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Dietary sodium restriction prevents kidney damage in high fructose-fed rats

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Sodium depletion has a protective effect on target-organ damage in hypertension independent of blood pressure. Here we tested whether chronic dietary sodium restriction may prevent the development of renal alterations associated with insulin resistance by reducing the inflammatory and oxidant state. Rats were fed normal-salt–60% fructose, low-salt–60% fructose, or control normal-salt diet for 12 weeks. Insulin resistance induced by high-fructose diet was associated with an increase in albuminuria, tubular and glomerular hypertrophy, and inflammation of kidney and adipose tissue. The low-salt diet improved insulin sensitivity and prevented kidney damage. These beneficial effects of sodium depletion were associated with a decrease in renal inflammation (macrophage infiltration, IL-6, TNF-α) and oxidative stress (NADPH oxidase activity), and a prevention of histologic changes in retroperitoneal fat induced by high fructose. Thus, dietary salt depletion has beneficial effects on renal and metabolic alterations associated with a high-fructose diet in rats.

Kidney International (2013) **83,** 674–683; doi:10.1038/ki.2012.478; published online 23 January 2013

KEYWORDS: albuminuria; dietary sodium; IL-6; insulin resistance; oxidative stress; TNF-α

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Received 20 June 2012; revised 18 October 2012; accepted 8 November 2012; published online 23 January 2013

The metabolic syndrome was first introduced as a concept to cluster cardiovascular risk factors such as hypertension, type 2 diabetes, obesity, and dyslipidemia, which culminate in high risk for atherosclerotic cardiovascular disease. Insulin resistance has been proposed as the metabolic link between all these cardiovascular risk factors.[1–3] Recently, consumption of dietary fructose was suggested to be one of the environmental factors contributing to the development of obesity and the accompanying abnormalities of the metabolic syndrome.[4] In fact, the high consumption of fructose is a well-known experimental model of metabolic syndrome.[5,6] Several studies have suggested that renal damages are associated with the metabolic syndrome. In humans, the multivariate-adjusted odds ratio of chronic kidney disease and microalbuminuria were higher in patients with the metabolic syndrome.[7] Similarly, it has been shown that fructose-fed rats in comparison with corn starch–fed rats show signs of renal dysfunction associated with renal hypertrophy, afferent arteriolopathy, glomerular hypertension, renal vasoconstriction, and nephropathic changes.[8] In addition, long-term (>6 months) exposure to high fructose consumption was associated with proteinuria, kidney enlargement, and focal tubulointerstitial injury and glomerulosclerosis.[9,10] Accumulating evidence now indicates that immunological and inflammatory mechanisms have a significant role in the development and progression of damages in chronic kidney diseases. Among the various inflammatory cytokines, mainly tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are relevant mediators that regulate inflammatory immune responses in diabetic nephropathy.[11] Interestingly, there is increasing body of evidence suggesting that insulin resistance may result from an inflammatory disorder, in which macrophages in adipose tissue and elsewhere may have an important role.[12] Together with inflammation, oxidative stress seems to be implicated in renal injury in obesity and hypertension[13,] as well as in type 2 diabetic nephropathy in mice and in fructose-fed rats.[5,14]

Sugar consumption has also been linked to sodium intake and renal sodium handling. Fructose–blood pressure association was stronger for individuals with high sodium consumption,[15] as well as in spontaneously hypertensive rats fed a high-sodium diet.[16] Conversely, a low-sodium diet prevented changes in blood pressure induced by high dietary sucrose[17] or fructose.[16] Besides its effect on arterial pressure,

we have previously reported that sodium withdrawal from the diet alleviated cardiovascular and renal damages in angiotensin II hypertension. The beneficial influence of dietary sodium restriction was independent of arterial pressure reduction and possibly related to attenuation of the prooxidant effect of the peptide.[18] However, the effects of dietary sodium restriction on functional and morphological modifications of the kidney associated with insulin resistance have not been yet explored. Thus, in the present study, we evaluated the putative beneficial influence of a drastic reduction in sodium intake on fructose-induced renal alterations. Furthermore, we tested the hypothesis that sodium restriction was related to a reduction in the inflammatory and oxidative stress responses to high fructose–induced insulin resistance in rats. As the podocyte is a key cell type involved in the initial development of albuminuria, particularly in obesity or type 2 diabetes,[19] renal ultrastructure was examined in fructose-fed rats. Finally, we evaluated the influence of sodium restriction on retroperitoneal adipose tissue, which may have a role in the development of insulin resistance.[20]

RESULTS

Metabolic parameters

Despite a higher calorie intake in fructose-fed rats, the final body weight was similar in sodium-replete, fructose-fed (normal-sodium, high-fructose (NSF)) and control group (normal-sodium control (NSC)) rats. However, the percentage of visceral adipose tissue was significantly higher in NSF rats (Table 1). Interestingly, body weight was lower in low-sodium, fructose-fed rats (low-sodium, high-fructose (LSF)), and sodium restriction prevented the increase in adipose tissue associated with the fructose diet. As reported in Table 1, plasma concentration of uric acid was higher in the NSF group as compared with the control group, and sodium depletion had no effect on this change. Plasma adiponectin was significantly decreased in NSF rats as compared with NSC rats, and sodium restriction did not influence this change. Plasma lectin concentration was similar in all groups.

No significant influence of high fructose intake on sodium and potassium excretion was observed. As expected, sodium excretion was reduced to $<50\,\mu$mol per day in the LS-fed rats. Direct and indirect blood pressure was comparable among the three experimental groups.

Glucose metabolism

Although fasting plasma glucose was not significantly different between groups, fasting plasma insulin and homeostasis model assessment (HOMA) index increased in NSF rats by 59% and 78%, respectively (Table 1). In addition, blood glucose response during insulin tolerance test was blunted in the NSF group when compared with the NSC group (Figure 1a). Sodium restriction precluded insulin resistance as evaluated by both HOMA index and insulin tolerance test.

As depicted in Figure 1b, blood glucose response to intraperitoneal glucose tolerance test was comparable in the three groups. However, insulin response was enhanced in the NSF rats, and significance was achieved when the area under the curve was calculated. Both the peak and area under the curve of plasma insulin in response to intraperitoneal glucose tolerance test were similar to that of NSC rats in animals fed the sodium-depleted fructose diet.

Renal morphology and histology

No significant difference in inulin clearance and plasma creatinine was observed among the three groups (Table 2). As depicted in Figure 2, a high-fructose diet was associated with a marked rise in albuminuria in sodium-replete rats. Albuminuria was comparable to standard control rats

Table 1 | Influence of high-fructose diet and sodium depletion on experimental parameters ($N=8$ in each diet)

	NSC	NSF	LSF
Final body weight, g	453 ± 8	434 ± 10	379 ± 13*,†
Food intake, g/day	19 ± 2	19 ± 1	20 ± 1
Calories intake, kcal/day	56 ± 6	76 ± 4*	76 ± 7*
Adipose tissue, % BW	1.84 ± 0.13	2.47 ± 0.17*	1.68 ± 0.18†
Sodium excretion, mmol/day	1.64 ± 0.08	1.58 ± 0.16	0.03 ± 0.00*,†
Potassium excretion, mmol/day	1.70 ± 0.17	1.56 ± 0.09	1.93 ± 0.13
Urine volume, ml/day	12 ± 1	13 ± 2	9 ± 1
Plasma glucose, mg/dl	126 ± 10	121 ± 3	104 ± 5
Plasma insulin, ng/ml	1.19 ± 0.10	1.89 ± 0.29*	1.44 ± 0.18*
HOMA-IR	1.58 ± 0.15	2.81 ± 0.44*	1.82 ± 0.21†
Plasma uric acid, mg/dl	1.64 ± 0.21	2.59 ± 0.35*	2.20 ± 0.29
Plasma adiponectin, μg/ml	22.8 ± 3.8	14.8 ± 0.6*	11.9 ± 1.7*
Plasma leptin, ng/ml	5.6 ± 1.3	5.1 ± 0.7	6.1 ± 0.9
Tail-cuff pressure, mm Hg	136 ± 3	137 ± 3	136 ± 3
Vigil mean arterial pressure, mm Hg	121 ± 4	122 ± 4	123 ± 5

Abbreviations: BW, body weight; HOMA-IR, homeostasis model assessment of insulin resistance; LSF, low-sodium, high-fructose diet; NSC, normal-sodium control diet; NSF, normal-sodium, high-fructose diet.
*$P<0.05$ versus NSC diet.
†$P<0.05$ versus NSF diet.
Food and calories intake, and urinary excretion of sodium, potassium, and volume are expressed as a daily mean value calculated over a 3-day collection period.