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ORIGINAL ARTICLE

The Effect of High-Fructose Feeding on Hemodynamic Behavior and Infarct Size of Isolated Rat Hearts Subjected to Low-Flow Ischemia

Düşük Akımlı İskemiye Maruz Kalan İzole Sıçan Kalplerinde Yüksek Fruktoz ile Beslenmenin Hemodinamik Davranış ve Enfarktüs Boyutu Üzerine Etkisi

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Note:

İzole sıçan kalbinde iskemi reperfüzyon hasarına bağlı oluşan hemodinamik yanıtlara yüksek fruktozlu ve yüksek glukozlu diyetin etkisi. 39. Ulusal Fizyoloji Kongresi, Ankara, P085, 2013.

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ABSTRACT

Objective: This study aimed to investigate the potentially deleterious effect of in vivo high-fructose feeding of rats on ex vivo hemodynamic recovery and infarct size of isolated rat hearts subjected to low-flow ischemia and reperfusion.
Methods: After feeding Sprague-Dawley male rats with a high-fructose (n=9), high-glucose (n=9), or a standard diet (n=9) for four weeks, the hearts were extirpated and perfused ex vivo with a Krebs-Henseleit solution for 15 minutes; after that, the hearts were subjected to low-flow (0.3 ml/minute) ischemia during 30 minutes followed by 60 minutes reperfusion. Left developed ventricular pressure, maximum and minimum rate changes of left ventricular pressure, and heart rate were recorded before ischemia and after reperfusion. The Infarct area was measured at the end of the reperfusion period.
Results: The relative myocardial infarct size did not differ between the three groups in isolated hearts subjected to ex vivo low-flow ischemia followed by 60 minutes of reperfusion. Post-ischemic cardiac contractile recovery appeared complete in the high-fructose and high-glucose groups at 60 minutes of reperfusion. In contrast, the left developed ventricular pressure and minimum rate change of left ventricular pressure were still depressed at the end of 60 minutes of reperfusion in the control group.
Conclusion: High-fructose diet in rats appears to positively affect the recovery of left ventricular contractile function after low-flow ischemia, compared to a standard diet, without a difference in relative myocardial infarct size. Similar results were obtained in the high-glucose-fed rats.

Keywords: Fructose, infarct size, ischemia, isolated heart, reperfusion

ÖZ

Amaç: Bu çalışmanın amacı, düşük akımlı iskemi ve reperfüzyona maruz bırakılan izole sıçan kalplerinde in vivo yüksek fruktozla beslenmenin, ex vivo hemodinamik iyileşme ve enfarktüs boyutu üzerindeki potansiyel zararlı etkisini araştırmaktır.
Gereç ve Yöntemler: Erkek Sprague-Dawley sıçanları dört hafta boyunca yüksek fruktozlu (n=9), yüksek glikozlu (n=9) veya standart bir diyetle (n=9) beslendikten sonra, kalpleri çıkarıldı ve Krebs-Henseleit solüsyonu ile 15 dakika ex vivo perfüze edildi. Daha sonra kalpler, 30 dakika boyunca düşük akımlı (0.3 ml/dk) iskemiye ve ardından 60 dakikalık reperfüzyona tabii tutuldu. Sol ventrikül gelişim basıncı, kasılma ve gevşeme fazındaki basınç gelişim oranları ve kalp hızı iskemi öncesi ve reperfüzyon sonrası kaydedildi. Enfarktüs alanı reperfüzyon periyodunun sonunda ölçüldü.
Bulgular: İzole kalplerde ex vivo düşük akımlı iskemi ve sonrasında 60 dakikalık reperfüzyonu takiben, miyokard enfarktüsü boyutu üç grup arasında farklılık göstermedi. Hem yüksek fruktoz hem de yüksek glikoz grubunda, iskemi sonrası kardiyak kontraktil iyileşmenin 60 dakikalık reperfüzyonda tamamlanmış olduğu görüldü. Buna karşılık, kontrol grubunda sol ventrikül gelişim basıncı ve sol ventrikül minimum basınç değişim oranı, 60 dakikalık reperfüzyonun sonunda hâlen baskılanmaktaydı.
Sonuç: Yüksek fruktozlu diyet standart diyetle karşılaştırıldığında, düşük akımlı iskemi sonrası sol ventrikül kontraktil fonksiyonunun iyileşmesinde olumlu etki göstermekte ancak miyokard enfarktüsü boyutunda farklılık oluşturmamaktadır. Yüksek glikozla beslenen sıçanlarda da benzer sonuçlar elde edilmiştir.

Anahtar Kelimeler: Enfarktüs boyutu, fruktoz, iskemi, izole kalp, reperfüzyon

Introduction

In recent years, fructose has received much attention due to the considerably increased more consumption in humans, than the others, by the widespread use of added sugars in the food industry. Fructose intake by humans was at about 16-20 g per day, mostly from natural sources, in the past. In the last thirty years, dietary consumption has increased to about 85-100 g per day due to industrial products such as industrial juices, canned fruits, jams, and jellies (1). Sucrose and high-fructose corn syrup are the most common industrial sweeteners containing fructose and glucose (2, 3). It is generally accepted that high-fructose intake may play an important role in the widespread increase in obesity and the symptoms of metabolic syndrome in humans (4-6). A recent study by Bahadoran et al. (7) disclosed an adverse effect of high-fructose intake on

cardiovascular function in rats.

Moreover, fructose was found to induce myocardial insulin resistance and alter calcium handling in cardiomyocytes (8). Excessive fructose consumption may play an important role in disturbing cardiac insulin signaling (9). High fructose intake appeared to be associated with the progression of diabetic cardiomyopathy and heart failure (10). A fructose-rich diet has also been shown to affect endothelial vasodilation in coronary vessels (11) negatively.

In contrast to studies showing harmful effects of high-fructose intake on cardiac function, several studies provided evidence that fructose feeding before ischemia (12, 13) and fructose administration during the post-conditioning period (14, 15) reduces infarct size in isolated rat hearts following ischemia-reperfusion (14, 15). The suggestion has been made that the protective effect of fructose feeding relates to the mitochondrial KATP channel-induced preconditioning in the myocardium (12). Consequently, fructose may reduce necrosis during the reperfusion period and enhance ATP production required for proper cardiac electro-mechanical functioning.

The present study aimed to explore the effect of a fructose-rich diet for four weeks in rats subjected to *ex vivo* low-flow ischemia followed by reperfusion on cardiac contractility and infarct size. To better understand the effects of a high-fructose diet on cardiac function, we compared the results of the four weeks of high-fructose feeding with those of a high-glucose and a standard starch diet.

Materials and Methods

Male Sprague-Dawley rats (weighing 250-350 g) were purchased from the Animal Care and Research Unit of Trakya University and housed in an air-conditioned room at 22±2 °C and humidity (55% ± 5%). All groups were exposed to a 12 h light-dark cycle, with *ad libitum* access to drinking water for four weeks. Animals were randomly allotted to 3 groups and supplied with three different diets for four weeks: C (control, n = 9), FRD (fructose-rich diet, n = 9), and GRD (glucose-rich diet, n = 9). The rats in the C group were fed with standard pellet feed (5% fat, 20% protein, and 65% starch, 5% cellulose, 1% vitamins, 3.5% minerals, and 0.5% metionin) (Optima Rat Chow, Bolu, Turkey). The nutritional content of the FRD group included high level of fructose (5% fat, 20% protein and 65% fructose, 5% cellulose, 1% vitamins, 3.5% minerals and 0.5% metionin) and GRD group contained high level of glucose (5% fat, 20% protein and 65% glucose, 5% cellulose, 1% vitamins, 3.5% minerals and 0.5% metionin). The diets were prepared commercially, similar to previous studies (13, 16) by MBD Rat Chow, Kocaeli, Turkey.

Body weight was measured at the beginning and at the end of the four weeks feeding period. The current study was approved by the Trakya University Local Ethics Committee and Trakya University Faculty of Medicine Animal Care and Use Committee (decision number 2011.07.05).

Isolated heart preparation

At the end of the four weeks feeding period, heparin was injected intraperitoneally (500 IU/kg; Nevparin Flakon, Mustafa Nevzat İlaç Sanayi A.Ş., Istanbul, Turkey), followed by intraperitoneal administration of thiopental for anesthesia (100 mg/kg, I.E., Ulagay A.Ş., Istanbul, Turkey) (17).

After the opening of the thorax, the hearts were quickly removed and placed on a Petri dish containing cooled Krebs-Henseleit solution. Then, the aortic stump of the heart was attached to the cannula of the Langendorff system, and a latex balloon was inserted in the left ventricle through the mitral valve. The heart was perfused with Krebs-Henseleit solution during a 15-min equilibration period under constant 65-70 mmHg pressure at 37 °C and pH 7.4. A peristaltic pump (Peri-Star Pro, World Precision Instruments, Inc. Germany) was used for pumping the Krebs-Henseleit solution through the heart mounted on the Langendorff system, varying the pump rate flow through the heart could be changed. The system allowed measuring the buffer flow rate, which was displayed digitally.

The first hemodynamic measurement (pre-ischemia) was performed at the end of the equilibration period. After that, the hearts were subjected to 30-min low-flow ischemia (0.3 ml/min) followed by 60-min reperfusion. We applied low-flow ischemia instead of zero-flow ischemia, prompted by Lloyd et al. (18) study. The level of low-flow ischemia (0.3 ml/min) was chosen because it is in the same range of blood flow in the infarct regions generally observed in humans and animals (18).

Hemodynamic parameters were re-recorded on the first (RP 1min) and 60th (RP 60min) minute of reperfusion. Left ventricular development pressure (LVDP), the first derivative of LV developed pressure during the systolic phase (dP/dt max), the first derivative of LV pressure relaxation during the diastolic phase (dP/dt min), and heart rate (HR) were recorded by a data acquisition system (Biopac MP36 System, Inc., USA).

Krebs-Henseleit solution contained (mmol/l) NaCl (118), NaHCO3 (25), KCl (4.7), KH2PO4 (1.2), MgSO4 (1.2), CaCl2 (1.8), and glucose (11.1). The perfusate was equilibrated with 95% O2 and 5% CO2 (19). All ingredients were dissolved in distilled water, and calcium chloride was added as the last ingredient to prevent precipitation (15).

Measurement of percentage infarcted tissue

At the end of ischemia-reperfusion, isolated hearts were removed from the Langendorff system, wrapped in a stretchable plastic film, and frozen at -20°C for 24 h. After that, the left ventricle tissue was cut into

2-mm thick slices. The slices were incubated in a buffer containing 1% tetrazolium for 15-20 min at pH=7.4. Tissue pieces were dried with filter paper and placed between two thin glass surfaces. Glass surfaces were tightened together. Then, a thin transparent acetate-plastic sheet was placed on the glass surface, and infarcted and non-infarcted areas were marked on the acetate sheet. Subsequently, the drawings were scanned. The size of the infarcted area was measured using the computerized planimetric method (20). The infarct size was expressed relative to the total tissue surface area measured.

Plasma glucose concentration and lipid profile

Blood samples (5 ml) were taken for metabolic analysis at the end of the four weeks feeding period following anesthesia. Plasma was obtained by centrifugation of the blood at 2600 x g for 10 min at room temperature. Plasma samples were portioned and stored at -20°C. Glucose, triacylglycerol, and cholesterol levels were measured with an automated analyzer using the ADVIA 1800 Clinical Chemistry System (Siemens, Camberley, UK).

Statistical method

The sample size was assessed at nine rats per group based on an effect size of 0.45, group number 3, measurements number 4, an alpha level of 5%, and a power of 80%. Values are expressed as mean ± standard deviation.

The Shapiro Wilk test tested the normality distribution of the numeric variables. Kruskal-Wallis Test was used to compare all numeric data among groups, and then the Dunn test with Bonferroni correction was used for multiple comparisons. A comparison of more than two related data belonging to each group was made using the Friedman Test. P<0.05 values were considered statistically significant. IBM SPSS 20.0 package program (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) analyzed the data.

Results

***In vivo* measurements**

Initial values of body weight did not differ between the three groups: C (271.4±19.0 g), FRD (286.2±19.2 g), and GRD (270.5±25.5 g) (p=0.277). In the FRD group, body weight increased significantly after four weeks of feeding (296.0 ± 15.4 g vs. 286.2 ± 19.2 g; p=0.024). The bodyweight of the FRD group was higher than that of the C group (p = 0.036) at the end of the feeding period; no significant difference was found between the FRD and GRD groups (p=0.052; Table 1).

Plasma glucose did not differ between the three groups at the end of the feeding period. Plasma triacylglycerol levels showed an almost 4-fold increase in the FRD group (p=0.053 compared to control and high-glucose-fed animals). The plasma cholesterol level of the GRD group was highly significant 50% higher than that of the C and FRD group (p=0.001; Table 1).

***Ex vivo* measurements**

The mean values of LVDP during the pre-ischemic period and after reperfusion did not significantly differ between the three groups. More detailed analysis per individual group showed a small but non-significant decline during the first minute after reperfusion of rat hearts of groups C and GRD (Table 2). Moreover, the degree of recovery of LVDP at 60 minutes of reperfusion of the FRD group exceeded that of the control C group (+15±48 mmHg vs. -51±44 mmHg, p=0.021).

In the pre-ischemic period, the mean values of dP/dtmax did not significantly differ between the three groups. Although dP/dtmax tended to decline in the control group, the mean values at 1st minute and 60th minute of reperfusion did not significantly differ between the C, FRD, and GRD groups (Table 2).

In the pre-ischemic period, the mean dP/dtmin did not differ between the three groups. In all groups, the relaxation rate declined at the first minute of reperfusion. However, only in group C and group FRD did this decline reach the significance level compared to pre-ischemic values (Table 2). DP/dtmin completely recovered both in group FRD and GRD at 60th minute of reperfusion, while dP/dtmin in group C remained significantly depressed at this time point (p<0.05).

Data in Table 2 show that the mean values of heart rate in the pre-ischemic period and after 1 minute and 60 minutes of reperfusion did not significantly differ between the three groups. However, detailed analysis per individual group revealed that only in the FRD group the post-ischemic recovery of heart rate was slightly but significantly delayed at 60th minutes of reperfusion compared to pre-ischemia (230±26 beats/minute vs. 266±30 beats/minute, p<0.05).

The relative myocardial infarct size of groups C, FRD, and GRD amounted to 10.9%±4.2%, 9.7%±7.2%, and 10.2%±4.2%, respectively. The differences did not reach statistical significance (p=0.927).

Table 1. Body weight, plasma glucose, cholesterol and triacylglycerol levels at the end of the 4-week *in vivo* feeding period

	C (n=9)	FRD (n=7)	GRD (n=9)	p
Body Weight (g)	263 ± 30	296 ± 15 *	270 ± 25	0.036
Glucose (mmol/l)	10.2 ± 1.7	11.5 ± 2.0	10.0 ± 1.7	0.174
Cholesterol (mmol/l)	1.05 ± 0.2	1.05 ± 0.24	1.56 ± 0.2 *#	0.001
Triacylglycerol (mmol/l)	0.58 ± 0.25	2.19 ± 1.09	0.43 ± 0.38	0.053

C; control, FRD; fructose-rich diet, GRD; glucose-rich diet
* p<0.05 compared with C group; # p<0.05 compared with FRD group

Table 2. *Ex vivo* measurements: Hemodynamic behavior of isolated rat hearts subjected to low flow-ischemia and reperfusion.

		C (n=9)	FRD (n=7)	GRD (n=9)	P
LVDP (mmHg)	Pre-ischemia	122 ± 37	104 ± 37	102 ± 39	0.911
	RP 1min	111±76	111±35	100±38	0.738
	RP 60min	71±56	119±43	102±49	0.115
	Δ Change pre-ischemia to RP 1min	-11 ± 67	7 ± 22	-2 ± 26	0.742
	Δ Change pre-ischemia to RP 60min	-51 ± 44	15 ± 48 ª	0 ± 43	0.021
dP/dtmax(mmHg/s)	Pre-ischemia	3164±1192	2776±1302	2364±931	0.513
	RP 1min	1898±1824	2866±977	2764±1537	0.557
	RP 60min	2017±2051	3609±1658	2552±1701	0.181
	Δ Change pre-ischemia to RP 1min	-1266 ± 1317	90 ± 1002	400 ± 1659	0.080
	Δ Change pre-ischemia to RP 60min	-1147 ± 1617	833 ± 1778	188 ± 1790	0.074
dP/dt min (mmHg/s)	Pre-ischemia	-2323±587	-2202±823	-1847±539	0.331
	RP 1min	-1210±455*	-1519±362*#	-1451±375	0.259
	RP 60min	-1445±806*	-2230±682	-1576±652	0.072
	Δ Change pre-ischemia to RP 1min	1113 ± 386	683 ± 654	396 ± 656	0.055
	Δ Change pre-ischemia to RP 60min	878 ± 450	-28 ± 846 ª	271 ± 864	0.037
HR (beats/min)	Pre-ischemia	236±30	266±30	254±22	0.169
	RP 1min	158±96#	192±46*#	191±53*	0.196
	RP 60min	257±64	230±26*	214±50	0.128
	Δ Change pre-ischemia to RP 1min	-78 ± 112	-74 ± 35	-63 ± 55	0.405
	Δ Change pre-ischemia to RP 60min	21 ± 79	-36 ± 35	-40 ± 53	0.172

LVDP: left ventricular developed pressure; dP/dt max: first derivative of the increase of left ventricular pressure (contraction phase); dP/dt min first derivative of the decline of left ventricular pressure (relaxation phase); HR: heart rate; C: control group; FRD: fructose-rich diet group: GRD: glucose-rich diet group; RP 1min: first minute of reperfusion; RP 60min: 60th minute of reperfusion; *: significant difference compared to pre-ischemia ($p<0.05$), #: Significant difference compared to RP 60min ($p<0.05$), a: Significant difference compared to C group.

Discussion

The present study aimed to investigate whether long-term feeding of rats with a high-fructose diet resulted in a decline in ischemia tolerance of the heart. The main conclusion of the present findings is that four weeks of high-fructose feeding in rats did not result in an impaired ischemia tolerance during *ex vivo* low-flow ischemia followed by reperfusion. This conclusion is based on the observation that the relative myocardial infarct size did not differ between rats fed with a high-fructose, high-glucose, and a standard starch diet. Moreover, the post-ischemic recovery of left ventricular pressure and its first derivative during the relaxation phase was even better in the high-fructose group than in the control and starch-fed group. It should be emphasized that post-ischemic hemodynamic recovery did not significantly differ between the high-fructose and the high-glucose group.

Conflicting findings have been published about the effect of fructose feeding on cardiac tolerance against ischemia. Faure et al. observed an improved hemodynamic response in 4 weeks of the high-fructose diet rat model compared to starch-fed control animals during the reperfusion period combined with smaller infarct size (13). Similarly, a recent study carried out by Haghi et al. showed that fructose consumption with glucose or fructose alone reduced the percentage of infarct size in isolated rat hearts (15). Protective effects against myocardial ischemia/reperfusion injury have also been reported by Jordon and coworkers (12) following a relatively short duration (3 days) of a fructose-rich diet in rats. It has been suggested that fructose feeding may directly enhance glycogen storages, resulting in a higher anaerobic store of energy in the myocardium (12). In addition, as a pro-oxidant factor, fructose may increase plasma Vitamin E levels and, hence, mitigate the deleterious effect of excess oxygen-free radicals on the hemodynamic response during cardiac ischemia and reperfusion (13).

In contrast to the beneficial findings, adverse hemodynamic effects during ischemia and reperfusion were reported in the studies. The animals were exposed to a fructose-rich diet with longer time duration (21, 22). Sakr et al. (21) observed a decline in left ventricle contraction and relaxation rate in rats exposed to a high-cholesterol and high-fructose diet for 15 weeks compared to the control group. In another study, Xing et al. (23) showed that 32 weeks of fructose-rich diet significantly impaired left ventricular diastolic function in rats. The mechanism of high-fructose feeding on cardiac function, either positive or negative, remains unclear. Some evidence points to insulin resistance induced by high-fructose feeding as an underlying factor altering the heart's tolerance to ischemia and reperfusion (24). On the other hand, it has been suggested that the deleterious effect of high-fructose feeding may be related to renal damage rather than cardiac dysfunction (25). An excessive increase of calories resulting from fructose consumption has been suggested to increase susceptibility to myocardial ischemia and reperfusion injury (26).

Although we observed an improved recovery of a post-ischemic hemodynamic period of rat hearts following a high-fructose diet compared with a standard starch diet, this beneficial effect appeared not specific to fructose. The post-ischemic recovery of left ventricular

pressure and the first derivative of the pressure decline during the relaxation phase was similar between high-fructose and high-glucose feeding. This exciting observation suggests that the mere presence of small 6-carbon sugars, either fructose or glucose, is more important than the type of low molecular weight sugar in increasing ischemia and reperfusion tolerance in isolated rat hearts. More experimentation is needed to disclose the underlying molecular mechanism of the beneficial effect observed after four weeks of high-fructose and high-glucose feeding.

An additional finding of the present study is the approximately 10% increase in body weight of rats after four weeks of high-fructose feeding. Although not measured in our study, this increase is most likely caused by increased body fat mass. In contrast, high-glucose feeding did not result in an increase in body mass compared to control animals. These findings point to essential differences between overall body fructose and glucose metabolism. In this respect, it is of note that fructose feeding possesses a more pronounced lipogenic potential than glucose (27).

Moreover, high-fructose diets result more likely in lipid abnormalities, including hypertriglyceridemia, than high-glucose diets (28, 29). In the present study, blood analysis also indicated a lipogenic action of the high-fructose diet. This diet resulted in an almost 4-fold increase in blood plasma triacylglycerol levels compared to the high-glucose and standard starch diets. However, it is of note that the difference was borderline significant (p=0.052). A cautious conclusion is that fructose's in vivo lipogenic effect does not impair hemodynamic recovery and increases infarct size in the *ex vivo* post-ischemic heart. Another interesting finding is that the significant 50% increase in plasma cholesterol level in the high-glucose fed group *in vivo* did not significantly decline in an *ex vivo* hemodynamic recovery or increased infarct size following low-flow ischemia and reperfusion.

It is not easy to investigate the impact of high-fructose feeding in humans because, in general, fructose consumption is always combined with other sugars' dietary intake. In one of the few studies addressing this issue, dietary intake of fructose for four weeks has been found to induce changes in lipid metabolism without a significant effect on insulin sensitivity in healthy humans (30). Consistent with the present study, fructose feeding compared to glucose appeared to considerably enhance plasma triacylglycerol levels with a minimal effect on plasma cholesterol levels in healthy people (31). Although it is known that high sugar intake, like fructose and glucose, increases the risk of fatal outcomes of cardiovascular diseases (32), detrimental or beneficial effects of high fructose consumption on the hemodynamic function of the human ischemic heart have not been explored in full detail. Therefore, the present study may provide a valuable starting point for future studies on the effect of high-fructose and high-glucose feeding on cardiac hemodynamic function after ischemia and reperfusion in the human context.

Long-term feeding with fructose can potentially disturb the myocardium's functions because dietary fructose is a contributor factor to insulin resistance (33). A previous study by Faure et al. (13) showed insulin resistance in the fructose-rich diet group for four weeks. This study could not include the effect of a fructose-rich diet on insulin levels and possible insulin resistance, which can be seen as a limitation.

Conclusion

The present study's findings in rats demonstrate that in addition to metabolic effects, high-fructose feeding for four weeks may provide positive hemodynamic effects on left ventricle function, without changing myocardial infarct size, during reperfusion after low-flow ischemia. This effect is not specific to fructose since high-glucose feeding resulted in a comparable outcome. The present study also suggests that polysaccharide intake such as starch may be more detrimental to cardiac hemodynamic function after low-flow ischemia than monosaccharide intakes like fructose and glucose.

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Conflict of Interest

None of the authors have potential conflicts of interest to be disclosed.

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