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Metabolic and Hormonal Indices in Rats with a Prolonged Model of the Metabolic Syndrome Induced by a High-Carbohydrate and High-Fat Diet

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Abstract—To develop approaches for the prevention and treatment of the metabolic syndrome (MS), a pathological state widespread in the modern population, that involves a complex of metabolic and functional disorders, appropriate animal models of the MS are required. One of these models is induced by the consumption of a combined high-carbohydrate and high-fat (HC/HF) diet. However, the character, temporal dynamics and severity of the metabolic abnormalities in MS induced by the HC/HF diet are still poorly understood. The aim of this work was to characterize the metabolic changes in *Wistar* rats with the MS induced by a 10- and 15-week HC/HF diet which included the consumption of a 30% sucrose solution (instead of drinking water) and food rich in saturated fats. The rats which received the HC/HF diet for 15 weeks had a number of features characteristic of the MS such as increased body mass and a specific content of abdominal fat, hyperglycemia, hyperinsulinaemia, impaired glucose tolerance, insulin resistance, dyslipidemia, as well as the markers of impaired function of the cardiovascular system, hyperhomocysteinemia, a reduced level of nitric oxide and increased concentration of endothelin-1. In the rats, which were on the diet for 10 weeks, the metabolic abnormalities were less pronounced, indicating an insufficiency of a 10-week duration of the HC/HF diet for the MS induction. Thus, the model of the MS induced by a 15-week HC/HF diet has the characteristic features which allow for extrapolation of the obtained data to similar pathologic changes in humans, and can be used in the study of the etiology and pathogenesis of the MS and in the search for effective ways of MS prevention and treatment.

Keywords: metabolic syndrome, high-carbohydrate and high-fat diet, glucose tolerance, insulin resistance, dyslipidemia, endothelial dysfunction, biomodelling

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INTRODUCTION

The metabolic syndrome (MS) is a widespread pathological state, which includes a range of metabolic and functional disorders such as abdominal obesity, insulin resistance, hypertension, dyslipidemia [3, 14]. Currently, MS affects about 200 million people worldwide, resulting in the development of effective approaches for the prevention and treatment of MS and associated diseases to be one of the most urgent problems of modern endocrinology. For its solution, it is necessary to study disorders and functional changes of physiological and biochemical processes, which are the components of the MS pathogenesis, and to identify biochemical and functional indicators that can be used most effectively for a timely diagnosis, MS monitoring and evaluation of the effectiveness of the therapy.

A model of the MS in animals plays an important role in the study of the MS and in the development and optimization of approaches for its diagnosis and monitoring of the treatment effectiveness. However, despite a large number of such test systems, many unresolved issues remain in respect of their adequacy for the study of the MS and the possibility of extrapolating the data on humans. Up to now, functional, biochemical and pathogenetic criteria have not been determined, which would allow for consideration of the complex of metabolic disorders in animals as the MS. As a result, sometimes the same model of metabolic disorders is described by different groups of authors as obesity, MS, diabetes of the 2nd type or nonalcoholic fatty liver disease. There are relatively few studies which have examined the dynamics of the emergence and development of metabolic disturbances in the induction of MS in the temporal aspect. At the same time, such studies are very important for assessing the timing of the experimental MS development. A significant part of the MS studies was performed on mutant lines of rodents. However, the development of metabolic disorders in this case is sig-

nificantly different from that in humans [6, 10, 13], which casts doubt on the adequacy of such models of the MS and does not allow them to be fully explored in the study of the developed treatment algorithms.

Of the most interest are the MS models caused by a prolonged consumption by the laboratory rats of an imbalanced diet. Such a diet may include excessive amounts of easily digestible carbohydrates, a high carbohydrate (HC) diet, plus fat, primarily enriched in saturated fatty acids, a high-fat (HF) diet or their combination (HC/HF diet) [4, 11, 13, 18]. The MS model version in rats induced by the HC/HF diet causes the pathological process which is most similar to the MS pathogenesis in humans. It is assumed that the main pathogenetic factor in this case is endotoxemia of the intestine, which leads to increased inflammation in the body, impairment of redox balance and, ultimately, causes insulin resistance, hyperglycemia, and dyslipidemia [11, 18]. The greatest number of works on the use of HC/HF diets for MS induction was performed on mutant animals [13, 18]. At the same time, data on the effect of the diet on the MS development in *Wistar* rats, which do not have a genetic predisposition to obesity and metabolic disorders, are very few [8, 11, 17]. The models on *Wistar* rats differed in the composition of the HC/HF diets and the design of experiments, and the dynamics of the MS development following this diet, was not studied for them. The aim of our study was to characterize a wide spectrum of metabolic and biochemical parameters in *Wistar* rats on a model of the MS induced by the HC/HF diet of various durations.

MATERIALS AND METHODS

All experiments with animals were performed in strict accordance with the rules developed and approved by the local ethics Committee IEPhB RAS (30.12.2015) and in accordance with the rules and requirements stipulated by the European Communities Council Directive, 1986, and outlined in the "Guide for the Care and Use of Laboratory Animals, 2010." Male *Wistar* rats were used in the work. Newborn rats until the 26th day were on dairy feeding, after which they were taken from their mother and randomized into two groups. The control group (C, $n = 10$) was kept on a standard diet, while the MS rats (MS, $n = 10$), beginning with the 26th day (after taking off from the mother) until the end of the experiment, received a special diet that included 30% solution of sucrose (instead of drinking water) and extruded complete dry feed P-120 (Laboratorkorm, Russia) with the addition of saturated fat in the form of margarine (5 g per rat in the first 5 weeks, 6 g per rat from the 6th to the 10th week, 7 g per rat from 11th to 15th week). The program duration was 10 (MS1, $n = 5$) or 15 weeks (MS2, $n = 5$), after which the animals of the age of 95 (MS1) or 130 (MS2) days were withdrawn from the study. These groups corresponded to the control groups of animals C1 ($n = 5$) and C2 ($n = 5$). During the experiment, the animals were weighed each week, the volume of the consumed solution of 30% sucrose and the amount of food consumed were measured. Twice a month the level of fasting glucose in the blood was determined, for that the rats were deprived of food for 12 hours. The choice of the HC/HF diet duration was due to the results of preliminary experiments, including the observation that, when the diet lasted for 6 weeks, changes of the glucose homeostasis, insulin sensitivity and lipid metabolism in rats were weakly expressed or absent (data not shown). To assess glucose tolerance two days before the end of the experiment, a glucose tolerance test (GTT) was conducted. The rats were administered glucose (Dalkhimfarm, Russia) at a dose of 2 g/kg after which the concentration of glucose and insulin was measured for 120 min. Measurement of glucose was performed in the whole blood obtained from the tail vein of the rats using test strips "One Touch Ultra" (United States) and a glucometer "Life Scan Johnson & Johnson" (Denmark). The concentration of insulin in serum was measured using a kit of "Rat Insulin ELISA" (Mercodia AB, Sweden) and a mikroplatten Elisa Reader "Anthos 2020" (Labtec Instruments, Austria) at a wavelength of 450 nm. To assess the sensitivity to insulin one week before the end of the experiment, an insulin glucose tolerance test (IGTT) was conducted. In its holding, the rats were simultaneously injected with glucose (i/p, 2 g/ kg) and insulin ("Humalog", s/c, 0.8 IU/kg), then for 120 min the concentration of glucose in blood was measured [2].

The taking of blood for biochemical and immunological studies was made by transcutaneous puncture of the heart chambers into a vacuum system (BD Vacutainer) with EDTA as an anticoagulant. Biochemical parameters of blood were investigated using an analyzer Random Access A-15 (BioSystems SA, Spain), using sets of reagents of the firm Vector-Best (Russia). The level of NO, endothelin-1, vascular endothelial growth factor and insulin-like growth factor-1 in the blood of animals was determined by ELISA using kits of reagents from Cusabio (China), in accordance with the manufacturer's instruction. The concentration of triglycerides, total cholesterol, and cholesterol complexes with low (C-LDL) and high (C-HDL) density lipoproteins was measured using colorimetric methods, with the kits of Olvex Diagnosticum (Russia).

The results were analyzed using the SPSS program, they are presented as $M \pm SD$. To assess the character of the data distribution, the Kolmogorov-Smirnov test was performed. Comparing averages of independent samples was performed using student's *t*-test (for normal version of the data distribution) and the *U*-Mann–Whitney test (for a distribution differing from normal). The level of difference was considered significant at a probability of at least 95% ($p < 0.05$).

Table 1. Indicators of lipid metabolism in the rats of the studied groups, $M \pm SD$

Indicator	Group			
	C1, $n = 5$	MS1, $n = 5$	C2, $n = 5$	MS2, $n = 5$
Triglycerides, mmol/L	0.86 ± 0.19	1.07 ± 0.25	0.80 ± 0.14	1.43 ± 0.31*
Total cholesterol, mmol/L	4.28 ± 0.31	4.78 ± 0.44	4.45 ± 0.36	4.97 ± 0.38
C-LDL, mmol/L	1.35 ± 0.17	1.66 ± 0.33	1.48 ± 0.17	2.41 ± 0.34**
C-HDL, mmol/L	2.58 ± 0.15	2.26 ± 0.25*	2.64 ± 0.18	2.20 ± 0.20*
Ratio C-LDL/C-HDL	0.524 ± 0.054	0.686 ± 0.062*	0.577 ± 0.097	1.069 ± 0.069**

All indicators were measured at the end of the experiment; *, ** differences between groups C1 and MS1 and between groups C2 and MS2 are statistically significant at $p < 0.05$ and $p < 0.001$, respectively.

Table 2. Body mass and glucose levels in the rats of the studied groups, $M \pm SD$

Group	The week of the experiment			
	9th	11th	13th	15th
Body mass, g				
C2, $n = 5$	209 ± 19	249 ± 14	275 ± 16	296 ± 13
MS2, $n = 5$	239 ± 24	298 ± 25*	341 ± 18**	372 ± 22**
Glucose, mmol/L				
C2, $n = 5$	3.8 ± 0.2	3.8 ± 0.2	4.1 ± 0.4	4.0 ± 0.3
MS2, $n = 5$	4.1 ± 0.3	4.4 ± 0.6	5.0 ± 0.4*	5.6 ± 0.5**

*, ** Differences between groups C2 and MS2 are statistically significant at $p < 0.05$ and $p < 0.001$, respectively.

RESULTS AND DISCUSSION

In the rats with the HC/HF diet duration of 10 weeks (group MS1), body mass and abdominal fat were 264 ± 31 and 5.1 ± 0.9 g, respectively, and these figures were significantly higher ($p < 0.05$) than those of the rats of the group C1 (218 ± 18 and 3.2 ± 0.5 g). The levels of glucose and insulin in rats of the group MS1 were higher than in the control, but the differences were not statistically significant. Thus, in the rats of the group MS1, concentrations of glucose and insulin were 4.5 ± 0.5 mmol/L and 0.64 ± 0.23 ng/mL, while in the C1 rats they were 4 ± 0.3 mmol/L and 0.42 ± 0.15 ng/mL, respectively. In the MS1 rats, the C-HDL level significantly decreased, and the ratio C-LDL/C-HDL increased, while differences in the level of triglycerides, total cholesterol and LDL between the groups K1 and MS1 were not statistically significant (Table 1).

In increasing the duration of the HC/HF diet (group MS2), a rise in body mass was observed, which in 11–15 weeks after the start of the study was significantly higher than in the control group, as well as the increase in the glucose level, which after 13 and 15 weeks significantly surpassed the level in the group C2 (Table 2). After the 15-week diet, the level of insulin in the group MS2 rats was 65% higher than in the group C2 (0.81 ± 0.21 vs. 0.49 ± 0.19 ng/mL, $p = 0.037$). Along with this, a significant increase in the levels of triglycerides, C-LDL and the ratio of C-LDL/C-HDL, and a reduction in the level of C-HDL were noted (see Table 1). In the MS2 group also, a mass gain of abdominal fat compared to the C2 group (8.1 ± 1.3 vs. 3.4 ± 0.9 g, $p < 0.001$) was revealed.

The study of the sensitivity of the MS rats to glucose showed that while the group MS1 rats, fed with the HC/HF diet for 10 weeks, had an initial stage of its reduction, in the MS2 group rats, which were on the diet for 15 weeks, glucose tolerance was disordered to a considerable extent (Fig. 1). More pronounced glucose concentration increase in GTT in comparison with the group MS1 is in favor of this. At all points of the glucose curve, with the exception of 15 min, the differences between the groups MS2, and C2 were statistically significant. In the group MS2, the values of AUC_{0-120} and AUC_{30-120} for glucose concentration curve were increased by 37 and 43% in comparison with the C2 group and were significantly superior to those of the group MS1 rats, and the value of AUC_{30-120} in the MS2 group was significantly higher than in the MS1 group ($p = 0.041$) (Table 3). In GTT for the group of MS2 rats, an increase of the insulin concentration after 60 and 120 min of the glucose load was discovered as well as a significant increase in the AUC_{30-120} value for the insulin concentration curve in the time range 30–120 min ($p = 0.008$) (see Table 3). It should be noted that, for the group of MS1 rats, the increase of the insulin concentration in the blood, caused by a glucose load, was expressed to a substan-

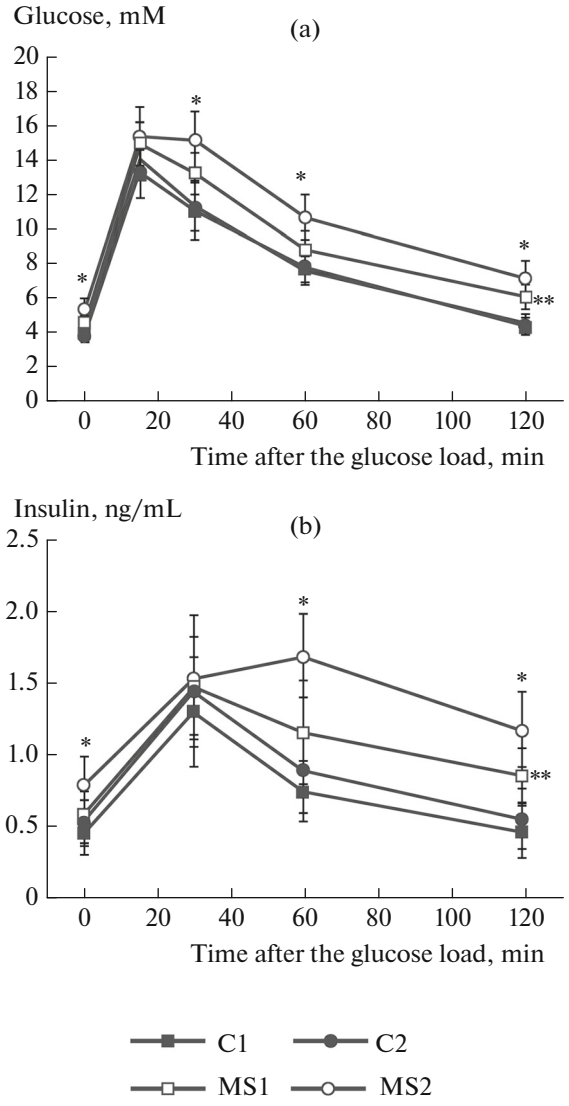

Fig. 1. The concentration curves for glucose (a) and insulin (b) during glucose tolerance test in the MS rats and of the control group rats. Here and in Fig. 2: C1—the control rats aged 95 days; C2—the control rats of age 130 days; MS1—the MS rats of age 95 days (10 weeks of the diet); MS2—the MS rats of age 130 days (15 weeks of the diet); the differences between the groups C1 and MS1 (*) and between the groups C2 and MS2 (**) statistically significant at $p < 0.05$; data are presented as $M \pm SD$.

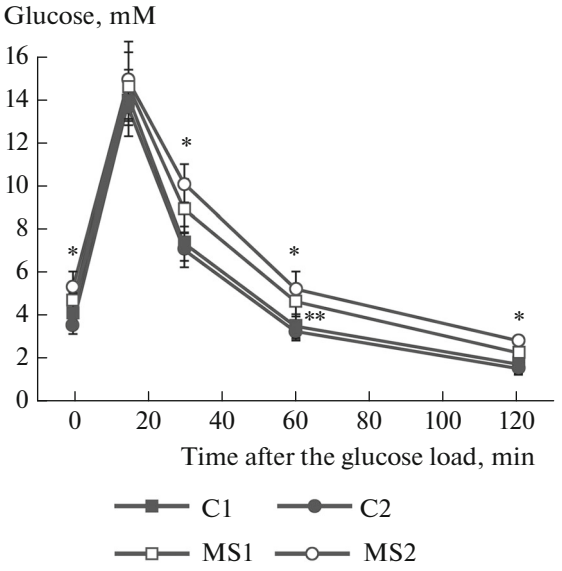

Fig. 2. The change of the glucose level in the blood of the MS rats and the rats of the control groups when conducting the insulin glucose tolerance test.

tially lesser extent, and significant differences with the group C1 were only after 120 min of the glucose load ($p = 0.012$) (see Fig. 1).

In the group of MS2 rats, insulin-induced glucose utilization was significantly attenuated, as illustrated by the results of IGTT, and the observed disorders were more pronounced in comparison with the MS1 group (Fig. 2). The AUC_{30-120} value for the glucose curve in the MS2 group was 59% higher than that in the control group, and 16% higher than that for the group MS1 (see Table 3). Thus, in total, the data suggest that in the rats which for 15 weeks were on the HC/HF diet, along with an impaired glucose homeostasis and lipid metabolism, a severe insulin resistance developed. This allows us to conclude that the 15-week HC/HF diet leads to the metabolic disorders which correspond to those in the MS, while the 10-week diet is not enough.

Profound metabolism disorders reflected in the changes of the blood biochemical indicators of the rats receiving the HC/HF diet for 15 weeks were accompanied by pronounced changes in the cardiovascular system (Table 4). In the blood of the group MS2 animals, the concentration of homocysteine-endotheliotropic endogenous toxin, a universal marker of the cardiovascular system disturbance, statistically significantly increased, which in average exceeded the control values by 19% ($p = 0.035$). Endothelial dysfunction was confirmed by the downward trend in the level of nitric oxide by 53% ($p = 0.117$) with the simultaneous increase in production of endothelin-1 on average by 41% ($p = 0.072$). The concentrations of vascular endothelial growth factor and insulin-like growth factor-1 in the group MS2 rats did not differ significantly from the values in the control group (see Table 4).

We propose a model of the MS in rats, caused by the combined HC/HF diet, which included consumption by the animals of readily available carbohydrates (sucrose) and saturated fat. The choice of the HC/HF diets for the MS induction was because a "cafeteria" diet, which is considered as one of the main reasons for the development of the MS and diabetes mellitus of the 2nd type in developed countries, includes excessive consumption of large amounts of readily available

Table 3. The values of the integrated area under the curves time–glucose concentration and time–insulin concentration (*AUC*) in glucose tolerance and insulin glucose tolerance tests in the rats of the studied groups, $M \pm SD$

Indicator	Group			
	C1, $n = 5$	MS1, $n = 5$	C2, $n = 5$	MS2, $n = 5$
Glucose tolerance test				
Glucose, AUC_{0-120}	949 ± 104	1115 ± 102*	943 ± 108	1290 ± 142**
Glucose, AUC_{30-120}	635 ± 64	770 ± 81*	643 ± 76	918 ± 109**, ***
Insulin, AUC_{30-120}	67 ± 18	100 ± 26	78 ± 25	135 ± 26**
Insulin glucose tolerance test				
Glucose, AUC_{0-120}	602 ± 66	716 ± 78*	571 ± 53	800 ± 88**
Glucose, AUC_{30-120}	314 ± 43	405 ± 47*	296 ± 32	471 ± 52**

*, ** Differences between the groups C1 and MS1 and between the groups C2 and MS2 are statistically significant at $p < 0.05$ and $p < 0.001$, respectively; *** differences between the groups MS1 and MS2 are statistically significant at $p < 0.05$.

Table 4. Some biochemical and hormonal blood parameters in the rats of the studied groups, $M \pm SD$

Indicator	Group C2, $n = 5$	MS2, $n = 5$
Total protein, g/L	75 ± 1.2	72.8 ± 4.4
Total bilirubin, mmol/L	4.1 ± 0.7	3.9 ± 0.7
ALT, IU/L	50.8 ± 7.9	50 ± 10.7
AST, IU/L	177 ± 85	140 ± 71
Alkaline phosphatase, IU/L	290 ± 71	344 ± 97
Uric acid, μmol/L	71 ± 17	91 ± 33
Creatinin, mmol/L	29 ± 6.8	31.8 ± 5.3
Urea, mmol/L	5.1 ± 0.8	4 ± 0.9 ($p = 0.076$)
Homocysteine, μmol/L	3.2 ± 0.6	3.8 ± 0.3* ($p = 0.035$)
Nitrogen oxide(II), μmol/L	53 ± 29	25 ± 7 ($p = 0.117$)
Endothelin-1, femtomol/L	1.7 ± 0.4	2.4 ± 0.6 ($p = 0.072$)
Vascular endothelial growth factor, pg/mL	32.4 ± 30.2	26.3 ± 8.9
Insulin-like growth factor, pg/mL	8.1 ± 1.1	9.2 ± 1.6

* The differences between the groups C2 and MS2 are statistically significant at $p < 0.05$.

carbohydrates (sucrose, fructose) and saturated fat [1, 7]. As noted above, most of the works on MS modeling in rats and mice were performed on mutant lines of animals who had a genetic predisposition to obesity and MS [13, 18]. This resulted in a weakening of adaptive and compensatory mechanisms aimed at protecting the body from the harmful effects of an unbalanced diet. Terms, schemes, and metabolic effects of the MS modeling in mutant animals differ from those for induction of this disease in the rats of *Wistar* line, which have a relatively high resistance to the influence of various negative external factors, including unbalanced diets.

There are only a few works, the authors of which induced the MS in *Wistar* rats using the HC/HF diet. In the male rats consuming food that was enriched in saturated fat and sucrose and contained 20% milk protein, after 7 weeks of the HC/HF diet, the increase in glucose, insulin, triglycerides was noted. After 9 weeks of the diet, insulin levels in the rats that were on the HC/HF diet were 125% higher than in the control group. The peak of insulin after a glucose load in the MS rats was higher than that in the control group by 42%, which was accompanied by a decrease in insulin sensitivity [8].

Other authors, for the induction of the MS in males of the *Wistar* rats used a longer 16-week HC/HF diet that included powdered milk (39.5%), beef fat (20%) and fructose (17.5%), and 25% fructose solution instead of drinking water. As a result, in these animals, a wide range of metabolic and functional disorders have developed, which pointed to the development of the MS [11]. For the MS rats, it was characteristic to gain an increased body mass and abdominal fat, impaired glucose tolerance, dyslipidemia, hyperinsulinemia, increased concentrations of leptin and MDA

in plasma, indicating the resistance to the leptin and the impairment of the redox balance. Disorders in the cardiovascular system, leading to increased blood pressure, endothelial dysfunction, myocardial hypertrophy and fibrosis and cardio sclerosis were noted. In the liver, fat deposits and fibrosis were revealed which were accompanied by elevation of transaminases. The pancreas was characterized by the increase in the size of pancreatic islets, which is consistent with the data on increased level of insulin in the MS rats' blood [11].

In 2015, data have indicated that, just after 1 week of the HC/HF diet, in the 2-month-old *Wistar* rats, marked hyperinsulinemia, hyperglycemia, dyslipidemia were noted, they had increased index of the insulin resistance, and all these processes were associated with increased activity of suppressor-3 of cytokine signaling (SOC-3) in hypothalamic neurons and hepatocytes [17]. It is established that SOC-3 is a negative regulator of the leptin signaling pathways and also indirectly suppresses the activity of the insulin signaling system [9]. In rats with the 8-week diet duration, metabolic disorders intensified and the signs of hepatic steatosis started to show, biochemical markers of which were the increased expression of the transcription factor SREBP-1c (sterol regulatory element binding protein 1c) and the enzyme phosphoenolpyruvate carboxykinase [17].

We used the HC/HF diet for induction of the MS, similar in composition to the diets that were selected by other groups. However, when the length of the HC/HF diet was six weeks, statistically significant changes in glucose homeostasis, insulin sensitivity and lipid metabolism in the MS rats were not detected (data not shown). After 10 weeks of the diet (group MS1), a significant increase in the body mass and adipose tissue was noted as well as initial stages of the lipid composition imbalance, which was reflected in the increase of the ratio C-LDL /C-HDL. However, differences in the concentration of C-LDL and C-HDL in the MS1 group rats compared with those in the control group were not statistically significant, although the trend of an increase in C-LDL and a decrease in C-HDL could be clearly seen. In the group MS1 rats, no significant changes in the level of glucose and insulin on an empty stomach were revealed. Statistically significant differences in the level of these indicators of GTT in the MS1 group compared with the group C1 was observed only after 120 min of the glucose load. In IGTT, in the group of MS1 rats, a reduction of glucose utilization under the action of exogenous insulin was noted, which was indicated by significantly increased glucose concentration 60 min after its introduction and a statistically significant increase in the values of AUC_{0-120} and AUC_{30-120} for the glucose concentration curve. These data indicate the initial stages of the development of insulin resistance. However, the weakening of glucose utilization in the MS1 group was less expressed than in the MS2 group, which was on the HC/HF diet for 15 weeks. The data indicate that the 10-week diet leads to metabolic disorders, but they are expressed moderately and insufficient for the classification of these pathological changes as MS. In this respect, it is highly surprising, given the results obtained by Chinese scientists, which showed hyperglycemia, hyperinsulinemia and dyslipidemia in *Wistar* rats under the HC/HF diet for only one week, and further after eight weeks of the diet found in the animals a range of highly expressed metabolic, hormonal and functional disorders [17].

We have identified significant differences with the control group in body mass and adipose tissue and in several metabolic and biochemical parameters only after 15 weeks of the HC/HF diet. The body mass of the group of MS2 rats differed significantly from the group C2 after 11 weeks, and the glucose level (on an empty stomach) differed 13 weeks after starting the diet. According to the results of GTT and IGTT, in the group MS2 rats, tolerance to glucose, its utilization under the action of exogenous insulin and increased insulin secretion in response to glucose load were clearly impaired. The differences between the values of AUC_{0-120} and AUC_{30-120} for glucose concentration curves in GTT and IGTT in the groups of MS2 and C2 rats have been detected with a high statistical significance level ($p < 0.001$). These data indicate the development of moderate hyperglycemia and insulin resistance in the rats having the HC/HF diet for 15 weeks. Along with this, in the group MS2 rats, lipid metabolism indicators were disordered, the levels of triglycerides, total cholesterol, C-LDL and the ratio C-LDL/C-HDL were increased, which indicated that the development in the MS rats of a severe dyslipidemia and increased risk of atherosclerotic vascular changes. In favor of the development of the cardiovascular system pathology was a significant increase in the blood of the group MS2 rats of the homocysteine concentration, a risk factor of vascular disorders [5] and the imbalance between vasodilation and vasoconstriction factors in favor of the latter. Also, the content of nitric oxide, mediating the relaxation of smooth muscles of the regional vessels in the MS2 group was reduced twice, and the concentration of endothelin-1, a hormone with pronounced vasoconstrictor activity, was largely increased. There is abundant evidence that the increase in the level of endothelin-1 and its precursor proendothelin-1 as well as reduced activity of the endothelial form of NO-synthase and, consequently, the level of nitric oxide production, are some of the characteristic signs of the MS in humans, evidencing the dysfunction of the endothelium and blood circulation [12, 15, 16].

CONCLUSIONS

Thus, using the *Wistar* rats, which were on the HC/HF diet for 15 weeks, we have developed a model of the metabolic syndrome with a number of features characteristic of this pathological state, such as body

mass and specific mass of adipose tissue (abdominal fat) increase, hyperglycemia, hyperinsulinemia, dyslipidemia, impaired glucose tolerance and insulin resistance, as well as hyperhomocysteinemia, reducing vasodilation factors (nitric oxide) and increased levels of vasoconstriction factors (endothelin-1), the characteristics typical for the cardiovascular pathology. In the 10-week diet, the metabolic disorders were relatively weakly expressed, indicating that this HC/HF diet duration is insufficient to induce the metabolic syndrome. The metabolic syndrome model we have proposed, induced by the 15-week HC/HF diet, can be used in the future for the study of the etiology and pathogenesis of the metabolic syndrome and to search for effective approaches and pharmacological agents for the treatment and prevention of this disease.

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