

A causal role for uric acid in fructose-induced metabolic syndrome

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Nakagawa, Takahiko, Hanbo Hu, Sergey Zharikov, Katherine R. Tuttle, Robert A. Short, Olena Glushakova, Xiaosen Ouyang, Daniel I. Feig, Edward R. Block, Jaime Herrera-Acosta, Jawaharlal M. Patel, and Richard J. Johnson. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 290: F625–F631, 2006. First published October 18, 2005; doi:10.1152/ajprenal.00140.2005.—The worldwide epidemic of metabolic syndrome correlates with an elevation in serum uric acid as well as a marked increase in total fructose intake (in the form of table sugar and high-fructose corn syrup). Fructose raises uric acid, and the latter inhibits nitric oxide bioavailability. Because insulin requires nitric oxide to stimulate glucose uptake, we hypothesized that fructose-induced hyperuricemia may have a pathogenic role in metabolic syndrome. Four sets of experiments were performed. First, pair-feeding studies showed that fructose, and not dextrose, induced features (hyperinsulinemia, hypertriglyceridemia, and hyperuricemia) of metabolic syndrome. Second, in rats receiving a high-fructose diet, the lowering of uric acid with either allopurinol (a xanthine oxidase inhibitor) or benzbromarone (a uricosuric agent) was able to prevent or reverse features of metabolic syndrome. In particular, the administration of allopurinol prophylactically prevented fructose-induced hyperinsulinemia (272.3 vs. 160.8 pmol/l, $P < 0.05$), systolic hypertension (142 vs. 133 mmHg, $P < 0.05$), hypertriglyceridemia (233.7 vs. 65.4 mg/dl, $P < 0.01$), and weight gain (455 vs. 425 g, $P < 0.05$) at 8 wk. Neither allopurinol nor benzbromarone affected dietary intake of control diet in rats. Finally, uric acid dose dependently inhibited endothelial function as manifested by a reduced vasodilatory response of aortic artery rings to acetylcholine. These data provide the first evidence that uric acid may be a cause of metabolic syndrome, possibly due to its ability to inhibit endothelial function. Fructose may have a major role in the epidemic of metabolic syndrome and obesity due to its ability to raise uric acid.

obesity; insulin resistance

METABOLIC SYNDROME CONSISTS of a cluster of cardiovascular disease risk factors that include obesity, glucose intolerance, hyperinsulinemia, dyslipidemia, and hypertension (32). The prevalence of metabolic syndrome is increasing and now affects 27% of the population in the United States (11). The epidemic correlates with pronounced changes in the environment, behavior, and lifestyle and is considered one of the main threats to human health worldwide. Metabolic syndrome confers a greater than threefold increased risk for cardiovascular

mortality (20). It is thus critical to identify mechanisms and strategies for preventing or treating this serious health problem.

As obesity and type 2 diabetes have escalated to epidemic proportions (28), the causal role of dietary components must be considered. The last 25 years have witnessed a marked increase in total per capita fructose intake, primarily in the form of sucrose (a disaccharide consisting of 50% fructose) and high-fructose corn syrup (HFCS; 55% fructose content) (3). Fructose intake is linked to the epidemic of obesity and diabetes (22, 35). Soft drink intake (high in HFCS) is associated with an increased risk for obesity in adolescents (22) and for type 2 diabetes in young and middle-aged women (35). Excess fruit juice (also rich in fructose) is associated with the development of obesity in children (8). Fructose-fed rats also develop features of metabolic syndrome (15).

One distinction between fructose and glucose is that fructose raises serum uric acid (38). Elevated serum uric acid predicts the development of obesity and hypertension (23). This raised the possibility that uric acid may have a pathogenic role in metabolic syndrome. In the current study, we show that fructose-induced metabolic syndrome is partially prevented by lowering serum uric acid in the rat. The reduction of endothelial nitric oxide (NO) bioavailability by uric acid may be a mechanism for insulin resistance and hypertension.

METHODS

In Vivo Studies

Experiment 1: treatment of fructose-induced hyperuricemia with allopurinol. Male Sprague-Dawley rats (150–200 g) were housed in standard conditions and fed a control ($n = 7$) or 60% fructose diet (Harlan, Madison, WI, $n = 14$) for 10 wk. The control diet contained 46% carbohydrate, which is mainly composed of starch, whereas the fructose diet contained 60% fructose as the carbohydrate. The caloric content of these diets are 3.1 and 3.6 kcal/g, respectively. At 4 wk, blood samples were obtained at 11 AM after 4 h of fasting. One-half of the fructose-fed rats were administered allopurinol (150 mg/l in the drinking water, Sigma, St. Louis, MO) for an additional 6 wk to lower serum uric acid. Fresh drinking water containing allopurinol was replaced every 2 days. Rats were divided into three groups: control, fructose, and fructose+allopurinol. At 10 wk, an oral glucose tolerance test (OGTT) was performed, in which rats were fasted overnight (16 h) and then administered 1.5 g/kg of a 50% glucose solution by gavage. Blood was sampled at 0, 30, 60, and 120 min for blood glucose and serum insulin measurement. The rats were then killed.

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Experiment II: prevention of fructose-induced hyperuricemia with allopurinol. To assess the effect of preventing hyperuricemia during the period of the study, allopurinol was initiated on the day when the fructose diet was given (from week 0 to week 8). Three groups (control, fructose, and fructose+allopurinol; $n = 8$ each) were designed for this prevention study. Body weight was measured every 2 wk. Food consumption was measured for 3 days at 8 wk.

Experiment III: effect of lowering of uric acid by either allopurinol or benzbromarone on body weight and food consumption. In this experiment, the effect of benzbromarone, a uricosuric agent (150 mg/l in the drinking water, Sigma), was also examined to confirm the effect of lowering of uric acid on body weight and food intake. Fresh drinking water containing benzbromarone was replaced every 2 days. Three groups (control, allopurinol, and benzbromarone; $n = 8$ each) were studied. All groups were fed with the control diet for 8 wk. Body weight and the consumption of food were measured weekly for 8 wk.

Experiment IV: comparison between 60% dextrose and 60% fructose in development of metabolic syndrome and effect of lowering uric acid with benzbromarone. Rats were pair-fed with a 60% dextrose diet or a 60% fructose diet for 4 wk, both of which are isocaloric. Because experiment II showed that each rat normally eats 25–30 g/day, we administered 25 g of the diet to each rat every day. At 4 wk, total food intake per animal was calculated from the food left over. Total food intake is the subtraction of the leftover food from the total food administered ($1,425 \text{ g} \cdot \text{rat}^{-1} \cdot 28 \text{ days}^{-1}$). In addition to the above two groups, a third group of fructose-fed rats was administered benzbromarone. Their body weight was measured weekly. At 4 wk, after 5 h of fasting, insulin, triglyceride, and uric acid were measured.

All protocols were approved by the Animal Care Committee of the University of Florida.

Measurements. Systolic blood pressure was assessed as the mean value of three consecutive measurements obtained in the morning using a tail-cuff sphygmomanometer (Visitech BP2000, Visitech Systems, Apex, NC). All animals were preconditioned for blood pressure measurements 1 wk before each experiment. Serum uric acid was measured by the uricase method. Blood glucose was measured with the ONE TOUCH system (Johnson&Johnson, Milpitas, CA). Rat insulin was measured by ELISA (Crystal Chem, Chicago, IL). The insulin sensitivity index was calculated using the formula of Matsuda and DeFronzo [$10,000/\text{square root of (fasting glucose} \times \text{fasting insulin)} \times (\text{mean glucose} \times \text{mean insulin during OGTT})$], which is highly correlated ($r = 0.73$, $P < 0.0001$) with the rate of whole body glucose disposal during the euglycemic insulin clamp (24). Serum lipids were measured with an autoanalyzer (VETAce, Alfa Wassermann, West Caldwell, NJ) or a Triglyceride-SL assay kit (Diagnostic Chemicals, Charlottetown, PE, Canada).

Vasorelaxation of Rat Aortic Artery Segments

Rat aortic artery (AA) segments (1- to 0.5-mm diameter \times 3- to 4-mm length) were isolated from 2- to 3-mo-old rats and suspended in individual organ chambers (Radnoti Four-Unit Tissue Bath System) with 5 ml in Earl's solution, oxygenated with 95% O_2 -5% CO_2 at 37°C. After 1-h equilibration of resting force of 1.5 g, the vascular smooth muscle cell or endothelium integrity of this AA segment was confirmed by monitoring 0.5 μM U-46619 (a thromboxane A_2 mimetic, Sigma)-mediated AA contraction or acetylcholine (5 μM)-mediated vasodilation, respectively. After being washed several times, the segments were incubated with various concentrations of uric acid (0–15 mg/dl) in an organ bath chamber for 30 min. Stable constriction was induced by 0.5 μM U-46619 for 10 min before acetylcholine-induced vasorelaxation. The vascular tensions were continuously monitored with an isometric force transducer (Harvard Apparatus, Holliston, MA). To standardize the data, the U-46619-induced stable increase in vascular tone was set as 100%.

Statistical Analysis

All values presented are expressed as means \pm SD and analyzed by one-way ANOVA or by unpaired Student's *t*-test. Significance was defined as $P < 0.05$.

RESULTS

In Vivo Studies

Serum uric acid levels, systolic blood pressure, and fasting insulin levels were elevated in fructose-fed rats compared with rats fed a control diet at 4 wk (Table 1). In addition, the body weight of fructose-fed rats tended to increase compared with rats fed a normal diet (Table 1). These data demonstrate that fructose feeding induces early features of metabolic syndrome in rats.

To examine the role of uric acid in this model, one-half of the fructose-fed rats were treated with allopurinol (a xanthine oxidase inhibitor) for 6 additional wk. This treatment was effective at lowering uric acid, whereas the fructose-fed rats that did not receive treatment continued to be hyperuricemic (Fig. 1A). In addition, we examined the urinary excretion of uric acid in these animals to clarify the mechanisms of hyperuricemia in fructose-fed rats. As shown in Fig. 1B, fructose-fed rats had a lower urinary excretion of uric acid. Interestingly, allopurinol prevented the reduced excretion of uric acid in fructose-fed rats.

Fructose-fed rats treated with allopurinol showed an improvement in metabolic syndrome. Allopurinol significantly reduced systolic blood pressure in fructose-fed rats (Fig. 1C), although pressures remained higher than that observed in control rats. Fructose-fed rats also developed marked hypertriglyceridemia that was abolished by allopurinol treatment (Fig. 1D). The reduction in serum uric acid correlated directly with the decrease in triglyceride levels (Fig. 1E). Fructose-fed rats also showed an increase in body weight compared with controls. Allopurinol prevented the increase in body weight, although this did not reach significance (522 ± 57 g in fructose vs. 470 ± 28 g in control and 474 ± 37 g in fructose+allopurinol, $P = \text{not significant}$).

While no groups developed fasting or postprandial hyperglycemia (Fig. 2A), fructose-fed rats developed fasting hyperinsulinemia that was reversed with allopurinol (Fig. 2B). Postprandial hyperinsulinemia also occurred in fructose-fed rats administered an OGTT, and this was partially but significantly lower in allopurinol-treated rats (Fig. 2B), resulting in improved insulin sensitivity (Fig. 2C).

We also examined the effectiveness of allopurinol in preventing the development of metabolic syndrome, as opposed to

Table 1. Experiment I: general characteristics of control and fructose groups at 4 wk

	Control ($n = 7$)	Fructose ($n = 14$)	
Initial body weight, g	190 \pm 12	188 \pm 0.1	NS
Body weight at 4 wk, g	357 \pm 15	375 \pm 22	$P=0.05$
Systolic BP at 4 wk, mmHg	127 \pm 3	148 \pm 15	$P<0.05$
Uric acid at 4 wk, mg/dl	1.3 \pm 0.3	2.4 \pm 0.3	$P<0.01$
Insulin at 4 wk, pmol/l	121 \pm 64	176 \pm 51	$P<0.05$

Values are means \pm SD. *n*, No. of rats; BP, blood pressure; NS, not significant.

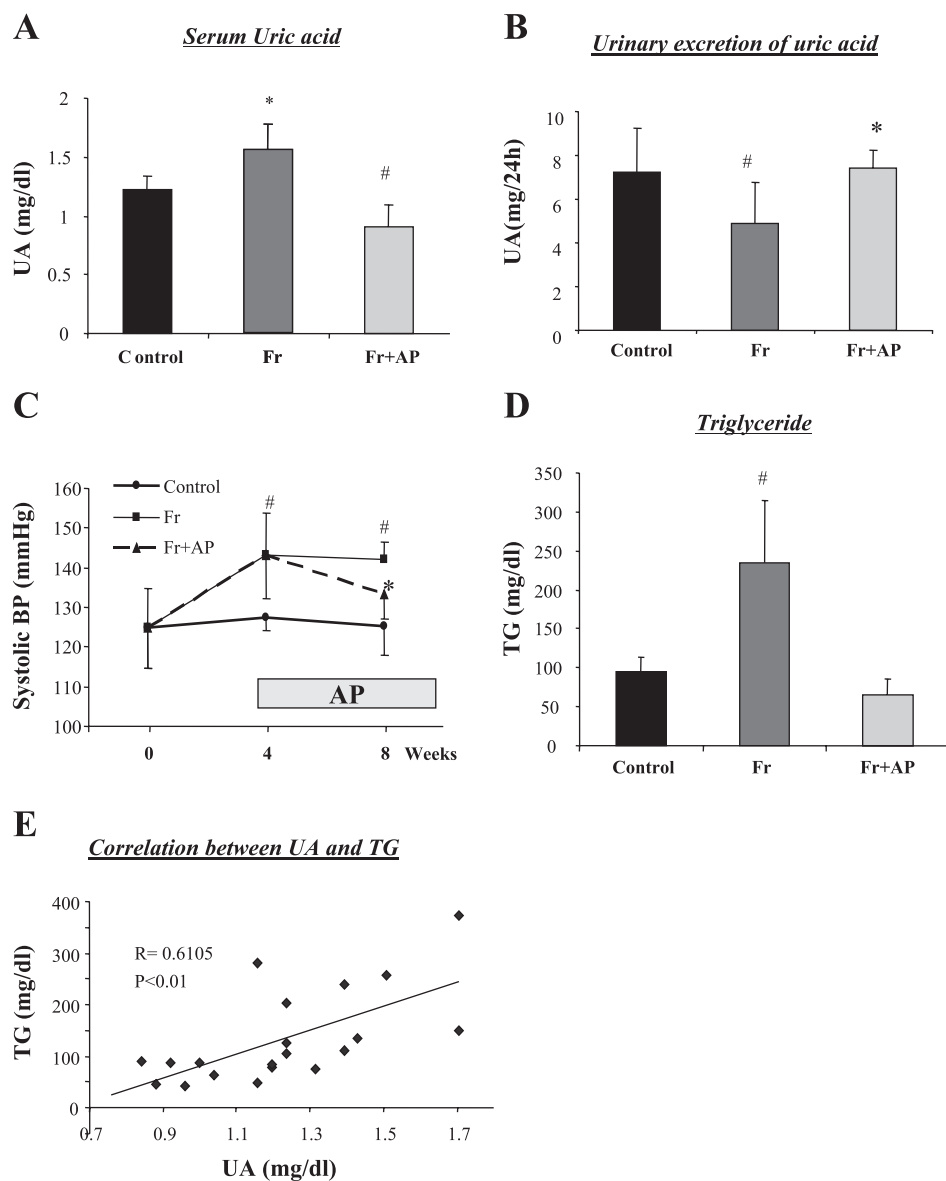


Fig. 1. Effects of allopurinol (AP) treatment for hyperuricemia on metabolic parameters in fructose-fed (Fr) rats. A: Fr rats are hyperuricemic at 9 wk, and this is prevented by AP (150 mg/l). * $P < 0.01$ vs. control. UA, uric acid. # $P < 0.05$ vs. Fr. B: Fr reduced urinary excretion of UA at 9 wk, and this is prevented by AP. * $P < 0.01$ vs. Fr. # $P < 0.05$ vs. control. C: hypertension develops in Fr rats, which is significantly reduced by AP. Values are means \pm SD. * $P < 0.01$ vs. control. # $P < 0.05$ vs. Fr. BP, blood pressure. D: serum triglycerides (TG) are increased in Fr rats, and this is completely prevented by AP. # $P < 0.01$ vs. control and Fr+AP. E: serum triglyceride level correlates directly with the serum UA.

treating rats to inhibit its progression. Allopurinol was given simultaneously with the fructose diet from the starting point to avoid fructose-induced hyperuricemia. As shown in Fig. 3A, the elevation of uric acid with the fructose diet was prevented over the 6-wk period in fructose-fed rats. Allopurinol-treated rats had significantly lower fasting insulin levels compared with fructose-fed rats (Fig. 3B), and the development of hypertriglyceridemia was completely prevented (Fig. 3D). In addition, while fructose-fed rats gained weight compared with control rats (456 ± 24 vs. 414 ± 24 g, final weights in fructose vs. control, $P < 0.01$), allopurinol-treated rats had lower weight gain (final weight 426 ± 26 g, $P < 0.05$ vs. fructose-fed rats). At 8 wk, the total food intake over 3 days in fructose-fed rats was slightly higher (92 ± 2 g) compared with that of the fructose+allopurinol group (88 ± 4 g), although this did not reach statistical significance.

The observation that administration of allopurinol to fructose-fed rats prevented obesity led to additional studies to ensure that allopurinol did not have specific effects on food

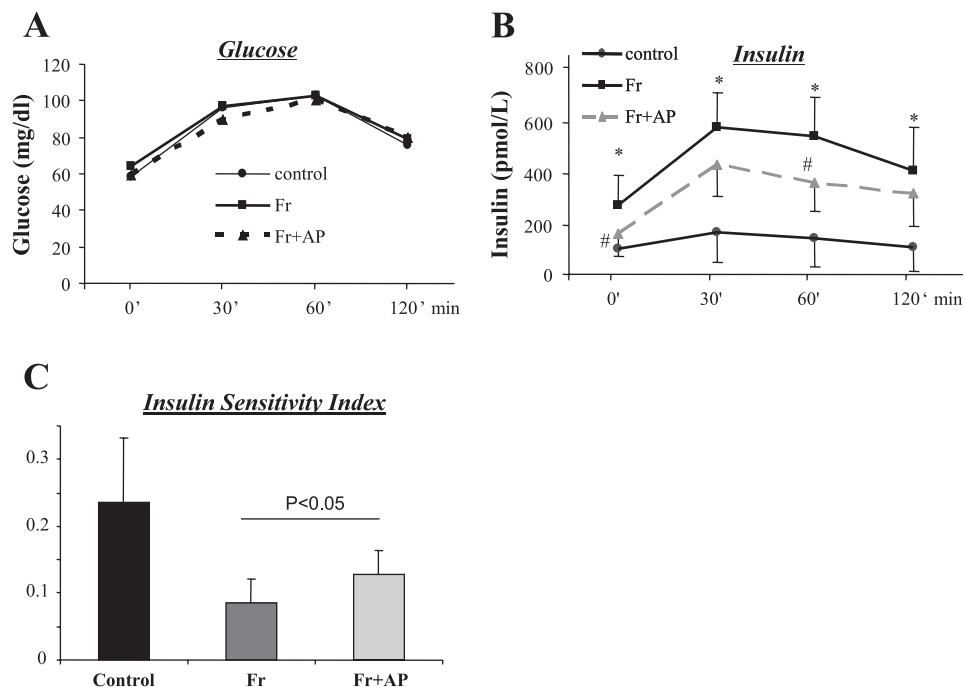
intake or body weight. To address this possibility, allopurinol or benzbromarone (a uricosuric agent) was administered to rats on control diets for 8 wk. A third group received the control diet alone. Total food consumption at 8 wk and final body weight were not different among the three groups (Table 2).

Finally, we compared the effects of the 60% dextrose and 60% fructose diets on the development of metabolic syndrome. In this experiment, food intake was controlled so that each group received the same intake of calories and had the same weight gain. Nevertheless, only the fructose-fed rats developed hyperuricemia, hypertriglyceridemia, and hyperinsulinemia (Table 3). Importantly, these effects observed in fructose-fed rats were significantly improved by lowering uric acid levels with benzbromarone, the uricosuric agent (Table 3).

In Vitro Studies

Endothelial dysfunction is common in metabolic syndrome. It is known that impaired NO response to insulin

Fig. 2. Effect of AP treatment on glucose metabolism in Fr rats. **A:** glucose tolerance test at 10 wk. Similar blood glucose levels were observed in all groups. **B:** plasma insulin levels following the glucose tolerance test. Fructose ingestion was associated with fasting and postprandial hyperinsulinemia. AP (150 mg/l) prevented basal hyperinsulinemia and significantly reduced postprandial hyperinsulinemia. * $P < 0.01$ vs. control. # $P < 0.05$ vs. Fr. **C:** insulin sensitivity index (ISI). Insulin sensitivity was reduced with a fructose diet and improved by AP. Values are means \pm SD. Statistical analysis among 3 groups was by ANOVA with Bonferroni correction in **B**. * $P < 0.01$ vs. control. # $P < 0.05$ vs. Fr. Comparison was done between Fr and Fr+AP using unpaired *t*-test in **C**.



may be a mechanism for the development of insulin resistance (36). Previously, uric acid has been shown to potently reduce NO levels in cultured bovine endothelial cells (18). To further examine this relationship, we examined the acute effect of uric acid on acetylcholine-induced vasodilation of rat AA rings. As shown in Fig. 4, uric acid dose dependently blocked the vasorelaxation of AA rings in response to acetylcholine.

DISCUSSION

In this study, we examined the role of uric acid in the development of insulin resistance syndrome (metabolic syndrome) in fructose-fed rats. Fructose, but not dextrose, caused metabolic syndrome. Allopurinol, a xanthine oxidase inhibitor that lowers serum uric acid, was able to both prevent and reverse features of metabolic syndrome in fructose-fed rats.

Fig. 3. Blocking of hyperuricemia in Fr rats with AP prevents features of metabolic syndrome. **A:** AP (150 mg/l) prevented the rise in UA in Fr rats. $P < 0.05$ vs. control and Fr+AP. **B:** AP treatment was associated with significantly lower fasting insulin levels compared with Fr rats at 8 wk. **C:** AP also prevented the increase in body weight induced with fructose. Statistical analysis among 3 groups was by ANOVA with Bonferroni correction.

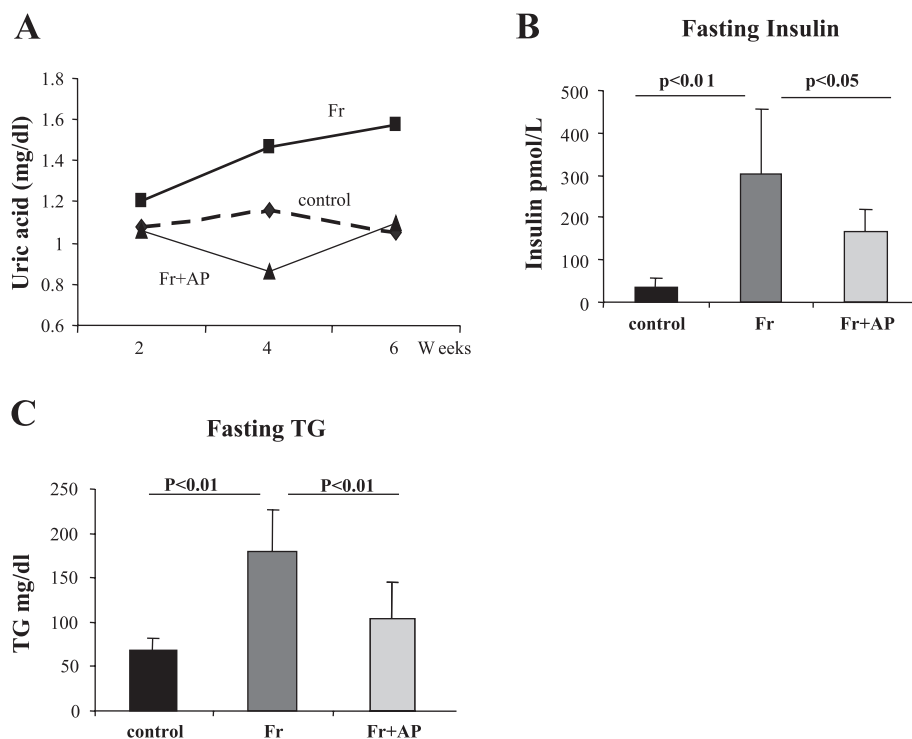


Table 2. Experiment III: effect of lowering uric acid on body weight and food consumption for 8 wk

	Control (n = 8)	Allopurinol (n = 8)	Benzbromarone (n = 8)
Initial body weight, g	162 ± 7	164 ± 3	160 ± 8
Final body weight at 8 wk, g	469 ± 69	504 ± 37	468 ± 43
Total food intake for 8 wk, g	1452 ± 68	1562 ± 118	1494 ± 90
Uric acid at 8 wk, mg/dl	1.5 ± 0.5	0.5 ± 0.4	1.1 ± 0.3

Values are means ± SD. n, No. of rats.

Allopurinol lowered systolic blood pressure, improved insulin sensitivity, and normalized triglyceride levels. Similar effects were observed with benzbromarone (a uricosuric agent). Allopurinol also prevented weight gain in fructose-fed rats, and this did not appear to be due to effects of allopurinol on diet, for rats on the control diet fed allopurinol gained weight normally. Thus these studies provide the first evidence that uric acid may have a causal role in the pathogenesis of fructose-induced metabolic syndrome.

There is supporting evidence that uric acid may have a pathogenic role in metabolic syndrome. Hyperuricemia has been found to predict the development of both obesity and type 2 diabetes (29). Hyperuricemia is also commonly observed in metabolic syndrome (41), as well as in secondary insulin resistance syndromes such as that associated with gout (2), diuretic usage (21, 31), or preeclampsia (39). There are also older studies that showed that rats made chronically hyperuricemic with uricase inhibitors develop features of metabolic syndrome (42). These data introduce the novel concept that uric acid may have a causal role in metabolic syndrome.

Most authorities consider hyperuricemia in metabolic syndrome to be the consequence of elevated serum insulin levels, which have been shown to stimulate renal reabsorption of uric acid (9). Consistent with this observation is the finding that thiazolidinediones, which improve insulin sensitivity and lower insulin levels, also reduce the level of serum uric acid in diabetic patients (16, 40). On the other hand, our study demonstrated that lowering uric acid with either a xanthine oxidase inhibitor or a uricosuric agent also improves insulin sensitivity as well as other features of metabolic syndrome, including hypertension, obesity, and hypertriglyceridemia. While multiple factors are known to drive metabolic syndrome (6), these

Table 3. Experiment IV: effect of pair-feeding with 60% dextrose and 60% fructose diets at 4 wk on development of metabolic syndrome and of lowering uric acid with benzbromarone

	60% Dextrose (n = 8)	60% Fructose (n = 8)	60% Fructose + Benzbromarone (n = 8)
Initial body weight, g	144 ± 7	144 ± 5	144 ± 7
Final body weight at 4 wk, g	353 ± 14	364 ± 17	360 ± 20
Total food intake for 4 wk, g	700 ± 10	709 ± 6	698 ± 15
Uric acid at 4 wk, mg/dl	1.4 ± 0.3	2.1 ± 0.9*	1.1 ± 0.4†
Triglyceride at 4 wk, mg/dl	112 ± 28	419 ± 60‡	293 ± 86§
Insulin at 4 wk, pmol/l	112 ± 43	204 ± 62‡	147 ± 42§

Values are means ± SD. n, No. of rats. **P* < 0.05 vs. dextrose. †*P* < 0.01 vs. fructose. ‡*P* < 0.01 vs. dextrose. §*P* < 0.05 vs. fructose.

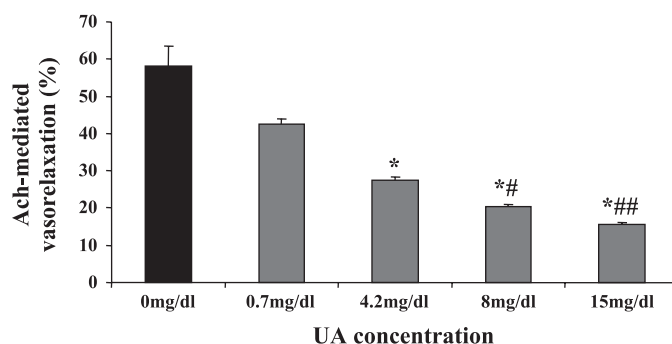


Fig. 4. UA inhibits ACh-mediated vasodilation in rat aortic artery segments. ACh (5 μ M)-induced vasorelaxation was assessed in the presence of various concentrations of UA for 10 min after stable constriction by U-46619 (0.5 μ M); n = 4. **P* < 0.01 vs. control. #*P* < 0.05 vs. 0.7 mg/dl UA. ###*P* < 0.01 vs. 0.7 mg/dl UA.

studies suggest that uric acid may also have a contributory role in the development of insulin resistance.

Hypertriglyceridemia was completely blocked by lowering of uric acid with allopurinol in this study. Compatible with our findings, it has been shown that the association of elevated serum uric acid with hypertriglyceridemia is stronger than with insulin sensitivity (41). Interestingly, treatment of hypertriglyceridemia with fenofibrate or atorvastatin also reduces serum uric acid (1, 12, 27). Uricosuric agents such as benzbromarone also lower serum triglycerides (12). Although the role of uric acid in the metabolism of triglycerides remains unknown, uric acid might be involved in either the overproduction or the reduction of clearance of triglycerides. A decrease in the clearance of triglycerides in fructose-fed rats has been attributed to a reduction in lipoprotein lipase activity in endothelial cells (19, 30); whether this is mediated by uric acid remains to be determined. An alternative explanation is the possibility that the de novo increase in purine synthesis observed in fructose-fed rats may be pathogenetically linked to hepatic fatty acid synthesis, resulting in overproduction of triglycerides (25, 41).

Endothelial dysfunction is a hallmark of metabolic syndrome (7). Therefore, we investigated the role of uric acid in endothelial dysfunction as a mechanism for insulin resistance. We showed that uric acid dose dependently blocked acetylcholine-mediated arterial dilation (Fig. 4), suggesting that uric acid can impair endothelial function. In addition, we have found that uric acid potently reduces endothelial NO bioavailability in both cell culture and in experimental animal models (18). In turn, reducing endothelial NO levels is a known mechanism for inducing insulin resistance (33). Thus endothelial NOS-deficient mice exhibit the features of metabolic syndrome (5). The mechanism is due to a blockade of insulin action, as insulin stimulates glucose uptake in skeletal muscle by increasing blood flow to these tissues through a NO-dependent pathway (33). In this scenario, allopurinol or benzbromarone may be acting to prevent metabolic syndrome by blocking hyperuricemia-induced endothelial dysfunction.

Unlike glucose, the oral ingestion of fructose results in a rapid increase in serum uric acid within 30–60 min in humans (38). The mechanism by which fructose raises serum uric acid has been previously studied. Fructose enters hepatocytes, where it is rapidly phosphorylated by fructokinase to fructose-1-phosphate (13). During this reaction, ATP donates the phos-

phate, resulting in the generation of ADP, which is further metabolized to uric acid (13). This is aided by a fructose-mediated increase in AMP deaminase (37).

In addition to an effect of fructose to increase hepatic production of uric acid, we found that urinary excretion of uric acid was decreased in fructose-fed rats. There are multiple potential explanations for this observation. First, we have found that experimental hyperuricemia causes endothelial dysfunction and renal vasoconstriction (18, 26, 34), which is known to impair urate excretion (10). Second, fructose results in lactate production, which is a competitive inhibitor for urate excretion (14). Finally, hyperinsulinemia itself can lead to an impairment in urate excretion (9). The observation that impaired urate excretion was due, in part, to hyperuricemia was shown by the observation that allopurinol could reverse this effect. This would support uric acid-induced endothelial dysfunction and/or hyperinsulinemia as the central mechanism for this effect.

While the above studies provide evidence supporting a role for uric acid in the development of metabolic syndrome induced by fructose, allopurinol also blocks oxidants generated by the xanthine oxidase pathway. Oxidants are involved in the pathogenesis of diabetes and its complications (4). It is therefore possible that the beneficial effects of allopurinol may be attributed, in part, to the lowering of oxidants rather than an effect on uric acid per se. However, most studies suggest that the oxidants driving diabetic complications are generated as a consequence of mitochondrial dysfunction or activation of NADPH oxidase, neither of which would be blocked by a xanthine oxidase inhibitor. The observation that the uricosuric agent benzbromarone also prevented features of metabolic syndrome further suggests that the mechanism by which allopurinol works likely includes lowering uric acid. While future studies will need to dissect the mechanism by which allopurinol provides benefit, the observation that uric acid also impairs endothelial function provides a potential mechanism by which uric acid could have a pathogenic role in fructose-mediated metabolic syndrome. While speculative, we suggest that the worldwide epidemic in hypertension, obesity, and metabolic syndrome may have its roots in the marked increase in fructose intake and in the progressive rise in mean serum uric acid that has been observed in both developing and industrialized nations in the last century (17).

GRANTS

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DISCLOSURES

R. J. Johnson is a consultant for TAP Pharmaceuticals.

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