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THE IMPACT OF SEX ON METABOLIC AND FUNCTIONAL ABNORMALITIES, INDUCED BY HIGH-FRUCTOSE DIET IN RATS*

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Metabolic syndrome (MetS) is defined as a cluster of interrelated metabolic and cardiovascular risk factors such as impaired glucose homeostasis, atherogenic dyslipidemia, arterial hypertension, abdominal obesity and other. MetS was found to be associated with a 5-fold increase in the risk of type 2 diabetes mellitus (T2DM) and with a 2-fold raise of risk of cardiovascular disease (CVD), stroke, myocardial infarction and mortality [1]. Clinical studies have reported that each component of MetS is supposed as independent cardiometabolic risk factor and coexistence of these factors dramatically increases the rate of cardiovascular complications.

Recently, it was established that the degree of cardiometabolic risk is influence by gender and sex hormones level throughout lifespan. Both male and female sex hormones, as well as the sex chromosomes, regulate the development of obesity and affect insulin homeostasis and blood pressure. Menopause is connected with development of central obesity, dyslipidemia and hypertension, which can lead to CVD risk escalation [2].

Estrogen deficiency, which occurs in women after menopause, is considered as an additional factor of significant increase in risk for T2DM and CVD [1].

A number of studies have shown that differences in cardiovascular risk factors between individuals with T2DM and normal glucose metabolism are more pronounced in women than in men. Thus, mortality due to coronary heart disease in women with diabetes increases by 2.2-3.8 times, while in men, an increase is noted by 1.9–2.8 times compared to persons without diabetes [3]. The causes of women's higher risk of diabetic CVD are not fully clarified but may be associated with greater metabolic risk deterioration during pre-diabetes in women than men [3].

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The significant differences in manifestation of some components of metabolic syndrome possibly exist due to dissimilar pathophysiological processes in women and men and accurate reasons of higher cardiovascular risk in women need future investigations.

The aim of the study was to determine the differences in impairment of glucose, lipid metabolism and cardiovascular systems function between male and female rats with different levels of estrogen sufficiency.

MATERIALS AND METHODS

All used chemicals were of analytical reagent grade quality.

The present study was approved by the bioethics committee of the «V. Danilevsky Institute for Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine» (Kharkiv, Ukraine) and performed in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986).

The experiment was performed on 12 male and 18 female Wistar rats (12-week-old, 160–190 g body weight (b.w.)), which were housed in Plexiglas cages (3 animals per cage) at a temperature of (22 ± 1) °C in a constant 12-hour light/dark cycle. Estrogen deficiency was reproduced by bilateral ovariectomy in female rats under light ether anaesthesia. Females with intact ovaries were sham-operated. MetS induction was started two weeks after surgery. MetS was modelled in male and female rats with different levels of estrogen by chronic (for eight weeks) intake of fructose with drinking water at a concentration of 200 g/L (HFD) [4]. Control intact rats were fed a standard diet during 8 weeks. The animals had free access to water. Experimental rats were divided into five groups: control male (n = 6), control female (n = 6), male with HFD (n = 6), female with intact ovaries and HFD (n = 6), ovarictomized (OVX) female with HFD (n = 6).

In 16 weeks, glucose homeostasis was assessed by basal glycemia, glycemia during the intra-abdominal glucose tolerance test (IGT) (3 g/kg b.w.) and fructosamine level in blood serum [5]. Insulin sensitivity was determined using the intra-abdominal insulin tolerance test (ITT) (insulin 0.5 U/kg b.w., glucose 2 g/kg in 10 min after insulin administration) [6]. Tail blood glucose levels were measured using a glucose analyzer Eksan-G (Analita, Republic of Lithuania). Areas under glycemic curves (AUC) were calculated using the Mathlab computer program. The animals were sacrificed according to the protocol of the ethics committee. Body weight gain and visceral fat, calculated as the sum of epigonadal, epinephric and mesenteric fat, were determined. The level of total cholesterol (TC) and triglycerides (TG) in blood serum was determined using a spectrophotometer Shimadzy [7, 8]. The levels of estradiol and testosterone in blood serum were determined by the enzyme immunoassay method on the Stat Fax. In females, the level of hormones was measured in the diestrus stage. Electrocardiograms (ECG) were obtained in three standard leads from the limbs using a veterinary Heart Screen 60G-VET cardiograph with a tape speed of 50 mm/s and a standard gain of 1 mV — 20 mm. Data are presented as mean ± standard error of mean (SEM). The Shapiro-Wilk test was used to test normality of data distribution. For multiple comparisons of data with a normal distribution, a parametric one-way analysis of variance (ANOVA) was performed and the Student-Newman-Keuls method was used to test differences in means. Values were considered statistically significant at $p < 0.05$.

RESULTS AND THEIR DISCUSSION

To study the impact of sex on development of metabolic syndrome and cardiovascular complications we used a model of pre-diabetes induced by chronic consumption of high level of fructose in rats. The results of same preclinical studies have shown that chronic intake of fructose leads to the development of some component of MetS: insulin resistance, T2DM, ectopic fat deposition, hypertriglyceridemia and elevated blood pressure in rodents [9].

It was established that the fasting glucose in blood of experimental animals with HFD

Table 1

Indexes of glucose homeostasis in male and female rats, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Index	Control		HFD		
	males	females	males	females	
				sham-operated	OVX
Basal glucose level, mmol/L	4.69 ± 0.28	4.30 ± 0.12	4.62 ± 0.35	4.39 ± 0.34	4.33 ± 0.12
AUC during IGT, mmol/L *min	683.1 ± 27.4	560.5 ± 31.7	1043.7 ± 82.5$^{*\#}$	592.6 ± 30.3$^{\#}$	802.3 ± 20.1$^{*\#+}$
AUC during ITT, mmol/L *min	379.9 ± 34.2	373.6 ± 25.4	547.1 ± 18.8^{*+}	427.5 ± 30.5$^{\#}$	536.1 ± 31.3^{*+}
Fructosamine level, mmol/L	1.26 ± 0.12	1.64 ± 0.20	2.34 ± 0.19^{*+}	1.87 ± 0.17$^{\#}$	2.34 ± 0.21^{*+}

Note:
Data are shown as mean ± standard error of the mean (SEM).
* $p < 0.05$ vs «Control rats of the corresponding sex»,
$^{\#}$ $p < 0.05$ vs «HFD rats of the opposite sex»,
$^{+}$ $p < 0.05$ vs «HFD sham-operated female rats».

Table 2

Body weight gain and relative mass of fat in male and female rats, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Index	Control		HFD		
	males	females	males	females	
				sham-operated	OVX
Body weight gain, %	12.24 ± 2.05	13.67 ± 1.25	21.19 ± 1.64$^{*\#}$	14.79 ± 0.78$^{\#}$	28.96 ± 2.00$^{*\#+}$
Relative mass of hypogonadal fat, %	0.83 ± 0.04$^{\#}$	2.28 ± 0.19$^{\#}$	1.66 ± 0.15$^{*\#}$	2.69 ± 0.18$^{\#}$	3.92 ± 0.25$^{*\#+}$
Relative mass of epinephrine fat, %	0.46 ± 0.06$^{\#}$	0.96 ± 0.06$^{\#}$	1.35 ± 0.18$^{*\#}$	1.07 ± 0.20	2.81 ± 0.24$^{*\#+}$
Relative mass of mesenteric fat, %	0.40 ± 0.06$^{\#}$	0.83 ± 0.08$^{\#}$	0.94 ± 0.12$^{*\#}$	0.88 ± 0.20	1.54 ± 0.13$^{*\#+}$
Relative mass of total visceral fat, %	1.68 ± 0.13$^{\#}$	4.07 ± 0.29$^{\#}$	3.95 ± 0.31$^{*\#}$	4.65 ± 0.34	8.27 ± 0.46$^{*\#+}$

Note:
Data are shown as mean ± standard error of the mean (SEM).
* $p < 0.05$ vs «Control rats of the corresponding sex»,
$^{\#}$ $p < 0.05$ vs «HFD rats of the opposite sex»,
$^{+}$ $p < 0.05$ vs «HFD sham-operated female rats».

does not differ from the levels of intact controls. At the same time, significant increase in fructosamine level, deterioration of glucose tolerance and development of insulin resistance were found in OVX female and male rats, fed HFD, compared to control animals of both sexes. It should be noted that neither fructosamine level nor glucose homeostasis and insulin sensitivity were modified by HFD in female rats with intact ovaries in comparison with control animals (Table 1).

OVX females had a less pronounced impairment of glucose tolerance in comparison with males with HFD, which may be the result of either compensatory increased insulin secretion or greater sensitivity to insulin in the liver

Table 3

Indexes of lipid profile in male and female rats, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Index	Control		HFD	
	males	females	males	OVX females
TG level, mmol/L	0,69 ± 0,05	0,85 ± 0,05	1,32 ± 0,07*#	1,93 ± 0,09*#
TC level, mmol/L	1,67 ± 0,09	2,02 ± 0,24	1,93 ± 0,07#	3,87 ± 0,27*#

Note:
Data are shown as mean ± standard error of the mean (SEM).
* $p < 0.05$ vs «Control rats of the corresponding sex»,
\# $p < 0.05$ vs «HFD rats of the opposite sex».

and muscles [10]. The causes of these differences in dysglycemia are fully unknown, but possibly involve the effect of gonadal hormones and sexual hormone-binding globulin levels.

Compared with control animals, both male and OVX female, fed HFD, had greater intensity of body weight gain and significantly higher levels of relative mass of hypogonadal, epinephrine, mesenteric and total visceral fat, but these indexes were more pronounced in female with estrogen deficiency than in male. Sham-operated HFD-treated female with intact ovaries have not shown the sings of obesity (Table 2).

Sex differences in adipose tissue distribution are determined by accumulation of fat mass in the gluteus–femoral area in women, while men predominately store fat in visceral region, which is associated with metabolic disorder and higher risks of T2DM and CVD in the male population. However, the transition from normoglycaemia state to T2DM is characterized by accumulation more visceral fat in women and increases the risk of female ischemic heart disease. Increased visceral fat deposition showed larger cardiometabolic risk in women, independent of glucose and lipid abnormalities, compared with men [11].

In addition, in menopause period the visceral depot as a result of reduced protective effect of estrogens, leads to development endothelial dysfunction, proinflammatory state and stiffness of arteries, which resulted in a higher risk of cardiovascular diseases in woman [11].

It was established that HFD does not cause the development of glucose intolerance, insulin resistance and obesity in female rats with intact ovaries, what is confirmed by many preclinical researches, and these animals were excluded from experiment [12, 13].

It is known that accumulation of abdominal fat mass, especially visceral fat, contributes to more pronounced deterioration of the lipid profile in women with impaired glucose tolerance. Data of recent epidemiological researches indicate that high TC and low-density lipoprotein levels are the most important cardiovascular risk factors in males, while in women, increased levels of TG and lipoprotein(a) are considered as the most significant cardiometabolic factors [14].

It was established that HFD causes the dyslipidemia development, which is manifested in a rise of TG level in the blood serum of both sexes' rats (Table 3). Moreover, compared with male, OVX female had shown more pronounced alterations of lipid metabolism with increased TC and significantly higher levels of TG, possibly, due to the dramatic decline of estrogen concentrations.

It is well-known that women show less atherogenic lipid profile compared with men as a result of the specific action of female hormones, but estrogen deficiency can modify metabolism unfavourably to proatherogenic and procoagulatory states [15].

It is common knowledge that androgen deficiency and low total testosterone are linked with increased risk of MetS in men, especially with obesity [16].

We found that the decline testosterone levels are accompanied by a slight increase in estradiol levels, resulting in a modification of estradiol/testosterone ratio in male with HFD (Table 4). It has been suggested that the change of circulating levels of estradiol occur from the conversion of testosterone into estradiol by aromatase mainly in the adipose tissue, leading to the vicious cycle between hypogonadism and obesity [16].

Table 4

Indexes of hormones in male and female rats, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Index	Control		HFD	
	males	females	males	OVX females
Testosterone level, ng/mL	8,23 ± 0,54*	2,82 ± 0,25*	6,33 ± 0,35*#	3,62 ± 0,29*#
Estradiol level, pg/mL	19,1 ± 1,42*	149,1 ± 7,92*	24,44 ± 1,85*#	18,9 ± 1,27*#

Note:
Data are shown as mean ± standard error of the mean (SEM).
* $p < 0.05$ vs «Control rats of the corresponding sex»,
\# $p < 0.05$ vs « HFD rats of the opposite sex».

Table 5

Duration and amplitude of the P-wave in male and female rats, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Index	Control		HFD	
	males	females	males	OVX females
Duration, sec	0,035 ± 0,002	0,036 ± 0,002	0,028 ± 0,002*#	0,020 ± 0,002*#
Amplitude, mV: I lead	0,042 ± 0,004	0,042 ± 0,004	0,038 ± 0,004#	0,060 ± 0,004*#
II lead	0,058 ± 0,005	0,066 ± 0,004	0,065 ± 0,005	0,067 ± 0,003
III lead	0,050 ± 0,004	0,053 ± 0,005	0,048 ± 0,006	0,048 ± 0,006

Note:
Data are shown as mean ± standard error of the mean (SEM).
* $p < 0.05$ vs «Control rats of the corresponding sex»,
\# $p < 0.05$ vs «HFD rats of the opposite sex».

OVX females with HFD have demonstrated a moderate significant increase in testosterone levels and dramatically decrease estradiol concentration as result of bilateral ovariectomy (Table 4). It is acknowledged, that androgen production in women decreases in ovarian at the menopausal stage due to the depletion of oocytes and ovarian follicles. At the same time, adipose tissue is considered as important source of estradiol production in postmenopausal women, that can explain the minor level of estradiol in serum of OVX female rats.

A direct relationship between same component of MetS and mortality due to CHD depending on gender has not been fully confirmed. However, it is known that obesity and dyslipidemia play an important role in the development of cardiac muscle fibrosis, induce destructive non-oxidative pathways and lead to the mitochondrial dysfunction in cardiomyocytes [17].

The functional state of the cardiovascular system of experimental rats was assessed using electrocardiography. HFD has been found to cause acceleration of atrial depolarization in experimental animals of both sexes, as evidenced by a reduction in P-wave duration in the second lead from the limbs in comparison with intact animals. It should be noted that the depolarization processes' disturbances were more pronounced in OVX females than in males. In addition, a significant increase in the amplitude of the P-wave was observed only in OVX females with HFD, which may indicate a substantial activation of the sympathetic nervous system or hypertrophy of the right atrium (Table 5) [18].

Neither HFD nor sex affect the amplitude and duration of the R and S waves in experimental rats ($p > 0.05$).

It was established that HFD, independently on sex, causes sinus tachycardia in experimental animals in comparison with their control counterparts (Table 6). It is known that cardiac arrhythmias lead to an increase in mortality in both sexes, but age-adjusted mortality for women is higher in comparison with men [19].

Table 6

The heart rate, systolic and diastole indexes in male and female rats, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Index	Control		HFD	
	males	females	males	OVX females
Heart rate, Hz	78,2 ± 2,7	82,7 ± 3,5	86,5 ± 4,7*	98,0 ± 9,0*
Interval P-Q, sec	0,048 ± 0,002	0,047 ± 0,003	0,045 ± 0,002	0,045 ± 0,002
Interval QRS, sec	0,033 ± 0,001	0,028 ± 0,003	0,031 ± 0,004	0,032 ± 0,001
Interval Q-T, sec	0,065 ± 0,006#	0,075 ± 0,003#	0,063 ± 0,006	0,063 ± 0,004*
Interval T-P, sec	0,025 ± 0,002	0,021 ± 0,002	0,020 ± 0,001#	0,013 ± 0,001*#
Q-T/T-P ratio	2,68 ± 0,23	3,10 ± 0,29	3,12 ± 0,26#	5,27 ± 0,71*#

Note:
Data are shown as mean ± standard error of the mean (SEM).
* $p < 0.05$ vs «Control rats of the corresponding sex»,
\# $p < 0.05$ vs «HFD rats of the opposite sex».

Table 7

Amplitude and duration of the T wave in male and female rats, ($\bar{X} \pm S_{\bar{x}}$), n = 6

Index	Control		HFD	
	males	females	males	OVX females
Duration, sec	0,035 ± 0,003	0,041 ± 0,005	0,039 ± 0,003#	0,022 ± 0,003*#
Amplitude, mV, I lead	0,105 ± 0,005	0,108 ± 0,005	0,108 ± 0,006	0,091 ± 0,003
II lead	0,105 ± 0,006	0,120 ± 0,007	0,113 ± 0,008#	0,153 ± 0,010*#
III lead	0,077 ± 0,008	0,077 ± 0,005	0,095 ± 0,008*	0,092 ± 0,008*

Note:
Data are shown as mean ± standard error of the mean (SEM).
* $p < 0.05$ vs «Control rats of the corresponding sex»,
\# $p < 0.05$ vs «HFD rats of the opposite sex».

Both HFD and sex did not disturb the atrial contraction and ventricular systole, as evidenced by the unchanged P–Q and QRS interval, respectively (Table 6).

It is known that and Q–T interval varies by age sex [20]. Compared with intact males, control females have shown significantly longer Q–T interval, which confirmed gender differences in total electrical activity in the heart ventricles due to the influence of sex hormones. At the same time, HFD led to a significant shortening of the Q–T interval in OVX females, which did not differ from the one in males. Thus, only female have shown the disturbance of the ventricle's depolarization and repolarization processes, possible, due to impact insulin resistance and estrogen deficiency (Table 6).

In contrast to males, OVX females with HFD have exhibited the sights of diastolic dysfunction, which was evidenced by the T–P interval shortening and an increase the ratio of ventricular systole to their diastole duration (Q-T/T-P index) compare to control rats (Table 6).

At the same time, ovariectomized HFD-treated female rats were shown a decline of the duration and increase in the amplitude of the T wave in the second and third leads from the limbs in comparison with control rats (Table 7). The obtained results are confirmed by the shortening of the Q–T interval and indicate a slowdown of ventricular repolarization processes due to possible damage in the myocardium as a result of insulin resistance and obesity development.

It is known that subclinical changes in the heart function occur long before the manifestation of T2DM and are mainly associated with insulin resistance. Moreover, MetS criteria

have a great impact on a progressive deterioration of diastolic parameters [21]. In addition, prediabetes has a greater negative impact on left ventricular relaxation parameters in postmenopausal women compared to men and premenopausal women, which indicates the important role of sex hormones in the development of diastolic dysfunction in insulin resistance state [22].

Compare to OVX female, HFD-treated male had no changes in the duration of the T wave, but one's amplitude was a significantly decrease in the third lead from the limbs. The obtained results indicate a greater tendency of women to develop heart diastolic dysfunction in contrast to men (Table 7).

Thus, components of MetS — insulin resistance, dyslipidemia and obesity — are the main risk factors for the development of diastolic dysfunction in women and men. Estrogen deficiency is an independent factor in the development of diastolic function disorders and additionally increases cardiometabolic risk in women.

CONCLUSIONS

We revealed that sex and estrogen levels have a great impact on the impairment of glucose and lipid metabolism and cardiovascular systems function, induced by HFD in rats.

Compared with male, HFD-treated ovariectomized female had greater body weight gain, significantly higher levels of relative mass of hypogonadal, epinephrine, mesenteric and total visceral fat, more pronounced deterioration of lipid profile and have shown signs of diastolic dysfunction.

However, males with HFD have exhibited the more pronounced impairment of glucose tolerance in contrast to ovariectomized female rats.

The obtained data justifies the necessity to take into account sex and estrogen sufficiency in the development of gender-specific prevention and treatment of metabolic syndrome.

REFERENCES

1. Lind L, Sundström J, Ärnlöv J, et al. *Sci Rep* 2021;11(1): 2978. doi: 10.1038/s41598-021-82398-8
2. Faulkner JL, Chantemèle EJB. *Biol Sex Differ* 2019;10: 30. doi: 10.1186%2Fs13293-019-0246-6
3. Ritter R, Sep SJS, Kallen CJH, et al. *BMJ Open Diabetes Res Care* 2019;7(1): e000787. doi: 10.1136%2Fbmjdrc-2019-000787
4. Mamikutty N, Thent ZC, Sapri SR, et al. *Biomed Res Int* 2014;2014: 263897. doi: 10.1155/2014/263897
5. Baker J, Metcalf P, Scragg R, Johnson R. *Clin Chem* 1991;37(4): 552-556.
6. Lundholm L, Bryzgalova G, Gao H, et al. *J Endocrinol* 2019;243(2): X1. doi: 10.1530/joe-08-0192e
7. Prohorova MI, Tupikova ZN. Bolshoy praktikum po uglevodnomu i lipidnomu obmenu, Leningrad, 1965: 218 p.
8. Fletcher MJ. *Clin Chim Acta* 1968;22(3): 393-397. doi: 10.1016/0009-8981(68)90041-7
9. Toop CR, Gentili S. *Nutrients* 2016;8(9): 577. doi: 10.3390/nu8090577
10. Vona R, Gambardella L, Straface E. Gender-associated biomarkers in metabolic syndrome [Internet]. Carotid artery – gender and health [Working Title]. IntechOpen; 2018. doi: 10.5772/intechopen.81103
11. Madonna R, Balistreri CR, Rosa S, et al. *J Clin Med* 2019;8(1): 98. doi: 10.3390/jcm8010098
12. Busserolles J, Mazur A, Gueux E, et al. *Exp Biol Med (Maywood)* 2002;227(9): 837-842. doi: 10.1177/153537020222700918
13. Koricanac G, Djordjevic A, Zakula Z, et al. *Arch Biol Sci* 2013;65: 455-464. doi: 10.2298/ABS1302455K
14. Peters SAE, Woodward M. *Curr Diab Rep* 2018;18(6): 33. doi: 10.1007/s11892-018-1005-5
15. Fonseca MIH, Silva IT, Ferreira SRG. *Diabetol Metab Syndr* 2017;9: 22. doi: 10.1186/s13098-017-0221-5
16. Winter AG, Zhao F, Lee RK. *Transl Androl Urol* 2014; 3(1): 50-58. doi: 10.3978/j.issn.2223-4683.2014.01.04
17. Mahajan R, Lau DH, Sanders P. *Trends Cardiovasc Med* 2015;25(2): 119-126. doi: 10.1016/j.tcm.2014.09.005
18. Mercik JS, Unkell M, Marinov M, et al. *Eur J Transl Clin Med* 2020;3(2): 22-28. doi: 10.31373/ejtcm/127800
19. Ehdaie A, Cingolani E, Shehata M, et al. *Circ Arrhythm Electrophysiol* 2018;11(3): e005680. doi: 10.1161/circep.117.005680
20. Satpathy S, Satpathy S, Nayak PK. *Natl J Physiol Pharm Pharmacol* 2018;8(2): 224-227. doi: 10.5455/njppp.2018.8.0832304092017
21. Kim HL, Kim MA, Oh S, et al. *Metab Syndr Relat Disord* 2016;14(10): 507-512. doi: 10.1089/met.2016.0078
22. Thirumurugan E, Gomathi K, Swathy P, et al. *J Clin Diag Res* 2022;16(11): OC24-OC27. doi: 10.7860/JCDR/2022/58660.17137

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Introduction. Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors, which manifestation may be different for men and women. Changes in sex hormone levels in men and women during lifespan contribute to increased cardiometabolic risk. Data of clinical researches suggest that transition from normal glucose tolerance to dysglycemia lead to more adverse differences in cardiometabolic risk factors in women than in men, suggesting an important impact of sex on the development of metabolic abnormalities. A significant increase in risk may be due to the sex differences in manifestation of some components of metabolic syndrome, but accurate reasons of these discrepancies need future investigations.

The aim of this study was to determine the differences in impairment of glucose, lipid metabolism and cardiovascular systems function between male and female rats with different levels of estrogen sufficiency.

Materials and Methods. MetS was modelled in male and female rats with different levels of estrogens by chronic (for 8 weeks) intake of fructose (high-fructose diet — HFD) with drinking water at a concentration 200 g/L. Estrogens deficiency was reproduced by bilateral ovariectomy. Experimental rats were divided into five groups: control males (n = 6), control females (n = 6), males with HFD (n = 6), sham-operated females with intact ovaries and HFD (n = 6), ovariectomized (OVX) females with HFD (n = 6). Glucose homeostasis was assessed by basal glycemia, glycemia during the intra-abdominal glucose tolerance test and fructosamine level. Insulin sensitivity was determined using intra-abdominal insulin tolerance test. Body weight gain, visceral fats, level of total cholesterol, triglycerides, levels of estradiol and testosterone in blood serum were determined. At the end of the study, electrocardiograms were recorded in three standard leads from the limbs. Data are presented as mean ± standard error of mean (SEM).

Results. It was established that HFD have not been induced metabolic abnormalities in female rats with intact ovaries. HFD, independently of sex, led to the development of insulin resistance and significant increase in fructosamine level in blood serum of rats. Ovariectomized females with HFD had greater intensity of body weight gain, significantly higher levels of relative mass of fats, more pronounced alterations of lipid metabolism with increased total cholesterol and significantly higher levels of triglycerides, than HFD-treated male rats. However, impairment of glucose tolerance, induced by HFD, was more pronounced in male than in OVX female rats. We found the decline testosterone levels and slight increase in estradiol levels in male rats with HFD. OVX females with HFD had a moderate significant increase in testosterone levels and dramatically decrease estradiol concentration as result of bilateral ovariectomy. HFD, independently from sex, induced the development of sinus tachycardia in experimental animals. Metabolic abnormalities, induced by HFD, in OVX female rats led to more pronounced disturbances of heart depolarization and repolarization processes and development of diastolic dysfunction compare to HFD-treated males.

Conclusions. We revealed that sex and estrogens levels have a great impact on the impairment of glucose and lipid metabolism and cardiovascular systems function, induced by high-fructose diet in rats. The obtained data justifies the necessity to take into account sex and estrogens sufficiency in the development of gender-specific prevention and treatment of metabolic syndrome.

Keywords: functional state of cardiovascular system, glucose homeostasis, lipid profile, sex differences, rats.

ВПЛИВ СТАТІ НА МЕТАБОЛІЧНІ ТА ФУНКЦІОНАЛЬНІ ПОРУШЕННЯ, ІНДУКОВАНІ ВИСОКОФРУКТОЗНОЮ ДІЄТОЮ У ЩУРІВ

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Вступ. Відомо, що метаболічний синдром є кластером факторів кардіометаболічного ризику, прояви яких можуть відрізнятися для чоловіків та жінок. Зміни рівнів статевих гормонів як у жінок, так і чоловіків протягом життя сприяють збільшенню кардіометаболічного ризику. Результати клінічних спостережень свідчать про те, що розвиток дисглікемії призводить до більш суттевого зростання кардіометаболічних факторів ризику у жінок у порівнянні з чоловіками, що свідчить про важливий вплив статі на розвиток метаболічних порушень. В той же час конкретні механізми, що обумовлюють статеві особливості прояву складових метаболічного синдрому, потребують подальших досліджень.

Метою даного дослідження було визначення відмінностей у порушенні глюкозного, ліпідного обміну та функції серцево-судинної системи у самців і самиць щурів з різним рівнем естрогенової забезпеченості.

Матеріали та методи. Метаболічний синдром моделювали у самців та самиць щурів з різним рівнем естрогенової забезпеченості шляхом хронічного (протягом 8 тижнів) споживання фруктози (високофруктозна дієта — ВФД) з питною водою в концентрації 200 г/л. Дефіцит естрогену відтворювали за допомогою двосторонньої овариектомії. Експериментальні щури були розділені на п'ять груп: контрольні самці (n = 6), контрольні самиці (n = 6), самці з ВФД (n = 6), псевдооперовані самиці з інтактними яєчниками та ВФД (n = 6), овариектомовані самиці з ВФД (n = 6). Глюкозний гомеостаз оцінювали за базальною глікемією, глікемією під час внутрішньочеревного тесту толерантності до глюкози та рівнем фруктозаміну. Чутливість до інсуліну визначали за допомогою внутрішньочеревного тесту толерантності до інсуліну. Визначали приріст маси тіла, вісцеральний жир, концентрацію загального холестерину й тригліцеридів, рівні естрадіолу та тестостерону в сироватці крові. Наприкінці дослідження реєстрували електрокардіограми в трьох стандартних відведеннях від кінцівок. Дані представлені як середнє ± стандартна помилка середнього (SEM).

Результати. Встановлено, що ВФД не призводить до метаболічних порушень у самиць щурів із інтактними яєчниками. ВФД, незалежно від статі, призводила до розвитку інсулінорезистентності та значного підвищення рівня фруктозаміну в сироватці крові щурів. Овариектомовані самиці з ВФД мали більш інтенсивний приріст маси тіла, вірогідно вищі рівні відносної маси жирів, більш виразні зміни ліпідного обміну з підвищенням загального холестерину та значно вищим рівнем тригліцеридів, ніж самці щурів із ВФД. Однак порушення толерантності до глюкози, спричинене ВФД, було більш виразним у самців щурів, ніж у овариектомованих самиць. Було виявлено зниження рівня тестостерону та підвищення рівня естрадіолу у самців щурів із ВФД. В овариектомованих самиць із ВФД спостерігали помірне вірогідне підвищення рівня тестостерону та різке зниження концентрації естрадіолу, як результат двосторонньої овариектомії. ВФД незалежно від статі індукувала розвиток синусової тахікардії в експериментальних тварин. Метаболічні зміни, індуковані ВФД, в овариектомованих самиць щурів призводили до більш виразних порушень процесів деполяризації та реполяризації серця та розвитку діастолічної дисфункції порівняно з самцями з ВФД.

Висновки. Встановлено, що стать і рівень естрогенів впливають на викликані високофруктозною дієтою порушення метаболізму глюкози і ліпідів та функції серцево-судинної системи у щурів. Отримані дані обґрунтовують необхідність урахування статі та естрогенової забезпеченості при розробці засобів гендерно-специфічної профілактики та терапії метаболічного синдрому.

Ключові слова: функціональний стан серцево-судинної системи, глюкозний гомеостаз, ліпідний профіль, статеві відмінності, щури.