage compared with other hypertensive strains (30, 31). Proliferation, migration, and accumulation of mesangial matrix are important biological responses of mesangial cells to injury (32). Angiotensin II (Ang II) plays an important role in this process (33, 34). We speculate that temocapril ameliorated glomerulosclerosis through the inhibition of Ang II production in SHR on HFD.

In the present study, plasma leptin level was significantly decreased by exercise training. Furthermore, GSI was positively correlated with plasma leptin concentration in rats on HFD. In cultured glomerular endothelial cells, leptin stimulates cellular proliferation and expression of transforming growth factor- β (TGF- β) (35). Chronic leptin infusion in normal rats induces proteinuria and focal glomerulosclerosis accompanied by elevated glomerular TGF- β and type IV

collagen expression (35). It is interesting that *ob/ob* mice, which are leptin-deficient, rarely develop renal disease, whereas *db/db* mice, which are hyperleptinemic, develop mesangial expansion similar to that of human diabetic nephropathy (36). Although the plasma leptin level was lower in the FRU group than in the control group, leptin may cooperate with other vasoactive factors such as Ang II and endothelin, which may play important pathophysiological roles in rats on HFD (35, 37, 38), to promote glomerular sclerosis. Therefore, a decrease in leptin levels due to exercise training may have contributed to the amelioration of the glomerular sclerosis in the present study.

Insulin-mediated glucose uptake, which may be related to muscle fiber composition, differs substantially among muscle groups (39). Type I fibers are slow twitch fibers, have an abundance of mitochondria, and work oxidatively, while type II fibers are fast twitch fibers, have fewer mitochondria, and use more glycolytic pathways (39). The former fiber type is more insulin-sensitive than the latter. Type II fibers are further subclassified as type IIa (oxidative/glycolytic) and type IIb (glycolytic) fibers. Our results are consistent with the previous reports that composite ratios of type I and type II fibers were altered in the soleus muscle of rats placed on HFD (18, 19). In the present study, temocapril restored composite ratios of type I and type II fibers to the same levels as those of the control rats, which is consistent with the previous report (18). An interesting finding is that exercise training restored the composite ratios of muscle fibers to the same degree as temocapril. Previous studies have demonstrated that the *M* value, an index of insulin sensitivity, had a positive correlation with the composite ratio of type I fibers and a negative correlation with the composite ratio of type II fibers (18, 19).

Although there was no significant change in glucose metabolism based on the blood chemistry profiles in the present study, the restoration of muscle fiber composition by the two treatments might reflect improved insulin sensitivity. Our study, however, was not designed to examine the effect of HFD, temocapril, or exercise on the peripheral sensitivity to the action of insulin, which could be evaluated by a euglycemic clamp technique (18, 19).

Hyperlipidemia has been implicated in the pathogenesis of mesangial expansion in a variety of renal diseases (40). As old rats have been reported to be refractory to the hyperlipidemic effect of HFD (41), we used young SHR in this study. There was, however, no significant lipid abnormality in the fructose-fed SHR in the present study. It is important to note that there is a discrepancy in the reported plasma insulin and triglyceride concentrations of rats fed fructose or sucrose. Some studies have shown an increase in plasma insulin and triglyceride concentrations (3, 5, 11), whereas others demonstrated no changes in plasma insulin or triglyceride concentrations (3, 42). It is also possible that HFD-induced insulin resistance is a transient phenomenon (29). As exercise training did not change the lipid profile compared with that in the

sedentary group, the improved structure of the kidney after exercise training is likely to be the result of other factors. Metabolic and neurohumoral changes associated with aerobic exercise, such as catecholamines, prostaglandins, kallikrein-kinin, and coagulability, may also be responsible for the amelioration of glomerulosclerosis in the trained rats (9). In the present study, the decreased heart rate in the EX group may suggest a reduced sympathetic nervous tone in this group. Although temocapril and exercise training might have ameliorated glomerular sclerosis through different mechanisms, their renoprotective effects were not additive in the present study. One possible explanation may be that the glomerular sclerosis in the fructose-fed rats was modest and either temocapril or exercise alone offered maximal glomerular protection in this model.

Exercise training did not reduce body weight in the fructose-fed rats in the present study. Furthermore, plasma glucose levels in the EX and TEM + EX groups were higher than that of the FRU group. These findings may have been due to the fact that the rats in the EX and TEM + EX groups consumed 17–19% more food than did the rats in the FRU group. Rats are known to feed through the night and the chow was removed from the cages on the morning of decapitation. Since the rats were not pair-fed, the influence of food intake could not be adequately evaluated in this study. Nevertheless, as mentioned before, the restoration of muscle fiber composition in the EX and TEM + EX groups may suggest improved insulin sensitivity in these groups. On the other hand, epididymal fat weight was significantly reduced in the EX and TEM + EX groups compared with that in the FRU group. Studies have shown that physical training generally results in a decrease in body fat (43). It has also been demonstrated that plasma leptin level is related to the amount of body fat (43, 44). Actually, in the present study, epididymal fat weight was found to be positively correlated with plasma leptin level. The weight gain of rats in the TEM group was less than that of rats in the FRU group. Such effects of ACE inhibitors on body weight have been demonstrated previously (45).

In summary, chronic fructose feeding induced modest glomerular sclerosis in SHR in the present study. Temocapril reduced blood pressure and ameliorated glomerular sclerosis in this model. Although exercise training was less effective than temocapril in reducing blood pressure, it was as effective as temocapril in ameliorating glomerular sclerosis in this model. In addition to the numerous pharmacological treatments, exercise training may be a useful tool to protect target organs in some diseases. Further investigation is needed to elucidate the mechanisms by which exercise training results in less histological change in the kidneys of fructose-fed rats.

References

1. Hwang IS, Ho H, Hoffman BB, Reaven GM: Fructose-induced insulin resistance and hypertension in rats. *Hypertension* 1987; **10**: 512–516.

2. el Zein M, Areas JL, Preuss HG: Long-term effects of excess sucrose ingestion on three strains of rats. *Am J Hypertens* 1990; **3**: 560–562.
3. Umeda M, Kanda T, Murakami M: Effects of angiotensin II receptor antagonists on insulin resistance syndrome and leptin in sucrose-fed spontaneously hypertensive rats. *Hypertens Res* 2003; **26**: 485–492.
4. Cohen AM, Teitelbaum A, Rosenman E: Diabetes induced by a high fructose diet. *Metabolism* 1977; **26**: 17–24.
5. Park SK, Meyer TW: The effects of fructose feeding on glomerular structure in the rats. *J Am Soc Nephrol* 1992; **3**: 1330–1332.
6. Mondon CE, Dolkas CB, Reaven GM: Site of enhanced insulin sensitivity in exercise trained rats at rest. *Am J Physiol* 1980; **239**: E169–E177.
7. Reaven GM, Ho H, Hoffman BB: Attenuation of fructose-induced hypertension in rats by exercise training. *Hypertension* 1988; **12**: 129–132.
8. Position Statement. Diabetes mellitus and exercise. *Diabetes Care* 1990; **13**: 804–805.
9. Arakawa K: Exercise, a measure to lower blood pressure and reduce other risks. *Clin Exp Hypertens* 1999; **21**: 797–803.
10. Vittinghus E, Mogensen CE: Graded exercise and protein excretion in diabetic man and the effect of insulin treatment. *Kidney Int* 1982; **21**: 725–729.
11. Reaven GM, Hoffman BB: Effects of a fructose-enriched diet on plasma insulin and triglyceride concentration in SHR and WKY rats. *Horm Metab Res* 1990; **22**: 363–365.
12. Yoshida K, Yasujima M, Kohzuki M, Kanazawa M, Abe K: Effect of chronic treatment with calcium channel blockers or angiotensin converting enzyme inhibitors on renal function in streptozotocin-treated hypertensive diabetic rats. *Hypertens Res* 1994; **17**: 35–41.
13. Yoshida K, Kohzuki M, Xu H-L, Wu X-M, Kamimoto M, Sato T: Effects of troglitazone and temocapril in spontaneously hypertensive rats with chronic renal failure. *J Hypertens* 2001; **19**: 503–510.
14. Yoshida K, Xu H-L, Kawamura T, Ji L, Kohzuki M: Chronic angiotensin converting enzyme inhibition and angiotensin II antagonism in rats with chronic renal failure. *J Cardiovasc Pharmacol* 2002; **40**: 533–542.
15. Kawamura T, Yoshida K, Sugawara A, et al: Impact of exercise and angiotensin converting enzyme inhibition on tumor necrosis factor- α and leptin in fructose-fed hypertensive rats. *Hypertens Res* 2002; **25**: 919–952.
16. Kohzuki M, Kamimoto M, Wu X-M, et al: Renal protective effects of chronic exercise and antihypertensive therapy in hypertensive rats with chronic renal failure. *J Hypertens* 2001; **19**: 1877–1882.
17. Shepherd RE, Gollnick PD: Oxygen uptake of rats at different work intensities. *Pflügers Arch* 1976; **362**: 219–222.
18. Higashiura K, Ura N, Takada T, et al: The effect of an angiotensin-converting enzyme inhibitor and an angiotensin II receptor antagonist on insulin resistance in fructose-fed rats. *Am J Hypertens* 2000; **13**: 290–297.
19. Takada M, Ura N, Higashiura K, Murakami H, Togashi N, Shimamoto K: Effects of cilnidipine on muscle fiber composition, capillary density and muscle blood flow in fructose-fed rats. *J Hypertens* 2003; **21**: 1877–1882.

- tose-fed rats. *Hypertens Res* 2001; **24**: 565–572.
20. van Damme B, Koudstaal J: Measuring glomerular diameters in tissue sections. *Virchows Arch A Pathol Anat Histol* 1976; **369**: 283–291.
21. Bennett WM, Walker RG, Kincaid-Smith P: Renal cortical interstitial volume in mesangial IgA nephropathy: dissociation from creatinine clearance in serially biopsied patients. *Lab Invest* 1982; **47**: 330–335.
22. Ward KM, Mahan JD, Sherman WM: Aerobic training and diabetic nephropathy in the obese Zucker rats. *Ann Clin Lab Sci* 1994; **24**: 266–277.
23. Albright AL, Mahan JD, Ward KM, Sherman WM, Roehrig KL, Kirby TE: Diabetic nephropathy in an aerobically trained rat model of diabetes. *Med Sci Sports Exerc* 1995; **27**: 1270–1277.
24. Heifets M, Davis TA, Tegtmeier E, Klahr S: Exercise training ameliorates progressive renal disease in rats with subtotal nephrectomy. *Kidney Int* 1987; **32**: 815–820.
25. Cornacoff JB, Hebert LA, Sharma HM, Bay WH, Young DC: Adverse effect of exercise on immune complex-mediated glomerulonephritis. *Nephron* 1985; **40**: 292–296.
26. Rosenmann E, Teitelbaum M, Cohen AM: Nephropathy in sucrose-fed rats, electron and light microscopic studies. *Diabetes* 1971; **20**: 803–810.
27. Yoshida K, Kohzuki M, Yasujima M, Kanazawa M, Abe K: Effects of benidipine, a calcium antagonist, on urinary kallikrein excretion and renal impairment in experimental diabetes. *J Hypertens* 1996; **14**: 215–222.
28. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy: the collaborative study group. *N Engl J Med* 1993; **329**: 1456–1462.
29. van der Schaaf MR, Joles JA, van Tol A, Koomans HA: Long-term fructose versus corn starch feeding in the spontaneously hypertensive rat. *Clin Sci* 1995; **88**: 719–725.
30. Raij L, Azar S, Keane WF: Role of hypertension in progressive glomerular immune injury. *Hypertension* 1985; **7**: 398–404.
31. O'Donnell MP, Kasiske BL, Keane WF: Risk factors for glomerular injury in rats with genetic hypertension. *Am J Hypertens* 1989; **2**: 9–13.
32. Lee LK, Meyer TW, Pollock AS, Lovett DH: Endothelial injury initiates glomerular sclerosis in the rat remnant kidney. *J Clin Invest* 1995; **96**: 953–964.
33. Anderson S, Meyer TW, Rennke HG, Brenner BM: Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 1985; **76**: 612–619.
34. Kagami S, Border WA, Miller DE, Noble NA: Angiotensin II stimulates extracellular matrix protein synthesis through induction of transforming growth factor-beta expression in rat glomerular mesangial cells. *J Clin Invest* 1994; **93**: 2431–2437.
35. Wolf G, Hamann A, Han DC, et al: Leptin stimulates proliferation and TGF- β expression in renal glomerular endothelial cells: potential role in glomerulosclerosis. *Kidney Int* 1999; **56**: 860–872.
36. Cohen MP, Sharma K, Jin Y, Wu VY, Tomaszewski J, Ziyadeh FN: Prevention of diabetic nephropathy in *db/db* mice with glycated albumin antagonist: a novel treatment strategy. *J Clin Invest* 1995; **95**: 2338–2345.
37. Navarro-Cid J, Maeso R, Perez-Vizcaino, et al: Effects of losartan on blood pressure, metabolic alterations, and vascular reactivity in the fructose-induced hypertensive rats. *Hypertension* 1995; **26**: 1074–1078.
38. Juan C-C, Fang VS, Hsu Y-P, et al: Overexpression of vascular endothelin-1 and endothelin-A receptors in a fructose-induced hypertensive rat model. *J Hypertens* 1998; **16**: 1775–1782.
39. James DE, Jenkins AB, Kraegen EW: Heterogeneity of insulin action in individual muscles *in vivo*: euglycemic clamp studies in rats. *Am J Physiol* 1985; **248**: E567–E574.
40. Kasiske BL, O'Donnell MP, Cleary MP, Keane WF: Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats. *Kidney Int* 1988; **33**: 667–672.
41. Nassir F, Mazur A, Felgines C, Rayssiguier Y: Age-related response to dietary fructose in the rat: discrepancy in triglyceride and apolipoprotein B synthesis as a possible mechanism for fatty liver induction in adults rats. *Proc Soc Exp Biol Med* 1993; **204**: 180–183.
42. el Zein M, Areas JL, Knapka J, et al: Excess sucrose and glucose ingestion acutely elevate blood pressure in spontaneously hypertensive rats. *Am J Hypertens* 1990; **3**: 380–386.
43. Kohrt WM, Landt M, Birge SJ Jr: Serum leptin levels are reduced in response to exercise training, but not hormone replacement therapy, in older women. *J Clin Endocrinol Metab* 1996; **81**: 3980–3985.
44. Considine RV, Sinha MK, Heiman ML, et al: Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996; **334**: 292–295.
45. Yoshida K, Casley DJ, Johnston CI: Angiotensin-converting enzyme inhibition and salt in experimental myocardial infarction. *J Cardiovasc Pharmacol* 1998; **32**: 357–365.