

Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats

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Sánchez-Lozada LG, Tapia E, Jiménez A, Bautista P, Cristóbal M, Nepomuceno T, Soto V, Ávila-Casado C, Nakagawa T, Johnson RJ, Herrera-Acosta J, Franco M. Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. *Am J Physiol Renal Physiol* 292: F423–F429, 2007. First published August 29, 2006; doi:10.1152/ajprenal.00124.2006.—Fructose intake has been recently linked to the epidemic of metabolic syndrome and, in turn, the metabolic syndrome has been epidemiologically linked with renal progression. The renal hemodynamic effects of fructose intake are unknown, as well as the effects of different routes of administration. Metabolic syndrome was induced in rats over 8 wk by either a high-fructose diet (60%, F60, $n = 7$) or by adding fructose to drinking water (10%, F10, $n = 7$). Body weight and food and fluid intake of each rat were measured weekly during the follow-up. At baseline and at the end of wk 8, systolic blood pressure, plasma uric acid, and triglycerides were measured. At the end of week 8 glomerular hemodynamics was evaluated by micropuncture techniques. Wall thickening in outer cortical and juxtamedullary afferent arterioles was assessed by immunohistochemistry and computer image analysis. Fructose administration either in diet or drinking water induced hypertension, hyperuricemia, and hypertriglyceridemia; however, there was a progressive increment in these parameters with higher fructose intake ($C < F10 < F60$). In addition, the F60 rats developed kidney hypertrophy, glomerular hypertension, cortical vasoconstriction, and arteriopathy of preglomerular vessels. In conclusion, fructose-induced metabolic syndrome is associated with renal disturbances characterized by renal hypertrophy, arteriopathy, glomerular hypertension, and cortical vasoconstriction. These changes are best observed in rats administered high doses (60% diet) of fructose.

uric acid; obesity

METABOLIC SYNDROME IS A PATHOPHYSIOLOGICAL entity characterized by insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and obesity (27). The risk for developing diabetes type 2, cardiovascular disease, and renal disease is increased with increasing manifestations of the various components of the syndrome within any individual.

The macronutrient content of the diet has been linked to the metabolic syndrome. Recently, consumption of dietary fructose has been suggested to be one of the environmental factors contributing to the development of obesity and the accompanying abnormalities of the metabolic syndrome (7). In fact, a

well-known experimental model of metabolic syndrome is induced by high consumption of fructose; this model induces hypertension, hypertriglyceridemia, hyperinsulinemia, and insulin resistance in rats (12). Fructose consumption is able to produce these effects because fructose is more lipogenic than glucose and usually causes greater elevations of triglycerides (10), which, in turn, increases intramyocellular triglyceride content in the skeletal muscle, causing insulin resistance.

Fructose is unique among sugars in that it also results in a marked synthesis of uric acid; this effect is secondary to fructose phosphorylation by fructokinase (also called ketohexokinase), which uses ATP as phosphate donor. Accumulation of fructose-1-phosphate causes depletion of hepatic ATP and increases the degradation of nucleotides to uric acid (10). In effect, it is well known that healthy individuals show a transient rise in serum uric acid following an oral or intravenous challenge of fructose, and this is greater in gouty patients or their siblings (8, 24).

Recently, the role of fructose-induced hyperuricemia in the development of metabolic syndrome was examined (20). In fructose-fed rats administration of allopurinol lowered uric acid levels and significantly reduced blood pressure, improved basal and stimulated insulin levels, corrected the hypertriglyceridemia, and prevented the weight gain (20). Since endothelial dysfunction is a hallmark of insulin resistance, it was interesting to find that vasorelaxation of arterial rings in response to acetylcholine, a process that is mediated by nitric oxide (NO), was blocked by uric acid (20). Thus uric acid-induced endothelial dysfunction with impaired NO production may participate in the development of insulin resistance in fructose-fed rats. On the other hand, renal arteriolar damage, glomerular hypertension, and cortical vasoconstriction have also been reported to be induced by hyperuricemia (29, 30) but it is not known whether this also occurs in fructose-overloaded rats.

Fructose-induced metabolic syndrome can be created experimentally either by feeding rats with a high-fructose diet (60%) (12, 20) or by adding fructose to drinking water (10–20%) (5); nevertheless, different routes of administration might induce a variable consumption of fructose and, in turn, result in variable manifestations of metabolic syndrome components.

Therefore, we hypothesized that different routes of fructose administration in rats probably induce variable degrees of metabolic syndrome that may induce different physiological and morphological renal responses.

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METHODS

Three groups of male Sprague-Dawley rats were studied (290–350 g, Harlan Mexico). Control group (C; $n = 7$) received regular diet (57.3% of carbohydrate, 41.2% as starch. cat. 2018S Harlan Teklad, Indianapolis, IN). Fructose 60 group (F60; $n = 7$) was fed a 60% fructose diet (Harlan Teklad). Fructose 10 group (F10; $n = 7$) was fed a regular diet, and fructose was administered as a 10% solution (prepared every 2 days) in drinking water. Animals consumed diets and fluids ad libitum. All groups were followed for 8 wk. Experiments were approved by the Ethics Committee of Instituto Nacional de Cardiología Ignacio Chavez.

Measurements. Body weight, food intake, and fluid intake of each rat were measured weekly during the follow-up. At baseline and at the end of 8 wk, systolic blood pressure (SBP) was measured in conscious rats by tail cuff sphyngomanometer (XBP-1000 Kent Scientific, Torrington, CT). All animals were preconditioned for blood pressure measurements 1 wk before each experiment. Plasma uric acid (Diagnostic Chem) and triglycerides (Spinreact) were measured at the same time points. In addition, plasma glucose (Spinreact) was measured at the end of *week 8* in C, F10, and F60 groups.

In all rats, a 24-h urine sample to assess the presence of albuminuria was collected in metabolic cages at the end of *week 8* of the study. Quantification of urinary rat albumin was performed by ELISA analysis (Nephra, Exocell, Philadelphia, PA).

Micropuncture. Animals were anesthetized with pentobarbital sodium (30 mg/kg ip) and placed on a thermoregulated table to maintain body temperature at 37°C. Trachea, jugular veins, femoral arteries, and the left ureter were catheterized with polyethylene tubing (PE-240, PE-50, and PE-10). The left kidney was exposed, placed in a Lucite holder, sealed with agar, and covered with Ringer solution. Mean arterial pressure (MAP) was monitored with a pressure transducer (model PT300; Grass Telefactor, Warwick, RI) connected to the catheter in the femoral artery and recorded on a polygraph (Grass Instruments, Quincy, MA). Blood samples were taken periodically and replaced with blood from a donor rat. Rats were maintained under euvoletic conditions by infusion of 10 ml/kg of body weight of isotonic rat plasma during surgery, followed by an infusion of 25% polyfructosan, at 2.2 ml/h (Inutest, Fresenius Kabi, Linz, Austria). After 60 min, five to seven samples of proximal tubular fluid were obtained to determine flow rate and polyfructosan concentrations. Intratubular pressure under free-flow (FF) and stop-flow (SFP) conditions and peritubular capillary pressure (P_c) were measured in other proximal tubules with a servo-null device (Servo Nulling Pressure System; Instrumentation for Physiology and Medicine, San Diego, CA). Glomerular colloid osmotic pressure was estimated from protein concentrations obtained from blood of the femoral artery (C_a) and surface efferent arterioles (C_e). Polyfructosan was measured in plasma and urine samples by the anthrone-based technique of Davidson and Sackner (6).

The volume of fluid collected from individual proximal tubules was estimated from the length of the fluid column in a constant bore capillary tube of known internal diameter. The concentration of tubular polyfructosan was measured by microfluorometric method of Vurek and Pegram (36). Protein concentration in afferent and efferent samples was determined according to the method of Viets et al. (35). Glomerular filtration rate (GFR), single-nephron GFR, glomerular capillary hydrostatic pressure (PGC), single-nephron plasma flow (QA), afferent (AR), efferent (ER) resistances, and K_f were calculated with equations previously reported (2).

Renal histology and quantification of morphology. After the micropuncture study, kidneys were washed by perfusion with PBS, fixed with 4% paraformaldehyde, and weighed. Renal biopsies were embedded in paraffin. Four-micrometer sections of fixed tissue were stained with periodic acid Schiff (PAS) reagent. Arteriolar morphology was assessed in outer cortical and juxtamedullary (JM) nephrons by indirect peroxidase immunostaining using a monoclonal rat anti-

human antibody specific for cardiac, smooth and striated muscle α actin and smooth muscle γ actin (Clone HHF35, DAKO, Carpinteria, CA) (15). Afferent arterioles were identified by their location adjacent to the vascular pole of the glomerular tuft, the presence of an internal elastic lamina, and by having fewer thin flattened endothelial cells than the efferent arteriole (25, 33). We excluded from measurement all vessels showing more than one layer of endothelium as suggested by Clapp and Croker (4). Renal sections incubated with normal rabbit serum were used as negative controls (29).

For each arteriole, the outline of the vessel and its internal lumen (excluding the endothelium) were generated using computer analysis to calculate the total medial area (outline-inline), in 5–10 arterioles per biopsy. The media/lumen ratio was calculated by the outline/inline relationship (29). Quantifications were performed blinded.

Previously, it was reported that mesangial cells change their phenotype and expressed α -smooth muscle actin in the glomeruli during the development of hypertensive renal damage (14). Thus we employed the same sections used for the assessment of arteriolar morphology to evaluate the immunostaining of muscle actin in mesangial areas. Twenty to 30 outer cortical and available juxtamedullary glomeruli ($\times 100$) per biopsy were analyzed using Image-Pro-Plus 5.0 (Media Cybernetics, Silver Spring, MD). Positive brown color mesangial areas were selected and quantified in pixel units in each glomerulus. The mean amount of positive brown areas/glomerulus was obtained by averaging the values from the examined glomeruli.

In addition, the presence of glomerulosclerosis and tubulointerstitial fibrosis was assessed by Masson's trichrome staining in all groups of rats.

Statistical analysis. Values are expressed as means \pm SE. Groups were analyzed by one-way ANOVA. Comparisons among groups were performed with Bonferroni's multiple comparison test. Comparisons between F10 vs. F60 were done with unpaired *t*-test. The relationship between variables was assessed by correlation analysis. Statistical analysis was performed with Prism version 3.03 (GraphPad Software, San Diego, CA). $P < 0.05$ was considered significant.

RESULTS

General parameters. Baseline values of SBP, plasma uric acid (UA), triglycerides (TG), and body weight (BW) are depicted in Fig. 1. We did not find differences in mean values of SBP (C: 115 ± 5 mmHg, F10: 123 ± 5 mmHg, F60: 107 ± 3 mmHg), UA (C: 0.53 ± 0.03 mg/dl, F10: 0.34 ± 0.045 mg/dl, F60: 0.43 ± 0.09 mg/dl), and BW (C: 325 ± 4 g, F10: 330 ± 5 g, F60: 328 ± 5 mg/dl) among the groups. Fasting TG levels were < 150 mg/dl in all groups at baseline, although they were slightly but significantly lower in the F10 group (C: 98 ± 11 mg/dl, F10: 50 ± 8 mg/dl, F60: 94 ± 10 mg/dl; $P < 0.05$ vs. C and F60).

Mean daily water and food consumption in control animals were 17 ± 0.21 g and 37 ± 0.7 ml of water. Similarly, the F60 group ingested 17 ± 0.41 g and drank 34 ± 0.8 ml of water (C vs. F60, $P =$ not significant). F10 rats ate 30% less food and drank 80% more water compared with C and F60 groups (12 ± 0.27 g, $P < 0.001$ vs. C and F60; 65 ± 6 ml, $P < 0.001$ vs. C and F60). The caloric intake was calculated based on daily food and fluid intakes and the caloric values of regular diet (3.3 Kcal/g) and fructose (4 Kcal/g). Fructose intake of rats accounted for $38 \pm 2\%$ of caloric intake in F10 and 66% in F60 ($P < 0.001$).

Absolute values of BW, SBP, and plasma UA and TG at *week 8* are depicted in Table 1. To better understand the changes induced by fructose intake, we calculated the ratio baseline/*week 8* of body weight, SBP, UA, and TG in each rat

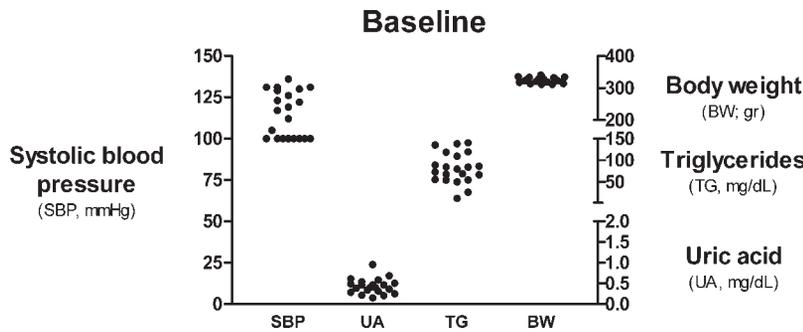


Fig. 1. Baseline values of systolic blood pressure (SBP), plasma uric acid (UA), triglycerides (TG), and body weight (BW).

and compared them among the groups. There were no significant differences in body weight gain among groups (C: 1.16 ± 0.02 , F10: 1.18 ± 0.03 , F60: 1.21 ± 0.01). SBP, UA, and TG changes were significantly higher in F10 and F60 compared with C (SBP: C, 0.96 ± 0.05 ; F10, 1.29 ± 0.07 ; F60, 1.39 ± 0.04 ; C vs. F10 and F60, $P < 0.05$. UA: C, 0.97 ± 0.19 ; F10, 2.97 ± 0.42 ; F60, 3.89 ± 0.94 , C vs. F10 and F60, $P < 0.05$. TG: C, 0.84 ± 0.06 ; F10, 2.20 ± 0.42 ; F60, 3.16 ± 0.32 , C vs. F10 and F60, $P < 0.05$). Although we did not find statistical differences in the ratios of BW, SBP, UA, and TG between F10 and F60, we observed a progressive increment in these parameters coupled with higher fructose intake (C<F10<F60). In addition, we found a linear relationship between fructose caloric intake vs. absolute values of UA and TG at week 8 (UA: $r = 0.57$, $P = 0.03$; TG: $r = 0.77$, $P = 0.001$) and between plasma uric acid and SBP ($r = 0.54$, $P < 0.01$).

Finally, we did not find differences in plasma glucose (C, 121 ± 6 mg/dl; F10, 107 ± 6 mg/dl; F60, 111 ± 4 mg/dl; $P =$ not significant; Table 1) and urinary albumin excretion (C, 11.6 ± 0.15 mg/dl; F10, 11.4 ± 0.22 mg/dl; F60, 11.1 ± 0.29 mg/dl; $P =$ not significant) among groups at the end of week 8.

Glomerular hemodynamics. Similarly to SBP, MAP was significantly higher in F10 and F60 groups compared with C rats (C: 116 ± 5 mmHg; F10: 145 ± 5 mmHg; F60: 142 ± 4 mmHg; C vs. F10 and F60, $P < 0.01$). Total GFR was similar among the groups (C: 0.78 ± 0.05 ml/min; F10: 1.00 ± 0.05 ml/min; F60: 1.02 ± 0.11 ml/min). In contrast, higher fructose caloric intake in F60 group was associated with a significant decrement of cortical single-nephron GFR (C: 38 ± 2 nl/min; F10: 50 ± 6 nl/min; F60: 25 ± 3 nl/min) and ultrafiltration coefficient (C: 0.058 ± 0.009 nl·s⁻¹·mmHg⁻¹; F10: 0.060 ± 0.006 nl·s⁻¹·mmHg⁻¹; F60: 0.025 ± 0.003 nl·s⁻¹·mmHg⁻¹) compared with C and F10 groups ($P < 0.05$; Fig. 2). In addition, glomerular plasma flow was numerically lower compared with C and reached statistical significance compared with F10 (C: 171 ± 11 nl/min; F10: 179 ± 18 nl/min; F60: 111 ± 15 nl/min; F10 vs. F60, $P < 0.05$; Fig. 2). The decrements in single-

nephron GFR and glomerular plasma flow in F60 resulted from the significant increase of afferent (C, 1.8 ± 0.15 dyn·s·cm⁻⁵; F10, 2.6 ± 0.28 dyn·s·cm⁻⁵; F60, 3.5 ± 0.41 dyn·s·cm⁻⁵; C vs. F60, $P < 0.01$) and efferent resistances (C, 1.0 ± 0.09 dyn·s·cm⁻⁵; F10, 1.1 ± 0.12 dyn·s·cm⁻⁵; F60, 1.7 ± 0.23 dyn·s·cm⁻⁵; F60 vs. C and F10, $P < 0.05$). Despite cortical vasoconstriction, F60 animals developed glomerular hypertension compared with the C group (C: 47 ± 1 mmHg; F10: 49 ± 1 mmHg; F60: 53 ± 1 mmHg; C vs. F60, $P < 0.01$; Fig. 2). In addition, we found a positive linear relationship between MAP and glomerular pressure ($r = 0.49$, $P < 0.05$) and a negative correlation between plasma uric acid and ultrafiltration coefficient ($r = -0.41$, $P < 0.05$).

Kidney size and renal histology. F60 rats had larger kidneys as percentage of BW than C and F10 groups (C: $0.36 \pm 0.02\%$; F10: $0.34 \pm 0.01\%$; F60: $0.40 \pm 0.01\%$; F10 vs. F60, $P < 0.01$). In addition, we found a positive correlation between fructose caloric intake and kidney size as percent of BW ($r = 0.57$, $P = 0.03$).

Figure 3 shows the renal arteriolar morphology in outer cortical glomeruli. We observed a progressive increment of arteriolar wall area with increasing fructose caloric intake, which was statistically significant when comparing Controls vs. F60 (C: 227 ± 8 μm²; F10: 264 ± 7 μm²; F60: 298 ± 16 μm²; C vs. F60, $P < 0.01$). In JM nephrons, we find a similar pattern, although it did not reach statistical significance (C: 210 ± 7 μm²; F10: 240 ± 30 μm²; F60: 289 ± 21 μm²; $P =$ not significant).

We also found positive linear relationships between plasma uric acid and outer cortical glomeruli arteriolar area ($r = 0.77$, $P < 0.0001$). Additionally, outer cortical glomeruli arteriolar area and glomerular pressure ($r = 0.57$, $P = 0.007$), and afferent resistance ($r = 0.49$, $P = 0.02$) correlated positively.

We did not find statistical significant differences in the media to lumen relationship among the groups in cortical (C: 2.4 ± 0.35 ; F10: 2.6 ± 0.3 ; F60: 2.8 ± 0.4 ; $P =$ not significant) and juxtamedullary nephrons (C: 2.0 ± 0.3 ; F10: 2.7 ± 0.5 ; F60: 1.7 ± 0.2 ; $P =$ not significant). However, when we compared cortical M/L vs. juxtamedullary M/L in the same group, we found a significant difference in F60 group ($P = 0.02$).

Additionally, we found a faint and nonsignificant α-actin staining in cortical (C: 197 ± 27 pixels/glomeruli; F10: 158 ± 20 pixels/glomeruli; F60: 134 ± 14 pixels/glomeruli; $P =$ not significant) and juxtamedullary (C: 253 ± 37 pixels/glomeruli; F10: 224 ± 23 pixels/glomeruli; F60: 177 ± 15 pixels/glomeruli) glomerular mesangial areas. Similarly, no differences were found in glomerulosclerosis and tubulointerstitial

Table 1. BW, SBP, and plasma UA, TG, and glucose at week 8

	BW, g	SBP, mmHg	UA, mg/dl	TG, mg/dl	Glucose, mg/dl
Control	376.7±5.5	108.3±4.2	0.51±0.10	79.1±8.5	121±6
F10	390.0±6.5	155.7±3.6*	0.86±0.06*	93.9±8.3	107±6
F60	397.6±4.5	147.8±2.4*	1.19±0.11*	280.1±16.5†	111±4

Values are means ± SE. BW, body weight; SBP, systolic blood pressure; UA, uric acid; TG, triglycerides. * $P < 0.05$ vs. C. † $P < 0.05$ vs. F10.

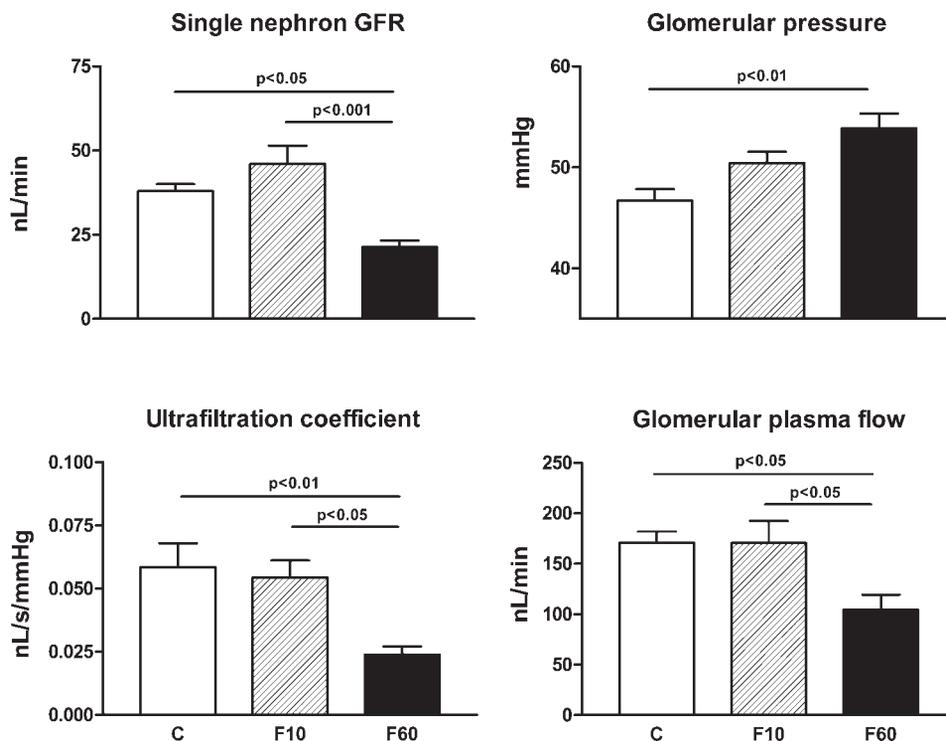


Fig. 2. Glomerular hemodynamics in control, F10, and F60 groups at the end of week 8.

fibrosis among groups and the Masson's trichrome-stained sections in F10 and F60 rats were comparable to Control animals.

DISCUSSION

In the present study, we examined the effect of two different methods of fructose administration in the development of metabolic syndrome and on glomerular hemodynamic changes and afferent arteriole morphology. Fructose administration either in drinking water or in the diet was able to induce systemic hypertension, hyperuricemia, and hypertriglyceridemia. However, 60% fructose diet resulted in a higher fructose caloric intake, which was associated with worsening metabolic syndrome parameters as well as renal arteriolar damage, glomerular hypertension, and cortical vasoconstriction. These data thus demonstrate a direct relationship between increasing fructose consumption and worsening features of the metabolic syndrome with deleterious effects on renal hemodynamics and morphology.

There is clinical and epidemiological evidence that suggests a progressive association between fructose consumption and the development of metabolic syndrome (7). Indeed, a marked increase in obesity and metabolic syndrome in the last 20 years within the United States has been linked to a 30% overall increase in fructose ingestion, in part, because of the introduction of high fructose corn syrup as a sweetener in soft drinks and other foods (22). In the present study, we observed a gradual but mild increment in blood pressure, plasma uric acid, and triglycerides with increasing caloric intake of fructose (C<F10<F60) supporting the causal role of greater consumption of fructose with the worsening of metabolic syndrome parameters. Although we did not observe changes in plasma glucose at the end of the study among the groups, this finding

is not atypical in this experimental model characterized by insulin resistance instead of hyperglycemia (12, 20).

Recent epidemiological evidence indicates that metabolic syndrome may be a risk factor for renal damage and is also a predictor of poor outcome in patients with chronic renal failure (3, 13, 17). In this regard, we found that higher fructose intake was associated with kidney hypertrophy; in other pathophysiological conditions such as diabetes mellitus, the development of irreversible renal changes is always preceded by early hypertrophic processes (31). Since glomerular hemodynamics changes are considered one of the main factors that lead to renal damage, we determined whether fructose-induced metabolic syndrome was able to produce glomerular hemodynamic disturbances. While we found that fructose induced features of metabolic syndrome, either in diet or drinking water, only rats that received 60% fructose diet developed glomerular hypertension and cortical vasoconstriction as indicated by a significant decrease of single-nephron GFR and ultrafiltration coefficient and a rise of afferent and efferent resistances. Due to the fact that glomerular hemodynamics are determined by microvascular structure and function (28), it was interesting to find that F60 rats developed thickening of the vascular wall of the afferent arterioles in outer cortical nephrons. We previously showed that arteriopathy of preglomerular vessels has a detrimental impact in glomerular function in hyperuricemic rats (29). In this study, we confirmed this association since arteriolar area and glomerular pressure ($r = 0.57$, $P = 0.007$), as well as arteriolar area and afferent resistance, ($r = 0.49$, $P = 0.02$) correlated positively. In addition, we found a positive linear relationship between MAP and glomerular pressure ($r = 0.49$, $P < 0.05$); this finding

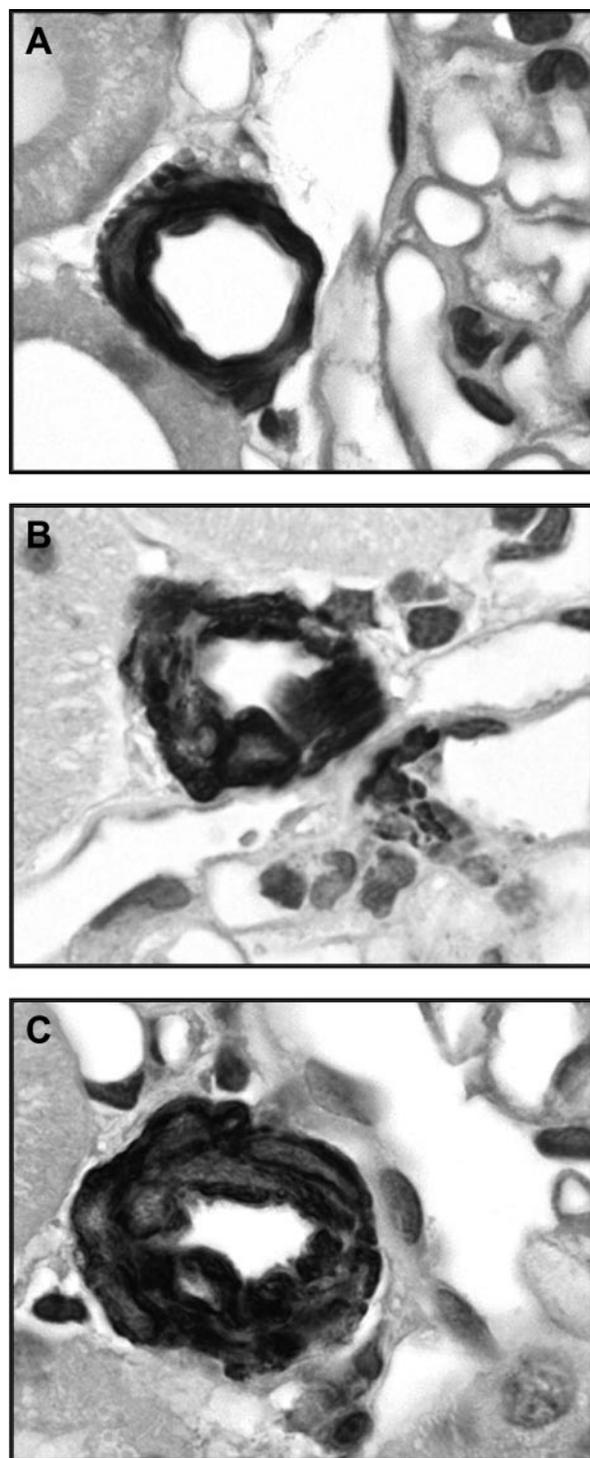


Fig. 3. Afferent arteriolar morphology in outer cortical nephrons in Control (A), F10 (B), and F60 (C) groups ($\times 1,000$).

suggests an impairment of the autoregulatory capacity of preglomerular vessels in F60 rats.

We do not have an explanation why mild differences in blood pressure, plasma UA, and TGs produced such a considerable effect on glomerular hemodynamics in the F60 rats. It was also interesting that F10 rats did not demonstrate cortical vasoconstriction; however, fructose in drinking water induced

a marked increment in water consumption; thus, volume expansion in F10 rats may have had a renal vasodilatory effect.

It is assumed that glomerular hemodynamic changes precede structural damage. In the present study, functional alterations in cortical nephrons in F60 rats were not accompanied by increased expression of mesangial α -actin, glomerulosclerosis, or tubulointerstitial fibrosis. In addition, urinary excretion of albumin was normal in the fructose-treated groups. Thus these findings suggest that, at this time point, renal alterations resulting in metabolic syndrome are limited to glomerular hemodynamic changes and that it likely takes a more prolonged period of time to produce glomerular or tubulointerstitial structural lesions. Indeed, we recently found that chronic feeding of fructose (60%) in the remnant kidney model does accelerate renal progression (Gersch M and Johnson R, unpublished data).

On the other hand, the selective alteration of superficial nephron dynamics implies a correlative increase in filtration in deeper nephrons as total GFR did not change in the F60 group. In this regard, there are a number of anatomical and functional differences between cortical and JM nephrons. JM glomeruli are larger and GFR is also higher than those of cortical nephrons (1). Hence, it has been suggested that in chronic arterial hypertension and ischemic nephropathies, such as may be occurring in F60 rats, that JM nephrons undergo a disproportionate rise in SNGFR, presumably associated with excessive high PGC and/or blood flow (23). In this study, we found a significant lower M/L ratio in JM compared with cortical afferent arterioles in F60 group, implying that JM nephrons have a larger lumen which could be associated with a higher blood flow in this population. This finding is in agreement with an increased GFR in deeper nephrons.

Hyperuricemia is considered a component of the metabolic syndrome. A unique feature of fructose ingestion is that it produces an increment of UA levels due to its hepatic catabolic pathway (10). In the present study, plasma UA levels correlated with fructose ingestion even in individual animals as demonstrated by the positive correlation between %fructose caloric intake and UA at *week 8*. Previously, we demonstrated that rats made hyperuricemic by inhibiting uricase with oxonic acid had increased blood pressure, afferent arteriole thickening, glomerular hypertension, and cortical vasoconstriction (29). In the present study, we found positive linear relationships between plasma uric acid and SBP ($r = 0.54$, $P < 0.01$) and arteriolar area ($r = 0.64$, $P < 0.001$) and a negative correlation with ultrafiltration coefficient, a marker of glomerular vasoconstriction ($r = -0.41$, $P < 0.05$). Therefore, higher UA levels induced by 60% fructose diet may be partially responsible for the glomerular hemodynamic alterations.

Several studies have shown that ANG II plays an important role in the alterations induced by high fructose consumption in rats. Actions of ANG II in this model are associated with the development of hypertension, suppression of adiponectin secretion (26), increase of adipocyte size (9), and generation of oxidative stress (32). In addition, blockade of ANG II abolished the increased VSMC proliferation, restored eNOS activity (19), and improved the insulin sensitivity (11). Since hyperuricemia is associated with activation of RAS (18, 21), it is tempting to speculate that increased synthesis of ANG II in this model could be secondary to the rise of plasma uric acid.

In summary, our results demonstrate several important new findings potentially related to the ongoing epidemic of metabolic syndrome. First, we provide evidence that increasing amounts of fructose result in increasing features of the metabolic syndrome. Second, we demonstrate that fructose-induced metabolic syndrome results in renal hypertrophy, afferent arteriopathy, glomerular hypertension, and renal vasoconstriction. These changes are similar to what we have observed with experimental hyperuricemia (29), and indeed, in previous experimental studies we have been able to largely block the features of fructose-induced metabolic syndrome by lowering serum UA (20). This latter finding is all the more relevant since humans lack uricase and hence develop hyperuricemia more readily than rodents in response to diet (16). Indeed, the administration of small doses of an uricase inhibitor to rats fed fructose dramatically increases the serum UA (34). Thus, while large doses (>60% caloric intake) of fructose were needed to observe the renal hemodynamic effects in these rats, it is likely that lower doses would be necessary in humans. Since the average fructose intake in young adults may approach 10–20% of overall caloric intake (7, 22), the observations in this study may be of great clinical relevance to the effects of fructose on the metabolic syndrome and the kidney in humans. Further studies to determine the effect of lowering UA on the renal hemodynamic and morphological changes in fructose-induced metabolic syndrome are planned.

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GRANTS

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DISCLOSURES

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