УДК 616-008.9-021.6:613.24/.25.038]-092.9:599.323.4
https://doi.org/10.20538/1682-0363-2020-4-14-20

High-fat, high-carbohydrate diet–induced experimental model of metabolic syndrome in rats

Birulina J.G.[1], Ivanov V.V.[1], Buyko E.E.[1, 2], Bykov V.V.[1, 3], Smagliy L.V.[1], Nosarev A.V.[1], Petrova I.V.[1], Gusakova S.V.[1], Popov O.S.[1], Vasilev V.N.[1]

[1] *Siberian State Medical University*
2, Moscov Trakt, Tomsk, 634050, Russian Federation

[2] *National Research Tomsk Polytechnic University*
30, Lenina Av., Tomsk, 634050, Russian Federation

[3] *Innovative Pharmacology Research*
79/4, Elizarovikh Str., Tomsk, 634021, Russian Federation

ABSTRACT

Aim. The study is focused on development of high-fat, high-carbohydrate diet-induced experimental model of metabolic syndrome (MS) in rats.

Materials and methods. The 6-week old Wistar rats *(n* = 20) were used for study. *Rats were* separated into control and *experimental* groups. The rats from the control group were fed standard rat chow. The rats from the experimental group had a high-fat, high-carbohydrate diet rich in lard (17%) and fructose (17%) and drank 20% fructose solution. At the end of the study, body weight and blood pressure (BP) were assessed. After 12 weeks of a diet load, an oral glucose tolerance test (GTT) and insulin tolerance test (ITT) were carried out. Lipid and protein biochemical parameters in plasma were analyzed. Adipose tissue and liver were measured at the end of the study. The levels of triacylglycerol (TAG) and cholesterol (Ch) in the liver were determined by enzymatic methods.

Results. High-fat, high-carbohydrate diet *feeding* in rats for 12 weeks led to BP elevation and increase in the *adipose tissue*/body weight ratio. Hyperglycemia, impaired glucose tolerance and insulin resistance were found in rats with MS by means of GTT and ITT. Elevation of plasma TAG level was observed in the experimental group, although plasma total Ch and HDL-Ch did not differ from those of controls. *Liver*/body weight ratio and the level of TAG and Ch in the liver were elevated in rats with MS.

Conclusion. Experimental rat model of diet-induced MS reproduces many aspects of MS in humans. This model may be useful for studying the pathophysiology of MS and methods for its prevention and treatment.

Key words: metabolic syndrome, high-fat, high-carbohydrate diet, obesity, dyslipidemia, hyperglycemia, insulin resistance.

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The study was funded by RFBR and Tomsk region according to the research project No. 19-415-703015 (No. 18-44-700009, 18-44703008) and by the Council for Grants of the President of the Russian Federation (CS-143.2020.4).

Conformity with the principles of ethics. The study was carried out in compliance with the principles of humanity set out in the directives of the European Community (86/609 / EEC) and the Declaration of Helsinki. The study was approved by the Ethics Committee at Siberian State Medical University (Protocol No. 7793 of 27.05.2019).

For citation: Birulina J.G., Ivanov V.V., Buyko E.E., Bykov V.V., Smagliy L.V., Nosarev A.V., Petrova I.V., Gusakova S.V., Popov O.S., Vasilev V.N. High-fat, high-carbohydrate diet-induced experimental model of metabolic syndrome in rats. *Bulletin of Siberian Medicine.* 2020; 19 (4): 14–20. https://doi.org/10.20538/1682-0363-2020-4-14-20.

✉ *Birulina Julia G.,* e-mail: birulina20@yandex.ru.

Экспериментальная модель метаболического синдрома у крыс на основе высокожировой и высокоуглеводной диеты

Бирулина Ю.Г.[1], Иванов В.В.[1], Буйко Е.Е.[1,2], Быков В.В.[1,3], Смаглий Л.В.[1], Носарев А.В.[1], Петрова И.В.[1], Гусакова С.В.[1], Попов О.С.[1], Васильев В.Н.[1]

[1] *Сибирский государственный медицинский университет (СибГМУ)*
Россия, 634050, г. Томск, Московский тракт, 2

[2] *Национальный исследовательский Томский политехнический университет (НИ ТПУ)*
Россия, 634050, г. Томск, пр. Ленина, 30

[3] *ООО «Инновационные фармакологические разработки» (ООО «Ифар»)*
Россия, 634021, г. Томск, ул. Елизаровых, 79/4

РЕЗЮМЕ

Цель. Разработать экспериментальную модель метаболического синдрома (МС) у крыс на основе высокожировой и высокоуглеводной диеты.

Материалы и методы. Исследование выполнено на 20 самцах крыс линии Вистар, которые были распределены на контрольную и опытную группы. Крысы контрольной группы находились на стандартной диете. Крысы опытной группы в течение 12 нед получали высокожировую и высокоуглеводную диету, содержащую животный жир (17%), фруктозу (17%) и 20%-й раствор фруктозы вместо питьевой воды. В конце исследования у животных измеряли массу тела, артериальное давление (АД), проводили глюкозотолерантный (ГТТ) и инсулинотолерантный (ИТТ) тесты. В плазме крови определяли отдельные показатели липидного обмена, в печени – содержание триацилглицеролов (ТАГ) и холестерина (ХС).

Результаты. Содержание животных на высокожировой и высокоуглеводной диете в течение 12 нед приводило к повышению АД, увеличению удельной массы висцеральной жировой ткани. Выполнение ГТТ и ИТТ позволило выявить у крыс с МС гипергликемию, нарушение толерантности к глюкозе и инсулинорезистентность. Было обнаружено увеличение концентрации ТАГ в плазме крови крыс опытной группы, при этом уровень общего ХС не отличался от контроля. У крыс с МС наблюдалось увеличение удельной массы печени, а также содержания в ней ТАГ и ХС.

Заключение. Полученная экспериментальная модель диет-индуцированного метаболического синдрома воспроизводит большинство типичных признаков МС у человека и может быть полезна в изучении патофизиологических основ развития МС и методов его профилактики и лечения.

Ключевые слова: метаболический синдром, высокожировая и высокоуглеводная диета, ожирение, дислипидемия, гипергликемия, инсулинорезистентность.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование выполнено при финансовой поддержке РФФИ и Томской области в рамках научного проекта № 19-415-703015 (№ 18-44-700009, 18-44703008) и Совета по грантам Президента Российской Федерации (МК-143.2020.4).

Соответствие принципам этики. Исследование выполнено с соблюдением принципов гуманности, изложенных в директивах Европейского сообщества (86/609/EEC) и Хельсинкской декларации. Исследование одобрено локальным этическим комитетом СибГМУ (протокол № 7793 от 27.05.2019).

Для цитирования: Бирулина Ю.Г., Иванов В.В., Буйко Е.Е., Быков В.В., Смаглий Л.В., Носарев А.В., Петрова И.В., Гусакова С.В., Попов О.С., Васильев В.Н. Экспериментальная модель метаболического синдрома у крыс на основе высокожировой и высокоуглеводной диеты. *Бюллетень сибирской медицины.* 2020; 19 (4): 14–20. https://doi.org/10.20538/1682-0363-2020-4-14-20.

INTRODUCTION

The prevalence of metabolic syndrome (MS) in modern society has been increasing rapidly over the last few years, which has caused an increase in morbidity and mortality. According to the International Diabetes Federation (IDF), 25–68% of people worldwide suffer from MS [1, 2]. Significant factors in the development of MS are abdominal obesity and insulin resistance [3, 4]. IDF defines MS as a condition of visceral obesity and at least two of the following parameters: high levels of triacylglycerols (TAG), low levels of high-density lipoproteins (HDL), high blood pressure (BP) and hyperglycemia [1]. Thus, MS is a complex of metabolic, hormonal and hemodynamic disorders that increases the risk of type 2 diabetes, non-alcoholic fatty liver disease and cardiovascular diseases [3, 5, 6].

To study the pathophysiological mechanisms of the MS development and methods for its prevention and therapy, it is necessary to develop accessible experimental models [7, 8, 9]. One of these approaches is focused on the use of animals with a genetic defect causing the development of various MS-typical pathological changes. Additionally, there is another approach to induce these disorders using special diets [7]. In recent years, the combination of a high-fat diet with a high content of carbohydrates (also referred to as the "Western diet", "the cafeteria diet") has become widespread [10, 11, 12]. It was shown that animal fats (lard or beef fat) are more effective for MS modeling compared with vegetable fats [11]. Glucose [12], fructose [13, 14] or sucrose [15] can be used as carbohydrates added to the diet. Such a diet is similar to the nutrition of a modern person and is considered as the most adequate for MS modeling and reproducing of the pathogenetic factors and the phenomenology of metabolic disorders in MS.

In this regard, the aim purpose of the study was to develop an experimental model of MS in rats based on a high-fat, high-carbohydrate diet.

MATERIALS AND METHODS

The MS model was performed using male Wistar rats (20 animals with weight of 200–250 g, 6 weeks-old). The studies were carried out in compliance with the principles of the European Community Directives (86/609/EEC) and the Declaration of Helsinki. Animals were fed ad libitum and housed in a 12-h light/dark cycle. Rats were separated into control (n = 8) and experimental (n = 12) groups. The rats from the control group were fed with standard chow for laboratory rats ("Delta Feeds", Biopro, Russia, total calories 3000 kcal/kg). The rats from the experimental group were fed with a high-fat, high-carbohydrate diet rich in lard (17%), fructose (17%) and drinking water was replaced with a 20% fructose solution (total calories 4,400 kcal/kg, 54% energy from fat).

Before and at the end of the study body weight and BP ("Systola", Neurobotics, Russia) were assessed. In the last week of the experiment, glucose tolerance (GTT) and insulin tolerance (ITT) tests were carried out [11, 16]. Fasted animals (12 h of food deprivation) were injected intragastrically with a glucose solution at a dose of 2 g/kg (D-glucose, Sigma-Aldrich, USA) or subcutaneously injected with short-acting insulin at a dose of 0.75 IU/kg ("NovoRapid Penfil", Denmark). The glucose concentration in the blood obtained from the rat's tail vein was determined after 0, 15, 30, 60, 90, and 120 min by spectrophotometric enzymatic method using a commercial kit ("Glucose-Novo V-8054", Vector-Best, Russia). The glucose utilization rates (K_{ITT}, % glucose/min) were calculated as $K_{ITT} = (0.693/t_{1/2}) \times 100$, $t_{1/2}$ – the time of the reduction of plasma glucose concentration by half after insulin administration [17]. Blood plasma was obtained by centrifugation (4 °C, 8,000 g, 6 min) and stored at −20 °C for subsequent analysis. The TAG, total cholesterol (Ch), and HDL-Ch plasma concentrations were measured with a biochemical analyzer (RX Imola, Randox, Japan).

At the end of the experiment the rats were euthanized by CO_2 asphyxiation. Visceral adipose tissue and liver were obtained and weighed using analytical balance, the ratios of their weight regarding to the body weight were calculated. The concentrations of TAG and Ch in the liver (mg/g of tissue) were determined after the extraction of the lipid fraction from the liver samples (50 mg) with chloroform-methanol (2:1) by the method of J. Folch [18]. The TAG and Ch levels in extracted lipids were determined by enzymatic methods using commercial kits (Chronolab, Spain). Before the analysis, a 20% chloroform solution of Thesit detergent (Sigma-Aldrich, USA) was added to the chloroform phase. Chloroform was removed by a stream of nitrogen; emulsified lipids were dissolved in distilled water. Reagents from the kits for the TAG and Ch determination were added directly to the aqueous emulsion. The Atherogenic Index of Plasma (AIP) was calculated [19].

Data were presented as mean and standard deviation ($M \pm SD$). The correspondence of the obtained

quantitative indicators to the normality was determined using the Shapiro-Wilk W-test. For statistical significance measuring between two groups the Student t-test was performed using the IBM SPSS Statistics 21 software. The alpha level of significance for all experiments was set at $p < 0.05$.

RESULTS

Experimental models of MS reproduce most of the specific signs of the human metabolic syndrome such as excess weight, visceral obesity, insulin resistance, impaired glucose tolerance, dyslipidemia, and arterial hypertension [8, 9].

High-fat, high-carbohydrate diet *feeding* of rats for 12 weeks led to systolic blood pressure (SBP) and diastolic blood pressure (DBP) elevation and increase in the *adipose tissue*/body weight ratio *and liver*/body weight ratio (Table 1).

One of the typical features of MS is central obesity. However, feeding the animals with a special diet does not always lead to a significant increase in the body weight [11, 12, 20]. In our experiment the final body weight did not differ between control and experimental groups. A possible explanation of this finding is the fact that animals of the experimental groups consumed less of the food enriched in fat and fructose, probably due to the higher caloric intake with this diet.

Table 1

Effect of high-fat and high-carbohydrate diet on the physiological parameters of rats from the control and experimental group (Metabolic syndrome model), *M ± SD*

Parameter	Group	
	Control ($n = 8$)	Metabolic syndrome ($n = 12$)
Body weight, g	425.8 ± 25.6	463.1 ± 22.4 ($p = 0.101$)
SBP, mm Hg	124.1 ± 9.2	136.2 ± 8.3 ($p = 0.007$)
DBP, mm Hg	87.4 ± 10.2	100.3 ± 13.6 ($p = 0.036$)
Adipose tissue/body weight ratio, g	2.4 ± 0.3	4.9 ± 1.3 ($p = 0.001$)
Liver/body weight ratio, g	2.7 ± 0.4	3.5 ± 0.3 ($p = 0.002$)
Food intake, g/day/group	130.2 ± 8.4	101.7 ± 9.8 ($p = 0.005$)
Fluid intake, ml/day/group	249.5 ± 11.9	347.5 ± 12.6 ($p = 0.011$)

Note. Here and in the Table 2: p – the level of statistical significance of differences in comparison with control.

At the same time, the *adipose tissue*/body weight ratio of the experimental rats, including mesenteric, epididymal and retroperitoneal fat, increased for more than 2 times, which is also an important symptom of MS. Obtained experimental data indicates the presence of obesity in rats of the experimental group (Table 1). This information is consistent with data from other diet-induced models of MS [12, 14, 21].

Feeding of experimental rats with high-fat, high-carbohydrate diet for 12 weeks led to hyperglycemia. It can be evidenced by an increased fasting plasma glucose level (Table 2). According to GTT, at 30 min after glucose administration, the blood glucose level in rats of the experimental group exceeded the level in the control group by 25.2% ($p = 0.005$). After 60 min, the blood glucose level in rats of the control and experimental groups began to gradually decrease, remaining high in the group of rats with MS model: the difference was 32.4% ($p = 0.003$). After 2 hours, the glucose level in the control group almost returned to the initial level, while in the experimental group it remained increased by 10% ($p = 0.093$) (Fig. 1, *a*). The area under the curve of glucose concentration – time ($AUC_{0\text{-}120}$) in the experimental group was 809.9 ± 81.9 mmol/l × 120 min and exceeded the control group value (585.5 ± 53.1 mmol/l × 120 min, $p = 0.001$) (Fig. 1, *b*).

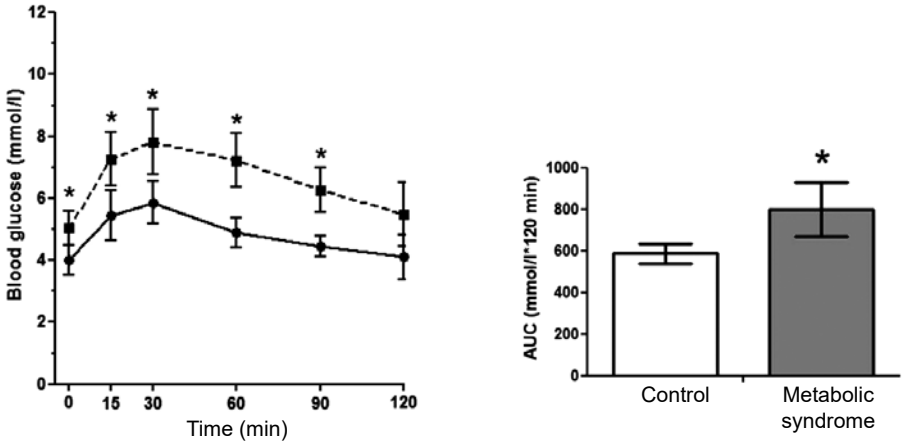
It is known that ITT can detect a change in the target cells response to insulin, which may be caused by a decrease in the sensitivity or number of insulin receptors [5, 22]. A gradual decrease of the glucose concentration in the blood of animals of the control and experimental groups was observed after subcutaneous injection of insulin. However, its level remained higher in the experimental group at the point of 30 min after the injection of insulin (the difference after 30 min was 30.1% ($p = 0.002$), after 60 min – 32.5% ($p = 0.001$), after 2 hours – 25.7% ($p = 0.011$) (Fig. 2, a)). The area under the curve "glucose concentration – time" ($AUC_{0\text{-}120}$) in the experimental group was 440.9 ± 57.4 mmol/l × 120 min and exceeded the same parameter in the control group (307.1 ± 31.1 mmol/l × 120 min, $p = 0.004$).

The progression of insulin resistance in the group of animals with MS model was confirmed by the study of K_{ITT}. It was found that K_{ITT} in rats fed a high-fat and high-carbohydrate diet was 1.3 ± 0.7% glucose/min, which is 36.5% lower than that parameter in the control group (2.1 ± 0.7 % glucose/min, $p = 0.001$) (Fig. 2, b). Thus, hyperglycemia, along with glucose tolerance and insulin resistance, indicates the development of MS in animals.

Dyslipidemia as the characteristic of MS demonstrates both quantitative and qualitative changes in the

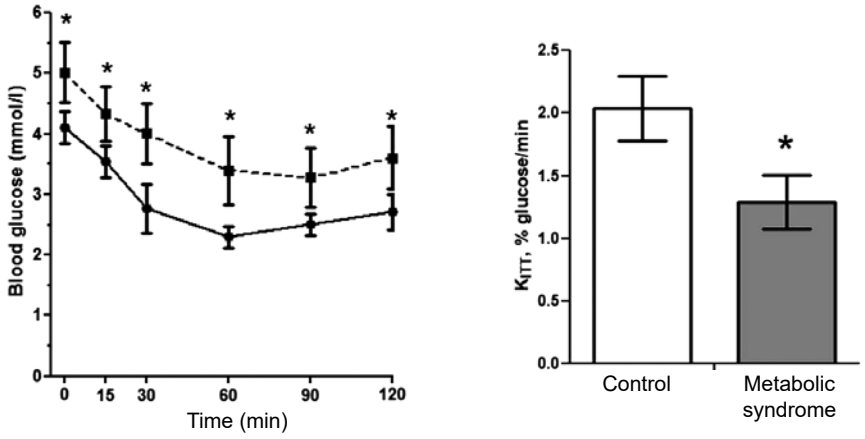
blood lipoproteins composition. The most important signs of dyslipidemia are: an increased level of TAG in very low-density lipoproteins (VLDL-Ch), which are the main transporters of endogenous fat synthesized in the liver. At the same time, the level of Ch in low-density lipoproteins (LDL-Ch) increases, and also decreases in high-density lipoproteins (HDL-Ch) [4].

In this study, rats of the experimental group had shown an increase in plasma TAG concentration by 2.1 times compared with the control group. This phenomenon may occur due to the excessive consumption of fructose with the diet that leads to the activation of lipogenesis in the liver [13, 23]. The total Ch level in animals fed with high-fat, high-carbohydrate diet did not significantly increase. At the same time, the level of atherogenic LDL-Ch increased in rats of the experimental group, while the level of HDL-Ch did not change (Table 2).



a *b*

Fig. 1. Dynamics of the blood glucose concentration in rats (*a*) and the area under the curve "glucose concentration-time" (*b*) in the oral glucose tolerance test**.** Here and in Fig. 2: the control group (solid line) and experimental group (dashed line). **p* < 0.05 in comparison with the control group



a *b*

Fig. 2. Dynamics of insulin-stimulated decrease in blood glucose concentration in rats (*a*) and glucose disposal rate (*b*) in the insulin tolerance test

Table 2

Effect of high-fat and high-carbohydrate diet on the biochemical parameters of plasma in rats from the control and experimental groups (Metabolic syndrome), *M* ± *SD*

Group	Parameter				
	Fasting glucose, mmol/l	TAG, mmol/l	Total Ch, mmol/l	HDL-Ch, mmol/l	LDL-Ch, mmol/l
Control (*n* = 8)	4.0 ± 0.5	1.8 ± 0.8	2.4 ± 0.5	0.9 ± 0.3	1.3 ± 0.3
Metabolic syndrome (*n* = 12)	5.3 ± 0.6 (*p* = 0.021)	3.7 ± 0.9 (*p* = 0.001)	2.8 ± 0.7 (*p* = 0.062)	0.8 ± 0.1 (*p* = 0.201)	1.9 ± 0.5 (*p* = 0.044)

The literary data on changes in the Ch levels and HDL-Ch, LDL-Ch levels in the blood of animals with diet-induced MS differ significantly. Some researchers have noted an increase in the total Ch content in plasma, for example, in experiments with diets rich in fructose or fats and fructose [10, 24]. Others noticed an absence of any changes in the level of Ch [12]. Data on the content of HDL-Ch in plasma also vary, with a predominance of facts on its reduction [15]. AIP of rats fed with a high-fat and high-carbohydrates diet had increased threefold (0.2 ± 0.1 in the control group versus 0.6 ± 0.2 in the experimental group, $p = 0.001$). This indicator is widely used in clinical medicine in case to assess cardiovascular risk in patients. This parameter is considered as a potential biomarker for early cardiovascular diseases diagnosis [25].

It is known that feeding of animals with high-fat [14] or high-fat and high-carbohydrate [21, 26] diets leads to the significant metabolic changes in the liver, as it can be noticed during a non-alcoholic steatohepatosis. In our experiment, there was an increase in the *liver*/body weight ratio in animals with the MS model, as well as an increase in the liver TAG level by 1.8 times (4.3 ± 1.5 mg/g in the control group versus 7.8 ± 3.4 mg/g in the experimental group, $p = 0.005$). Ch liver level had increased by 2.4 times ($1.1 \pm \pm 0.4$ mg/g in the control group versus 2.6 ± 0.6 mg/g in the experimental group, $p = 0.020$). Thus, the results of the study demonstrate that a high-fat and high-carbohydrate diet can contribute to the development of fatty liver disease.

CONCLUSION

It has been established that the use of the proposed high-fat and high-carbohydrate diet in rats reproduces most of the typical MS features: obesity, increased blood pressure, hyperglycemia, decreased glucose tolerance, insulin resistance, and dyslipidemia with triglyceridemia. This diet is similar to the high-calorie diet of a modern man. This model of diet-induced MS may be useful in studying the causes of the metabolic and hemodynamic disorders development and progression in the state of MS, as well as in exploring the potential approaches to its prevention and treatment.

REFERENCES

1. Alberti K.G., Zimmet P., Shaw J. Metabolic syndrome-a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet. Med.* 2006; 23 (5): 469–480. DOI: 10.1111/j.1464-5491.2006.01858.x.
2. Saklayen M.G. The global epidemic of the metabolic syndrome. *Curr. Hypertens. Rep.* 2018; 20 (2): 12. DOI: 10.1007/s11906-018-0812-z.
3. Aydin S., Aksoy A., Aydin S., Kalayci M, Yilmaz M., Kuloglu T., Citil C., Catak Z. Today's and yesterday's of pathophysiology: Biochemistry of metabolic syndrome and animal models. *Nutrition*. 2014; 30 (1): 1–9. DOI: 10.1016/j.nut.2013.05.013.
4. Potenza M.V., Mechanick J.I. The metabolic syndrome: definition, global impact, and pathophysiology. *Nutr. Clin. Pract.* 2009; 24 (5): 560–577. DOI: 10.1177/0884533609342436.
5. Fowler M.J. Microvascular and macrovascular complications of diabetes. *Clinical Diabetes*. 2008: 77–82. DOI: 10.2337/diaclin.26.2.77.
6. Rojtberg G.E. Metabolic syndrome. Moscow: MED-M54 press-inform, 2007: 224 (in Russ.).
7. Kravchuk E.N., Galagudza M.M. Experimental models of metabolic syndrome. *Arterial Hypertension*. 2014; 20 (5): 377–383 (in Russ.). DOI: 10.18705/1607-419X-2014-20-5-377-383.
8. Bayrasheva V.K., Pchelin I.Y., Egorova A.E., Vasilkova V.N., Kornyushin O.V. Experimental models of alimentary obesity in rats. *Juvenis Scientia*. 2019; 9–10: 8–13 (in Russ.). DOI: 10.32415/jscientia.2019.09-10.02.
9. Kwitek A.E. Rat models of metabolic syndrome. *Methods Mol. Biol.* 2019; 2018: 269–285. DOI: 10.1007/978-1-4939-9581-3_13.
10. Panchal S.K., Brown L. Rodent models for metabolic syndrome research. *J. Biomed. Biotechnol*. 2011; 2011: 351982. DOI: 10.1155/2011/351982.
11. Gancheva S., Zhelyazkova-Savova M., Galunska B., Chervenkov T. Experimental models of metabolic syndrome in rats. *Scripta Scientifica Medica.* 2015; 47 (2): 23–30. DOI: 10.14748/ssm.v47i2.1145.
12. Moreno-Fernández S., Garcés-Rimón M., Vera G., Astier J., Landrier J.F., Miguel M. High fat/high glucose diet induces metabolic syndrome in an experimental rat model. *Nutrients*. 2018; 10 (10): 1502. DOI: 10.3390/nu10101502.
13. Lim J.S., Mietus-Snyder M., Valente A., Schwarz J.M., Lustig R.H. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat. Rev. Gastroenterol. Hepatol.* 2010; 7: 251–264. DOI: 10.1038/nrgastro.2010.41.
14. Panchal S.K., Poudyal H., Iyer A., Nazer R., Alam A., Diwan V., Kauter K., Sernia C., Campbell F., Ward L., Gobe G., Fenning A., Brown L. High-carbohydrate high-fat diet-induced metabolic syndrome and cardiovascular remodeling in rats. *J. Cardiovasc. Pharmacol.* 2011; 57 (5): 611–624. DOI: 10.1097/FJC.0b013e31821b1379.
15. Sadowska J., Bruszkowska M. Comparing the effects of sucrose and high-fructose corn syrup on lipid metabolism and the risk of cardiovascular disease in male rats. *Acta Sci. Pol. Technol. Aliment.* 2017; 16 (2): 231–240. DOI: 10.17306/J.AFS.0482.
16. Dupas J., Feray A. Goanvec C., Guernec A., Samson N., Bougaran P., Guerrero F., Mansourati J. Metabolic syndrome and hypertension resulting from fructose enriched diet in Wistar rats. *Biomed. Res. Int.* 2017; 2017: 2494067. DOI: 10.1155/2017/2494067.

17. Patarrao R.S., Lautt W.W., Macedo M.P. Assessment of methods and indexes of insulin sensitivity. *Rev. Port. Endocrinol. Diabetes Metab.* 2014; 9 (1): 65–73. DOI: 10.1016/j.rpedm.2013.10.004.
18. Folch J., Lees M., Sloane-Stanley G.H. A simple method for the isolation and purification of total lipides from animal tissues. *J. Biol. Chem.* 1957; 226 (1): 497–509.
19. Dobiásová M., Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER (HDL)). *Clin. Biochem.* 2001; 34 (7): 583–588. DOI: 10.1016/s0009-9120(01)00263-6.
20. Nagai Y., Yonemitsu S., Erion D.M., Iwasaki T., Stark R., Weismann D., Dong J., Zhang D., Jurczak M.J., Löffler M.G., Cresswell J., Yu X.X., Murray S., Bhanot S., Monia B.P., Bogan J.S., Samuel V., Shulman G.I. The role of peroxisome proliferator-activated receptor gamma coactivator-1 beta in the pathogenesis of fructose-induced insulin resistance. *Cell Metab.* 2009; 9 (3): 252–264. DOI: 10.1016/j.cmet.2009.01.011.
21. Dos Santos Lacerda D., Garbin de Almeida M., Teixeira C., De Jesus A., Da Silva Pereira J.E., Martins Bock P., Pegas Henriques J.A., Gomez R., Dani C., Funchal C. Biochemical and physiological parameters in rats fed with high-fat diet: the protective effect of chronic treatment with purple grape juice (Bordo Variety). *Beverages*. 2018; 4 (4): 100. DOI: 10.3390/beverages4040100.
22. Tkachuk V.A., Vorotnikov A.V. Molecular mechanisms of insulin resistance development. *Diabetes Mellitus.* 2014; 2: 29–40 (in Russ.). DOI: 10.14341/DM2014229-40.
23. Schaefer E.J., Gleason J.A., Dansinger M.L. Dietary fructose and glucose differentially affect lipid and glucose homeostasis. *J. Nutr*. 2009; 139 (6): 1257–1262. DOI: 10.3945/jn.108.098186.
24. Alam M.A., Kauter K., Brown L. Naringin improves diet-induced cardiovascular dysfunction and obesity in high carbohydrate, high fat diet-fed rats. *Nutrients*. 2013; 5 (3): 637–650. DOI: 10.3390/nu5030637.
25. Fernández-Macías J.C., Ochoa-Martínez A.C., Varela-Silva J.A., Pérez-Maldonado I.N. Atherogenic index of plasma: novel predictive biomarker for cardiovascular illnesses. *Arch. Med. Res.* 2019; 50 (5): 285–294. DOI: 10.1016/j.arcmed.2019.08.009.
26. Basaranoglu M., Basaranoglu G., Sabuncu T., Sentürk H. Fructose as a key player in the development of fatty liver disease. *World J. Gastroenterol*. 2013; 19 (8): 1166–1172. DOI: 10.3748/wjg.v19.i8.1166.

Authors contribution

Birulina J.G., Ivanov V.V. – conception and design, drafting of the manuscript. Smagliy L.V., Vasilev V.N., Popov O.S. – interpretation and analysis of the data. Nosarev A.V., Petrova I.V., Gusakova S.V. – substantiation of the manuscript, approval of the manuscript for publication. Buyko E.E., Bykov V.V. – experimental part of the study.

Authors information

Birulina Julia G., Cand. Sci. (Biology), Assistant Professor, Department of Biophysics and Functional Diagnostics, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0003-1237-9786.

Ivanov Vladimir V., Cand. Sci. (Biology), Head of the Center for Preclinical Research of Central Research Laboratory, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0001-9348-4945.

Buyko Evgeniy E., Laboratory Assistant, Center for Preclinical Research of Central Research Laboratory, Siberian State Medical University, Research School of Chemistry & Applied Biomedical Sciences, National Research Tomsk Polytechnic University, Tomsk, Russian Federation. ORCID 0000-0002-6714-1938.

Bykov Vladimir V., Post-Graduate Student, Department of Biochemistry and Molecular Biology with a Course of Clinical Laboratory Diagnostics, Head of the Department of Pharmacological Research, Innovative Pharmacology Research, Tomsk, Russian Federation. ORCID 0000-0002-5145-2184.

Smagliy Lyudmila V., Cand. Sci. (Med.), Assistant Professor, Department of Biophysics and Functional Diagnostics, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0002-5263-027X.

Nosarev Alexey V., Dr. Sci. (Med.), Professor, Department of Biophysics and Functional Diagnostics, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0002-0119-9707.

Petrova Irina V., Dr. Sci. (Biology), Professor, Department of Biophysics and Functional Diagnostics, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0001-9034-4226.

Gusakova Svetlana V., Dr. Sci. (Med.), Head of the Department of Biophysics and Functional Diagnostics, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0001-5047-8668.

Popov Oleg S., Dr. Sci. (Med.), Professor, Department of General Surgery, SSMU, Tomsk, Russian Federation.

Vasilev Vladimir N., Dr. Sci. (Biology), Professor, Department of Physical Education and Health, SSMU, Tomsk, Russian Federation.

(✉) **Birulina Yulia G.,** e-mail: birulina20@yandex.ru.

Received 03.03.2020
Accepted 29.09.2020