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GENDER MODULATES DEVELOPMENT OF THE METABOLIC SYNDROME PHENOTYPE IN FRUCTOSE-FED RATS

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Abstract - We analyzed the effects of a fructose-rich diet (FRD) to test the assumption that the expression of metabolic syndrome phenotype is different in male and female rats. Two-way ANOVA revealed a significant effect of FRD on feeding behavior and carbohydrate/lipid metabolism. The increased caloric intake in FRD rats of both sexes was followed by a cluster of gender-specific changes typical for the metabolic syndrome. Female rats were characterized by decreased glycemia, increased triglycerides, enlarged visceral adipose tissue and increased absolute mass of liver, without changes in systolic blood pressure and insulin sensitivity. In contrast, male rats developed less disturbances in physical and biochemical characteristics, but blood pressure and insulin sensitivity were impaired by FRD. The results emphasize the detrimental effects of fructose consumption on cardiovascular risk and insulin action in males, whereas females are affected by other metabolic disturbances. These results support the idea of gender-dependent differences in the expression of the metabolic syndrome phenotype.

Key words: Fructose rich diet, metabolic syndrome, gender, glucose tolerance test, blood pressure, lipid metabolism

INTRODUCTION

The metabolic syndrome is an assemblage of pathologies, including obesity, insulin resistance (IR), dyslipidemia, and hypertension. High fructose consumption is a risk factor for the development of metabolic syndrome. Fructose-fed rats (FFR) serve as a model of acquired hypertension; they also exhibit insulin resistance, hyperinsulinemia and hypertriglyceridemia (Galipeau et al., 2002). Fructose has been shown to be involved in the genesis and progression of metabolic syndrome through the dysregulation of many signaling and metabolic pathways (Miller and Adeli, 2008; Ferder et al., 2010). A high flux of fructose to the liver perturbs glucose metabolism and glucose uptake pathways and leads to a significantly enhanced rate of lipogenesis and triacylglycerol synthesis (Tran et al., 2009).

The pattern of clinical symptoms in patients with the metabolic syndrome is not consistent. Furthermore, in animal models of this complex disorder, different types of diet (high-fat, high-cholesterol, high-fructose, high-sucrose) present different characteristics of the metabolic syndrome (Axelsen et al., 2010). Gender differences have been also shown to influence the progression of metabolic syndrome pathology (Galipeau et al., 2002; Song et al., 2004; Onat et al., 2005; Vasudevan et al., 2005; Regitz-Zagrosek et al., 2006).

In hypertensive FFR it has been shown that male rats had significant hypertension and hyperinsulinemia after exposure for 9 weeks to a high-fructose diet, whereas female rats did not (Galipeau et al., 2002). In addition, it has been demonstrated that hyperinsulinemia and insulin resistance are associated with hypertension in male rats only (Galipeau et al., 2002). The development of IR and hypertension in FFR is governed by the interactions of specific sex hormones such as estrogen and testosterone (Vasudevan et al., 2005). The protective effects of estrogen and permissive effects of testosterone in the development of hypertension secondary to IR have been demonstrated in several studies (Vasudevan et al., 2005). Females generally do not develop hypertension or hyperinsulinemia upon fructose feeding, except after ovariectomy, suggesting that female sex hormones may confer protection against the effects of a fructose diet. Furthermore, literature data suggest that the presence of androgens is necessary for the development of fructose-induced hypertension (Song et al., 2004). Variations in hepatic fructose-metabolizing enzyme activities between males and females have also been observed (Millo and Werman, 2000), which can directly influence the fructose lipogenic potential in liver. Even the expression of some fructose transporter variants seems to be sex-dependent (Brandstatter et al., 2008).

Despite several studies, we believe that the role that gender plays in the development of the hallmark symptoms of metabolic syndrome in animals and humans exposed to high fructose intake is still controversial. On the other hand, our recent results and studies of other authors indicate several unique features of the metabolic syndrome in females (Schneider et al., 2006; Koricanac et al., 2012). We believe that gender differences do exist, but that the level of protection described in females is quite questionable. Are females protected against metabolic syndrome or does the disorder develop with different timing or in a different form? In order to test our assumption we performed a comparative study on the development of metabolic syndrome phenotype in male and female rats that were subjected to a 9-week-long diet with 10% fructose in drinking water, which resembles an increased consumption of fructose-sweetened beverages in the human population.

MATERIALS AND METHODS

Chemicals

Fructose was purchased from API-PEK (Bečej, Serbia). The RIA insulin kit was a product of INEP (Zemun, Serbia). Insulin and other chemicals of high purity were purchased from Sigma-Aldrich Corporation (St. Louis, MO, USA).

Animals

Male and female 21-day-old Wistar rats were separated from their mothers and divided into two main groups according to the diet regimen. All animals were kept under standard temperature and dark/light conditions. Control animals had free access to tap water and standard laboratory chow (Table 1). Animals on a fructose-enriched diet were fed with the same food, but water was replaced by a 10% (w/v) fructose solution in tap water (Table 1). The animals were exposed to these diets for 9 weeks and thereafter killed by decapitation.

Animal experiments were conducted according to the standards approved by the official Vinča Institute's Ethical Committee for Experimental Animals and conform to national guidelines for animal usage in research.

Food and liquid intake, body mass and mass of heart, visceral adipose tissue and liver

The body mass of rats in two experimental groups was not significantly different at the beginning of the diet. Food and fluid intake and body mass were recorded during the treatment. The caloric intake of the FFR was calculated as the sum of calories ingested as food and fructose solution. Heart, visceral adipose tissue (VAT) and liver mass were determined immediately after the animals were killed. All tissues were excised, washed in saline and dried before measurement.

Table 1. Diet composition
Control animals had free access to tap water and standard laboratory chow. Animals on fructose-enriched diet were fed by the same food, but water was replaced with 10% (w/v) fructose solution in tap water. Animals were exposed to these diets during 9 weeks.

Chemical composition	Normal diet	Fructose rich diet
Metabolizable energy, not less than	11000 kJ/kg	11000 kJ/kg diet + 1720 kJ/L solution
Protein, not less than	20%	20%
Fructose as solution	0	100 g/L
Moisture, not more than	13 %	13 %
Ash, not more than	10 %	10 %
Cellulose, not more than	8 %	8 %
Calcium, not less than	1 %	1 %
Lysine, not less than	0.90 %	0.90 %
Methionine + Cystine, not less than	0.75 %	0.75 %
Phosphorus, not less than	0.50 %	0.50 %
Sodium	0.15-0.25 %	0.15-0.25 %
Vitamin A, not less than	10 000 IU/kg	10 000 IU/kg
Vitamin D_3, not less than	1600 IU/kg	1600 IU/kg
Vitamin E, not less than	25 mg/kg	25 mg/kg
Vitamin B_{12}, not less than	0.02 mg/kg	0.02 mg/kg
Zinc, not less than	100 mg/kg	100 mg/kg
Iron, not less than	100 mg/kg	100 mg/kg
Manganese, not less than	30 mg/kg	30 mg/kg
Copper, not less than	20 mg/kg	20 mg/kg
Iodine, not less than	0.5 mg/kg	0.5 mg/kg
Selenium, not less than	0.1 mg/kg	0.1 mg/kg
Antioxidant, not less than	100 mg/kg	100 mg/kg

Determination of blood glucose and triglycerides

Prior to measurement of glucose and triglyceride concentrations, the animals were fasted overnight before the collection of blood samples in order to avoid changes in insulin and glucose induced by food intake. Blood glucose and triglyceride concentrations were measured using an Accutrend glucometer (Roche Diagnostics GmbH, Mannheim, Germany).

Measurement of plasma insulin

The blood was collected from the overnight fasted rats at decapitation, in EDTA-pretreated tubes, followed by centrifugation at 3,000 rpm for 10 min. The separated plasma was transferred to Eppendorf tubes and kept at -20°C until analysis. The concentration of plasma insulin was determined by the RIA method, using rat insulin standards. Assay sensitivity was 0.6

Table 2. Food, liquid and caloric intake
Male and female rats, 21-day-old (9 or 10 per group, in two independent experiments), were exposed to normal or fructose-rich diet for 9 weeks. Food and liquid intake were recorded throughout experiment and caloric intake was calculated from data concerning food and 10% fructose consumption. Results are expressed per day per animal as mean ± SD.

	Normal Diet-Females	Fructose Rich Diet-Females	Normal Diet-Males	Fructose Rich Diet-Males	Two-Way ANOVA		
					Gender	Fructose	GxF
Food intake (g/day/animal)	17.41±2.99	12.59±0.67 **	20.57±2.63	14.20±2.01 *	< 0.05	< 0.001	NS
Liquid intake (mL/day/animal)	33.02±6.58	56.19±20.41 *	49.33± 5.39	74.10±11.36 *	< 0.05	< 0.01	NS
Caloric intake (kJ/day/animal)	191.51±32.89	236.06±30.21 *	226.23 ± 28.90	283.65 ±24.51*	< 0.05	< 0.01	NS

Abbreviations: NS - not significant; G - gender; F - fructose.
Normal diet *vs.* Fructose * p<0.05; ** p<0.01

Table 3. Body mass, absolute and relative mass of heart, visceral adipose tissue and liver
Body mass of rats in two experimental groups of both sexes was not significantly different at the beginning of diet regime. Body mass was measured at the end of experiment, while mass of organs was recorded immediately after sacrifice and presented as absolute units and in relation to body mass. Results are expressed as mean ± SD from 9 or 10 rats per group.

	Normal Diet - Females	Fructose Rich Diet - Females	Normal Diet - Males	Fructose Rich Diet - Males	Two-Way ANOVA		
					Gender	Fructose	GxF
Body mass (g)	259±28.66 ###	271.23±25.44 $	338.89±40.45	311.25±37.58	< 0.001	NS	NS
Mass of heart (g)	0.82±0.11 ###	0.82±0.08	1.05±0.14	0.94±0.16	< 0.001	NS	NS
Mass of VAT (g)	3.20±1.32	5.06±2.48 *	2.59±1.14	3.16±1.80	< 0.05	< 0.05	NS
Mass of liver (g)	7.93±0.97 ###	9.37±1.69 *	12.48±1.82	10.77±1.46	< 0.001	NS	< 0.01
Heart-to-body ratio (x1000)	3.17±0.16	3.04±0.21	3.11±0.19	3.00±0.26	NS	NS	NS
VAT-to-body ratio (x1000)	12.43±5.23	18.29±7.52 *$	7.48±2.84	10.06±4.81	< 0.001	< 0.05	NS
Liver-to-body ratio (x100)	3.07±0.33	3.41±0.89	3.67±0.25	3.48±0.41	NS	NS	NS

Abbreviations: VAT - visceral adipose tissue; NS - not significant; G - gender; F - fructose.
Normal diet *vs.* Fructose * p<0.05
Normal Diet - Females *vs.* Normal Diet - Males ### p<0.001
Fructose Rich Diet - Females *vs.* Fructose Rich Diet - Males $ p<0.05

mIU/l and the intra-assay coefficient of variation was 5.24 %.

Systolic blood pressure and heart rate measurement

Systolic blood pressure and heart rate were measured in conscious rats using the indirect tail-cuff method (Song et al., 2004) with external preheating.

Quantification of insulin sensitivity/resistance – HOMA index and IPGTT

Two different approaches were chosen for assessing insulin sensitivity (Muniyappa et al., 2008), i.e., the homeostasis model assessment (HOMA) index calculation and the intraperitoneal glucose tolerance test (IPGTT). The HOMA index, as an indicator of

insulin sensitivity, was calculated from fasted plasma insulin and glucose concentrations using the formula described by Matthews et al. (Matthews et al., 1985):

insulin (mU/L) × [glucose (mmol/l)/22.5].

IPGTT was performed three days before the end of the experimental period. Food was removed the night before and the fructose solution was replaced with water. A glucose challenge was given intraperitoneally (1 g/kg) (without anesthesia in order to avoid the effect of anesthetic on the glucose concentration and the kinetics of glucose disposal. Blood samples were taken from the tip of the tail at 0, 15, 30, 60, 90 and 120 min after injection in order to determine the plasma glucose concentration (Miatello et al., 1998).

The area under the concentration *vs*. time curve (AUC glucose 0-120 min, mmol/l *vs*. min) was calculated by the trapezoidal rule. The biological half-life (elimination half-life) of blood glucose (min) and the elimination rate constant of blood glucose (%/min) were calculated by linear regression analysis of the semilogarithmic plot of glucose concentration versus time between 15 and 120 min after glucose administration (Ahren and Filipsson, 2000).

Statistical Analysis

Values are expressed as the means ± S.D. of at least two independent experiments performed with 9-10 animals per group. To determine the effects of gender and fructose treatment, as well as their interaction, two-way ANOVA, followed by the post-hoc Tukey test was used. The statistical significance was accepted at $p<0.05$. Statistically significant between-group differences, the separate effects of the gender and fructose factors, as well as their interaction, are given in the Tables.

RESULTS

Food, liquid and caloric intake in male and female FFR

Two-way ANOVA analysis revealed significant effects of the main factors, gender and fructose (Table 2) on food, liquid and caloric intake. Post-hoc analysis showed that, in comparison to the control rats, the FFR had significantly decreased food intake (**p<0.01 for females, *p<0.05 for males, normal diet *vs*. fructose), and increased liquid intake (*p<0.05 for males and females, normal diet *vs.* fructose), which could be attributed to the palatable effect of the sweet fructose solution. Total caloric intake was raised in both male (*p<0.05 normal diet *vs.* fructose) and female (*p<0.05 normal diet *vs*. fructose) FFR, indicating disturbances in appetite regulation.

Body mass and the absolute and relative mass of the heart, visceral adipose tissue and liver

After two-way ANOVA analysis, a significant effect of gender was detected for body mass, mass of the heart, visceral adipose tissue and liver, and for the VAT-to-body ratio (Table 3). A significant effect of the fructose diet was detected for the mass of VAT and for the VAT-to-body ratio; the interaction of factors was significant only for the mass of the liver (Table 3). As shown by the post-hoc test, body mass was significantly different between males and females in both control and FFR (Table 3, ### p<0.001 normal diet-females *vs* normal diet-males; $ p<0.05 fructose rich diet-females *vs* fructose rich diet-males). Despite the increased caloric intake in the FFR, the body mass of these rats did not change significantly, either in females or in males (normal diet *vs.* fructose). The absolute mass of the whole heart, as well as the relative heart-to-body ratio, were not altered in FFR *vs.* control rats, giving no indication for heart hypertrophy. The only significant change was observed between genders in the control animals (Table 3, ### p<0.001 normal diet-females *vs.* normal diet-males). The mass of diabetogenic VAT and its ratio to body mass were increased in female FFR compared to control rats (*p<0.05 normal diet *vs.* fructose). The tendency of the increase of VAT mass and adipose tissue-to-body ratio in male FFR was not significant. A significant difference in the VAT-to-body ratio was observed between genders of the FFR ($ p<0.05 fructose rich diet-females *vs.* fructose rich diet-males). Absolute liver mass was increased in females

Table 4. Fasting glucose, triglycerides and insulin level at the end of the diet regime
Blood glucose and TG level was determined at the end of experiment, after overnight fasting of animals, while insulin level was measured in isolated plasma samples. Results are expressed as mean ± SD from 9 or 10 rats per group.

	Normal Diet - Females	Fructose Rich Diet - Females	Normal Diet – Males	Fructose Rich Diet - Males	Two-Way ANOVA		
					Gender	Fructose	GxF
Glucose (mmol/L)	5.38±0.65	4.58±0.84 *	5.20±0.42	4.84±0.62	NS	< 0.05	NS
Triglycerides (mmol/L)	1.39±0.29	1.87±0.38 **	1.49±0.36	1.90±0.35*	NS	< 0.01	NS
Insulin (mIU/L)	6.60±2.50 #	8.87±3.97	12.68±6.33	7.51±4.94	NS	NS	< 0.05

Abbreviations: NS - not significant; G - gender; F - fructose.
Normal diet *vs.* Fructose * $p<0.05$; ** $p<0.01$
Normal Diet - Females *vs.* Normal Diet - Males # $p<0.05$

Table 5. Systolic blood pressure and heart rate
Systolic blood pressure and heart rate were measured a week before the end of experiment by indirect tail-cuff method. Results are expressed as mean ± SD from 6 rats per group.

	Normal Diet – Females	Fructose Rich Diet – Females	Normal Diet – Males	Fructose Rich Diet – Males	Two-Way ANOVA		
					Gender	Fructose	GxF
Systolic blood pressure (mmHg)	121.43±7.61	124.14±12.40	109±4.33	120.6±7.92 *	< 0.05	NS	NS
Heart rate (beats/min)	433.71±47.21	437.14±24.84	479.33±43.63	475.2±36.60	< 0.05	NS	NS

Abbreviations: NS - not significant; G - gender; F - fructose.
Normal diet *vs.* Fructose * $p<0.05$

Table 6. Insulin sensitivity parameters-HOMA index and IPGTT
HOMA index was calculated using fasting glucose and insulin values for all animals at the end of experiment. IPGTT was performed three days before sacrifice. Results are expressed as mean ± SD from 6 rats per group.

	Normal Diet – Females	Fructose Rich Diet – Females	Normal Diet – Males	Fructose Rich Diet - Males	Two-Way ANOVA		
					Gender	Fructose	GxF
HOMA index	1.62±0.69	1.86±0.92	2.94±1.49	1.72±1.29	NS	NS	NS
IPGTT-glucose peak (mmol/L)	8.96±1.76 ##	11.96±5.23 $	20.32±2.35	20.61±1.52	< 0.001	NS	NS
IPGTT-glucose AUC	852.90±66.25	995.85±251.95 $$	1141.16±198.26	1445.04±126.43 *	< 0.001	< 0.05	NS
IPGTT-glucose disposal $T_{1/2}$ (min)	78.63±33.24	92.60±65.64	38.28±8.23	50.77±9.57*	< 0.05	NS	NS
IPGTT-glucose elimination rate (%/min)	0.38±0.21 ##	0.57±0.48	1.21±0.34	1.10±0.30	< 0.001	NS	NS

Abbreviations: NS - not significant; G - gender; F - fructose.
Normal diet *vs.* Fructose * $p<0.05$

(*p<0.05 normal diet *vs.* fructose) and tended to decrease in male FFR compared to the controls, while the relative liver-to-body ratio did not differ between FFR and control rats of both sexes (Table 3). In addition, liver mass was significantly different between males and females in control rats (Table 3, ### p<0.001 normal diet-females *vs.* normal diet-males).

Unlike the body mass, heart and liver mass, which were generally higher in males, the mass of visceral adipose tissue was higher in the female age- and diet-matched counterparts (Table 3).

Fasting glucose, triglycerides and insulin concentrations at the end of the diet regimen

Two-way ANOVA revealed the significant effect of a fructose diet on blood glucose and TG levels as well as interaction between the effects of gender and fructose on the concentration of insulin (Table 4). A significant hypoglycemia (*p<0.05 normal diet *vs.* fructose) and hypertriglyceridemia (**p<0.01 normal diet *vs.* fructose) were observed in female FFR, while male FFR showed only a tendency toward decreased glucose blood concentration and had increased blood TG in comparison to the animals on a normal diet (*p<0.05 normal diet *vs.* fructose) (Table 4). The plasma insulin concentration tended to increase in female FFR, whereas, in contrast, it tended to decrease in male FFR compared to the rats on the control diet regimen; however, the post-hoc test detected a significant difference in insulin level between the genders in the control rats (Table 4, # p<0.05 normal diet-females *vs.* normal diet-males).

Effects of a fructose rich diet on systolic blood pressure and heart rate in male and female rats

Two-way ANOVA detected a significant effect of the gender on both systolic blood pressure and heart rate (Table 5). Despite the fact that we generally did not observe the expected drastic changes in systolic blood pressure in the rats on the 10% fructose, a modest rise observed in male FFR was significant (*p<0.05 normal diet *vs.* fructose). The systolic blood pressure of females, as well as heart rate in both sexes, was not significantly changed in FFR compared to rats on normal diet (Table 5). An expected increase in blood pressure was probably missed due to the massive urination observed in the FFR.

HOMA index and intraperitoneal glucose tolerance test

The insulin sensitivity/resistance of rats was estimated by two different tests, HOMA index calculation and IPGTT (Fig. 1). The HOMA index, calculated from the fasting glucose and insulin concentrations, was not altered in FFR rats, regardless of sex (Table 2). Two-way ANOVA showed a significant effect of gender on all IPGTT parameters, and a significant effect of fructose on IPGTT-AUC in particular (Table 6). The post-hoc test detected the difference in both IPGTT-glucose peak and elimination between genders of control rats (Table 6, ## p<0.01 normal diet-females *vs.* normal diet-males). In the case of FFR, a difference in the glucose peak and AUC was detected between the genders (Table 6, $ p<0.05 and $$ p<0.01 fructose rich diet-females *vs.* fructose rich diet-males). In female FFR (normal diet *vs.* fructose), in accordance with the unchanged insulin sensitivity estimated by the HOMA index, we did not observe significant changes in GTT parameters, including the glucose peak level, AUC and glucose disposal. However, in male rats on the fructose-rich diet, the halftime of glucose disposal and AUC were increased in comparison with the control rats (Table 6, Fig. 1,*p<0.05 normal diet *vs.* fructose).

DISCUSSION

Females are protected against different disorders during their reproductive phase, probably by their sex hormone status (Murphy and Steenbergen, 2007; Bryzgalova et al., 2008). A recent burst of metabolic syndrome, which coincides with changes in modern lifestyle and nutrition habits, also shows a sex-dependent pattern (Onat et al., 2005; Mitrakou, 2006). An increased intake of fructose is a feature of the modern western diet. In this study, we analyzed the development of different disturbances that belong to the metabolic syndrome cluster in male and female

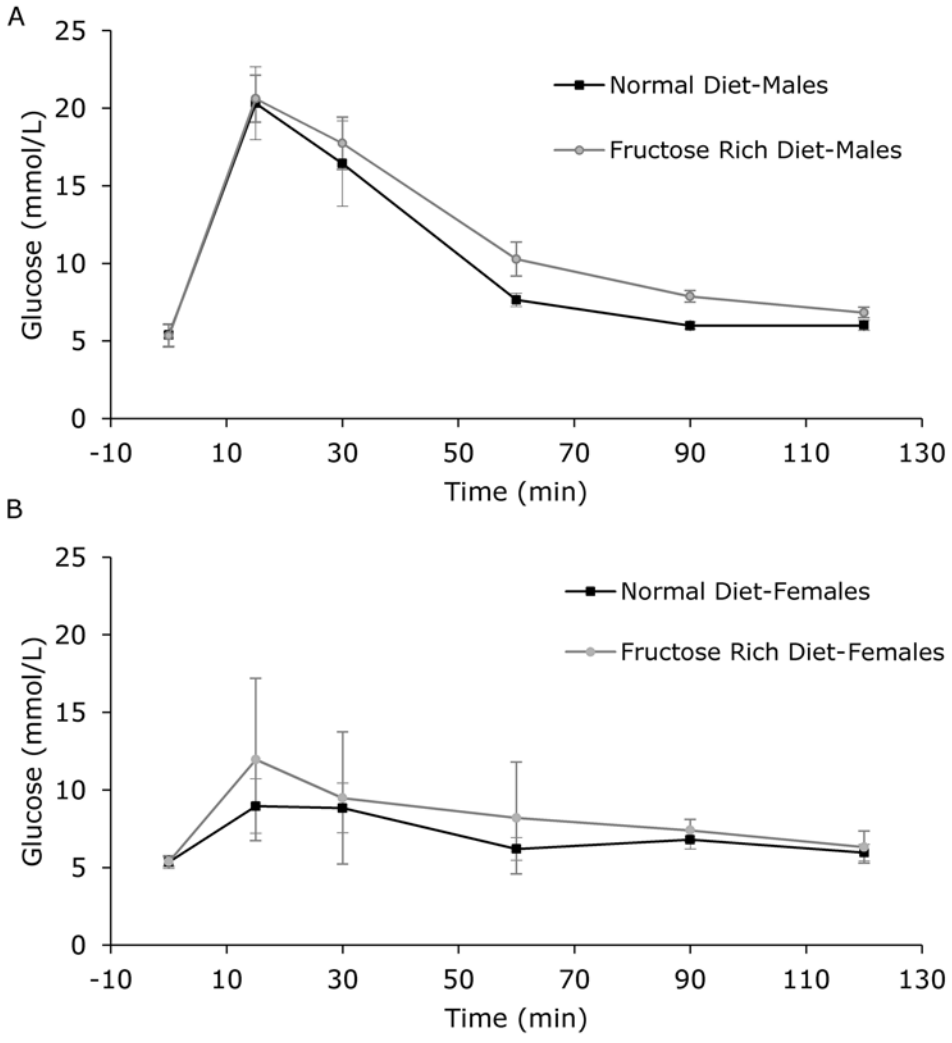

Fig. 1. Intraperitoneal glucose tolerance test. Male (a) and female (b) rats were exposed to overnight fasting before the test. After determination of the basal glucose value, animals were challenged with 1 g/kg of glucose given intraperitoneally to conscious rats. Glucose was measured 15, 30, 60, 90 and 120 min after glucose injection, and glucose concentration *vs.* time was plotted. Each experimental point represents mean ± SD from 6 rats per group.

rats that were provided with 10% fructose instead of water for nine weeks.

It was observed that decreased food consumption in FFR of both sexes was accompanied by an increase in liquid (10% fructose) intake. Together, this resulted in an increased caloric intake (Table 2), probably due to the palatable effects of fructose and changes in appetite regulation, indicating leptin resistance (Shapiro et al., 2008). However, an increased caloric intake did not influence the body mass of the rats, regardless of sex. In females, it led to an increase in the absolute and relative mass of visceral adipose tissue (Table 3), which could be important in terms of IR and metabolic syndrome development (Lemieux, 2001; Despres, 2006). The duration of the diet regimen was probably too short to expect the changes in heart mass that indicate cardiac hypertrophy (Axelsen et al., 2010). The observed increase in the absolute mass of the female

FFR liver might be related to enhanced fat accumulation, a characteristic for fructose-induced metabolic syndrome (Dekker et al., 2010). In the context of expected fat accumulation, the tendency for the absolute mass of the male FFR liver to decrease is unexpected (Table 3).

The fructose-rich diet initiated hypoglycemia and hypertriglyceridemia in female rats. This points to increased insulin activity, although the rise of plasma insulin concentration was not significant (Table 4). A change of glucose concentration was not observed in male FFRs.

Although FFR are established as a model for hypertension (Tran et al., 2009), we observed only a slight but significant increase of the systolic blood pressure in male rats (Table 5). We believe that the changes in blood pressure were annulated by the enhanced urination observed in the FFR.

Despite some tendency of the glucose peak value, AUC value and glucose elimination rate to change, the IPGTT performed on female FFR did not show significant differences between FFR and control animals. In contrast, male FFR had a higher AUC value and longer glucose disposal halftime than males on the normal diet (Table 6, Fig. 1), indicating decreased insulin sensitivity.

Two-way ANOVA ascertains the significant effect of gender with respect to food, liquid and caloric intake, body mass and mass of analyzed organs, systolic pressure and heart rate, even GTT parameters. The effect of the fructose diet factor on feeding behavior (food, liquid and caloric intake) was stronger than that of gender. The fructose diet also expressed significant effects on carbohydrate/lipid metabolism parameters (glycemia and triglyceridemia, as well as VAT mass and AUC glucose). Interactions between gender factor and fructose on the analyzed parameters were almost negligible.

In summary, the increased caloric intake in FFR of both sexes was followed by a gender-specific pattern of changes typical for the metabolic syndrome. Despite the fact that this study is limited to specific metabolic syndrome symptoms, the results emphasize the harmful effects of fructose consumption on cardiovascular risk and insulin action in males (Busserolles et al., 2002), whereas females exhibit other metabolic disturbances such as increased liver and adipose tissue, hypoglycemia and hypertriglyceridemia. The obtained results question the protection of females against high fructose consumption (Shrestha et al., 2009) and support our idea of gender-dependent differences in the expression of metabolic syndrome phenotype.

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