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The experimental model of type 2 diabetes mellitus caused by a high-fat diet with low-dose streptozotocin in rats

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ABSTRACT

Aim. To develop a pathogenetically reasonable model of type 2 diabetes with marked peripheral insulin resistance and relative insulin deficiency in rats using a high-fat diet and a single injection of streptozotocin in the low dose.

Materials and methods. Experiments were conducted on 16 outbred male rats. Type 2 diabetes model in experimental animals was achieved by feeding them with high-fat diet (55% of energy from fat) for 28 days followed by a single injection of streptozotocin (35 mg/kg). The serum glucose and insulin concentrations in rats were measured before streptozotocin administration and at the end of the experiment. To estimate insulin resistance, insulin tolerance test and glucose tolerance test were performed. Total protein, albumin, total and direct bilirubin, urea, uric acid, total cholesterol, high-density lipoproteins and low-density lipoproteins, and activity of alanine aminotransferase and aspartate aminotransferase were measured in the blood serum.

Results. A high-fat diet with a single injection of streptozotocin resulted in lipid and protein metabolism disorders and peripheral tissues insulin resistance in experimental animals. Basal insulin levels did not change against the backdrop of high glucose level.

Conclusions. These results indicate that feeding rats with a high-fat diet (55% of calories from fats) and a single administration of streptozotocin at a low dose (35 mg/kg) reproduce general pathological processes of type 2 diabetes. This model can be used to study the pathogenesis of type 2 diabetes as well as to investigate the effect of potential hypoglycemic agents.

Key words: type 2 diabetes, a high-fat diet, streptozotocin, insulin resistance, hyperglycemia.

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Экспериментальная модель сахарного диабета 2-го типа у крыс, вызванная диетой с высоким содержанием жиров и стрептозотоцином в низкой дозе

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РЕЗЮМЕ

Цель исследования – разработать с помощью диеты с высоким содержанием жиров и однократной инъекции стрептозотоцина в низкой дозе патогенетически обоснованную модель сахарного диабета 2-го типа у крыс с выраженной периферической инсулинорезистентностью и относительным дефицитом инсулина.

Материалы и методы. Эксперименты проводили на 16 аутбредных самцах крыс. Сахарный диабет 2-го типа моделировали кормлением экспериментальных животных высокожировой диетой (55% калорий за счет жиров) в течение 28 сут с последующей однократной интраперитонеальной инъекцией стрептозотоцина в дозе 35 мг/кг. Концентрацию глюкозы и инсулина в сыворотке крови крыс измеряли до введения стрептозотоцина и по окончании эксперимента. Для оценки инсулинорезистентности проводили глюкозотолерантный и инсулинотолерантный тесты. В сыворотке крови определяли содержание общего белка, альбуминов, общего и прямого билирубина, мочевины, мочевой кислоты, общего холестерина, холестерина липопротеинов высокой плотности и низкой плотности, активности аланинаминотрансферазы и аспартатаминотрансферазы.

Результаты. Диета с высоким содержанием жиров в сочетании с однократной инъекцией стрептозотоцина приводила у экспериментальных животных к нарушению липидного и белкового обменов и развитию инсулинорезистентности. Уровень базального инсулина не изменялся на фоне выраженной гликемии.

Заключение. Полученные результаты свидетельствуют о том, что при кормлении крыс диетой с высоким содержанием жиров и однократном введении стрептозотоцина в низкой дозе (35 мг/кг) воспроизводятся патологические процессы, характерные для сахарного диабета 2 типа. Созданная модель может использоваться для изучения патогенеза сахарного диабета 2-го типа, а также для исследования действия потенциальных гипогликемических средств.

Ключевые слова: сахарный диабет 2-го типа, высокожировая диета, стрептозотоцин, инсулинорезистентность, гипергликемия.

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

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INTRODUCTION

The incidence of type 2 diabetes mellitus (T2DM) and obesity has become an epidemic. According to the International Diabetes Federation, more than 422 million people (2017) suffer from diabetes around the world [1]. According to Government Register statistics (2015), about 4.5 million people have type 2 diabetes in the Russian Federation [2]. The key points in the pathogenesis of type 2 diabetes are insulin resistance and pancreatic β-cell dysfunction, which corrupt the regulatory effect of insulin on glucose, protein and lipid metabolism. The progress of diabetes proceeds in several stages. The transition from the state of prediabetes to diabetes in humans progresses during several years [3]. It is necessary to create clinically relevant experimental models of these diseases to develop effective methods for treatment of type 2 diabetes and obesity. It will allow to reproduce the pathogenetic stages of type 2 diabetes formation in a short time.

Genetic models of spontaneous diabetes and models based on pancreatic islet damage by chemical agents are known [4]. To simulate type 2 diabetes, rodents are administered with streptozotocin against the background of a high-fat or high-carbohydrate diet. The antibiotic streptozotocin selectively binds to the pancreatic β-cell marker – the GLUT 2 transporter, then converts into free radicals, causes a detergent effect, and dissociates oxidative phosphorylation that leads to energy deficiency and DNA point mutations with subsequent β-cell necrosis. The severity of β-cell necrosis depends on the route of administration, dose, frequency, and time between streptozotocin injections [5–7]. Variations of these parameters allow to simulate early or late stages of explicit diabetes.

A diet rich in fats and carbohydrates leads to the development of obesity, hyperinsulinemia, insulin resistance and/or glucose intolerance [8, 9]. The ratio of fats, proteins and carbohydrates in the animals' diet and the duration of feeding affect body weight, basal levels of glucose, insulin, triglycerides, cholesterol and fatty acids in plasma. Most often, a high-fat diet with normal amount of carbohydrates is used. Fats of animal (ghee, lard) or vegetable (olive, coconut, soybean) origin are added to the standard diet to obtain energy mainly from fats. Short-term (2 weeks) intake of food enriched with fats, as a rule, causes insulin resistance and/or glucose intolerance. Its longer (more than 4 weeks) intake contributes to an increase in the fat mass, which corresponds to the state of prediabetes [10].

Thus, the combination of streptozotocin injection in a low dose (from 25 mg/kg to 40 mg/kg) and long-term (for 4 weeks to 4 months) feeding of animals with a high-fat diet makes it possible to model pathological characteristics of type 2 diabetes in animals in a short time.

The aim of this study was to develop a pathogenetically reasonable model of type 2 diabetes with marked peripheral insulin resistance and relative insulin deficiency in rats using a high-fat diet and a single injection of streptozotocin in the low dose.

MATERIALS AND METHODS

The experiments were carried out on 16 outbred male rats weighing 300–400 g, obtained from the department of experimental biological models of the E.D. Goldberg Research Institute of Pharmacology and Regenerative Medicine. The animals were kept under standard conditions in a vivarium with natural light and free access to water and food.

The standard ProCorm feed (BioPro, Novosibirsk) for laboratory rats consisted of granules with mineral and vitamin supplements, containing fat 6%, carbohydrates 59%, protein 19%, vitamin–mineral mixture 3%, and water 13%. The energy value of 100 g of feed was 3 660 kcal/kg. It is known that the caloric rate of proteins and carbohydrates is 4 kcal g, fats – 9 kcal/g, therefore, 100 g of this feed provides 236 kcal from carbohydrates, 76 kcal from proteins, 54 kcal from fats and 336 kcal in total. The high-fat diet contained 26 grams of coconut oil, 2 grams of cholesterol and 72 grams of standard food for laboratory animals in 100 g; 55% of the energy was provided by fats [10,13].

The animals were divided into two groups: group 1 – control animals fed with standard laboratory food, group 2 – animals with experimental type 2 diabetes, caused by feeding them with a high-fat diet for 28 days and a single injection of streptozotocin. After a 12-hour fasting, these animals were injected once intraperitoneally with a freshly prepared solution of streptozotocin (35 mg/kg in a 0.1 M citrate buffer at pH 4.5). On the 44th day from the start of the experiment, a glucose tolerance test (GTT) was performed in animals of both groups: 2 g/kg of a 20% glucose solution was injected and after 15, 30, 60 and 120 minutes, fasting glycemia was measured. On the 47th day from the start of the experiment, an insulin tolerance test (ITT) was performed: insulin was administered subcutaneously (NovoRapid Penfil, Novo Nordiks A/C, Denmark) at a dose of 0.75 U/kg. The glucose area under the curve (AUC) was calculated. The body mass of animals was determined during the formation of groups, before the streptozotocin injection and after the end of the experiment. The water and food intake ware measured one day before the end of the experiment.

After the experiment, rats were euthanized by carbon dioxide asphyxia. The content of glucose, total protein, albumin, total and direct bilirubin, urea, uric acid, and the activity of alanine aminotransferase (ALT) and aspartate

aminotransferase (AST) were determined in the serum using the reagent kits and the ARCHITECT C4000 analyzer (USA). The total cholesterol (reagent kits from Randox, UK), and high-density and low-density lipoprotein cholesterol (reagent kits from Chronolab, Spain) were measured spectrophotometrically. The index of atherogenicity (IA) was calculated by the formula: total cholesterol –high density lipoprotein cholesterol / high density lipoprotein cholesterol. The amount of insulin was evaluated by enzyme immunoassay using the ALPCO Diagnostics (USA) ELISA kit. The HOMA-IR index (insulin content, pmol/L*glucose, mmol/L)/155) [https://www.dtu.ox.ac.uk/homacalculator/download.php] and the constant glucose utilization rate based on ITT (KITT) were calculated to characterize the insulin resistance [12].

The results were processed using the methods of one-way analysis of variance using the SPSS Statistics 12.0 package. Quantitative indicators were presented as the median, 25th and 75th percentiles. When comparing two independent samples, the Mann – Whitney test was used. The significance of differences was achieved at $p < 0.05$.

RESULTS AND DISCUSSION

The body weight of control animals steadily increased throughout the experiment (Table 1). The body weight of animals in the group with the T2DM model (receiving a high-fat diet) increased more significantly before the steptozotocin injection, the serum insulin concentration increased by 20%, the HOMA-IR index, which characterizes the development of glucose tolerance, became 23% higher. Compensatory increase in insulin secretion prevented the development of hyperglycemia in the serum of experimental animals in the second group (Table 1). Weight gain, hyperinsulinemia, insulin resistance and the absence of hyperglycemia confirm the development of prediabetes in animals with the T2DM model. Partial loss of the β-cell functional mass is necessary for the transition from prediabetes to explicit type 2 diabetes, therefore, animals were injected once intraperitoneally with streptozotocin on the 29th day of the experiment (35 mg/kg).

On the 50th day of the experiment (21 days after the administration of streptozotocin), the body weight of the animals decreased by 10.7% compared to the weight of control rats. Such a decrease in body weight is probably associated with the transition of energy products from the carbohydrate oxidation to the oxidation of fats. The daily water consumption by animals of the second group increased by 3.9 times. The amount of feed intake in both groups did not differ (Table 1), but the energy intensity of food was significantly higher for animals in the second group.

Table 1

The effect of a high-fat diet (55% calories from fats) and streptozotocin (single injection, 35 mg/kg) on body weight, food and water consumption, glucose and insulin serum levels in rats, *Me* [Q_1; Q_3]

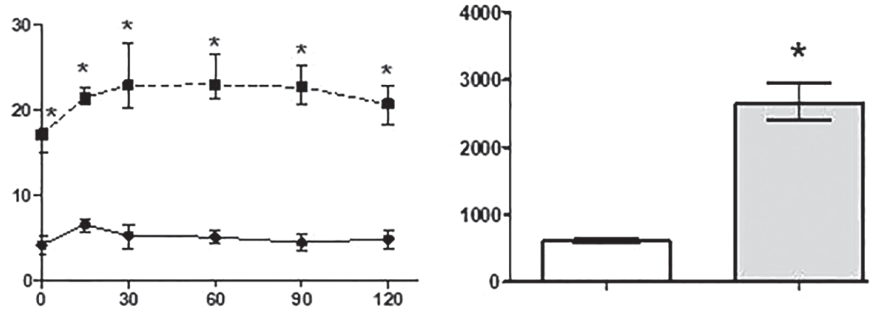
Parameter		Experimental groups	
		Control $n = 8$	High-fat diet + streptozotocin $n = 8$
Glucose, mmol/l		5.2 [4.6; 5.6]	5.6 [5.2; 5.9]
Insulin, pg/ml		229.1 [212.7; 234.0]	280.1 [260.5; 284.3]*
HOMA-IR		1.3 [1.1; 1.4]	1.7 [1.6; 1.8]*
Weight, g	0th day	311.0 [305.0; 320.0]	319.0 [310.0; 323.0]
	29th day	424.0 [398.0; 439.0]	459.0 [426.0; 481.0]*
	50th day	465 [446; 475]	420 [380; 447]*
Food intake, g/day		31.2 [30.0; 36.0]	36.7 [31.9; 39.1]
Water intake, ml/day		49.0 [39.4; 54.9]	189.5 [147.9; 205.4]*

* $p < 0.05$ comparing the experimental group with the controls.

15 days after the streptozotocin administration, GTT revealed significant impaired glucose sensitivity compared to the control group. The initial blood glucose level was significantly elevated after nightly fasting and at all time intervals after glucose administration (Fig. 1) in rats with the experimental T2DM model. In the T2DM model, the area under the curve increased by 4.4 times compared with the area in the control.

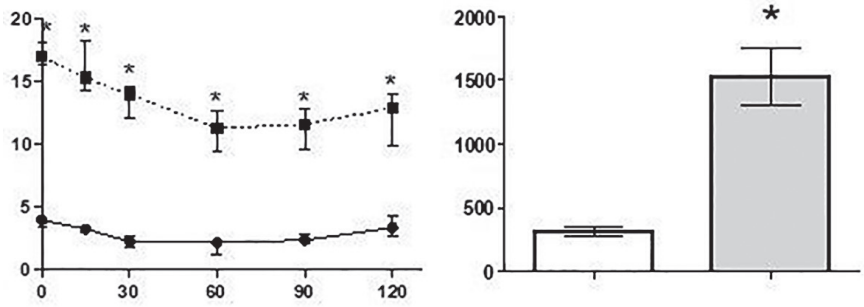
During the ITT, which characterizes the sensitivity of tissues to exogenous insulin, the concentration of glucose in the blood of control animals decreased as much as possible (2.3 [1.9; 2.8] mmol/L) at 30 minutes after the insulin administration (0.75 U/kg). In the blood of animals with the model of type 2 diabetes, the concentration of glucose decreased as much as possible after 60 minutes (11.3 [9.4; 12.7] mmol/l) (Fig. 2). It indicates slow utilization of glucose by peripheral tissues due to the development of insulin resistance. According to ITT data, the area under the curve in animals with the experimental T2DM model became 4.8 times larger than in the control group (Fig. 2). K_{ITT}, calculated on the basis of ITT, in animals of the control group was 2.7 [1.9; 3.1] % glucose/min. In the group of animals with the experimental T2DM model, the glucose utilization rate decreased by 53% (1.4 [1.0; 1.7] % glucose/min) (Fig. 3).

The pathogenesis of type 2 diabetes is characterized by a combination of tissue resistance to insulin and insufficient pancreatic β-cell function [13]. Violation of carbohydrate homeostasis in animals with experimental type 2 diabetes is confirmed by a three-fold increase in the serum glucose concentration (Table 2). The insulin



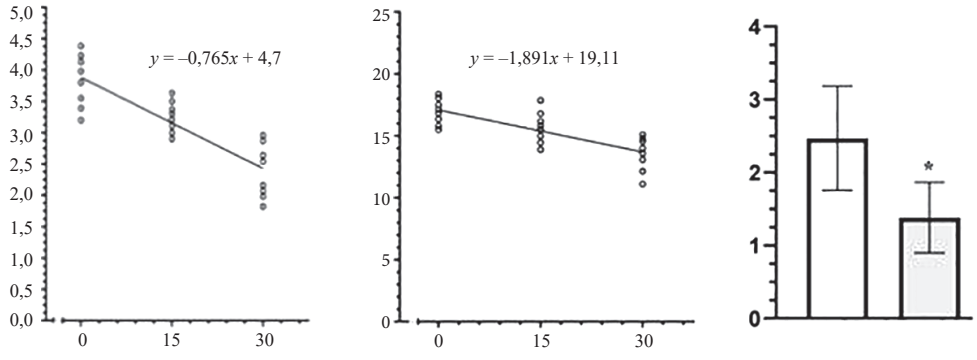
a *b*

Fig. 1. The glucose tolerance test results in male Wistar rats fed with high-fat diet (55% calories from fats) and administered with a single intraperitoneal injection of streptozotocin (35 mg/kg) (day 15 after injection): *a* – the blood glucose concentration dynamics in the control (solid line, $n = 8$) and experimental (dashed line, $n = 8$) rats after intraperitoneal administration of glucose (2 g/kg). The abscissa axis represents the time after intraperitoneal glucose administration, min; the ordinate axis represents the blood glucose concentration, mmol/l; *b* – the area under the curve "glucose concentration – time" in the control (light column) and type 2 diabetes model (dark bar) groups, min × mmol/l. * the significance of differences compared with the control group, $p < 0.05$



a *b*

Fig. 2. The insulin tolerance test results in male Wistar rats fed with high-fat diet (55% calories from fats) and administered with a single intraperitoneal injection of streptozotocin (35 mg/kg) (day 18 after injection): *a* – the blood glucose concentration dynamics in the control (solid line, $n = 8$) and experimental (dashed line, $n = 8$) rats after subcutaneous administration of insulin (0.75 U/kg). The abscissa axis represents the time after subcutaneous administration of insulin, min; the ordinate axis represents the blood glucose concentration, mmol/l; *b* – the area under the curve "glucose concentration – time" in the control (light column) and type 2 diabetes model (dark bar) groups, min × mmol/l. * the significance of differences compared with the control group, $p < 0.05$



a *b* *c*

Fig. 3. The insulin tolerance test results in male Wistar rats fed with high-fat diet (55% calories from fats) and administered with a single intraperitoneal injection of streptozotocin (35 mg/kg) (day 18 after injection): a and *b* – blood glucose concentration dynamics in the control (*a,* $n = 8$) and type 2 diabetes model (*b*, $n = 8$) groups after subcutaneous administration of insulin (0.75 U/kg). The abscissa axis represents the time after subcutaneous administration of insulin, min; the ordinate axis represents the blood glucose concentration, mmol/l; c – the glucose rate utilization constant (K_{ITT}) during the insulin tolerance test in the control (light column) and type 2 diabetes model (dark column) rats, $\%_{glucose}$/min. * significance of differences compared with the control group, $p < 0.05$

content in the serum of control animals and animals with the T2DM model did not differ, but the HOMA-IR was 2.8 times higher in animals with the experimental T2DM model (Table 2). Streptozotocin causes pancreatic β-cell necrosis, while a compensatory increase in their mass and insulin secretion is observed [13]. A high level of glucose in the serum of animals with the experimental T2DM model and the same insulin level as in the control group indicate the impossibility of insulin resistance compensation by increased insulin secretion. Such disturbances are characteristic of the late stage of T2DM. Gluconeogenesis and glycogenolysis intensify, and glycogen synthesis in the liver and skeletal muscles decreases in animals with the T2DM model [1].

Lipid and protein metabolism also disrupts during type 2 diabetes progression. In the serum of animals with experimental type 2 diabetes, the content of total cholesterol increased significantly (by 7.5 times), the amount of low-density lipoprotein cholesterol elevated, the atherogenic index rose, and the high-density lipoprotein cholesterol was not changed. Impaired lipid metabolism was accompanied by the development of dyslipidemia, one of the most common causes of cardiovascular complications of diabetes (Table 2) [11]. In animals with the T2DM model, the content of circulating free fatty acids and triglycerides increased by 2 times due to stimulation of lipolysis in adipose tissue caused by insulin resistance. Free fatty acids accumulated in the liver triglycerides and ectopic tissues, which further exacerbated insulin resistance. The urea and uric acid content became 2.8 and 1.6 times higher in animals with the T2DM model than in the control. These metabolic disorders are explained by the activation of protein catabolism, mainly in the muscles and liver. The symptoms of liver dysfunction appeared in animals with the T2DM model: the content of albumin decreased in the serum, the activity of the hepatic enzyme ALT increased, while the activity of AST and the concentration of bilirubin did not differ from the control group. (Table 2).

Table 2

The effect of a high-fat diet (55% calories from fats) and streptozotocin (single injection, 35 mg/kg) on biochemical blood parameters in rats, *Me* [Q_1; Q_3]

Parameter	Control (n = 8)	T2DM model (n = 8)
Alanine aminotransferase, U/L	53.0 [49.0; 57.5]	97.0 [93.,0; 109.0]*
Aspartate aminotransferase, U/L	113.0 [108.0; 134.5]	134.0 [121.5; 146.0]
Total bilirubin, mmol/l	2.6 [2.4; 2.9]	3.2 [2.5; 4.2]
Direct bilirubin, mmol/l	1.6 [1.4; 1.7]	1.8 [1.5; 3.1]
Total protein, g/l	76.0 [72.0; 79.0]	72.5 [71.0; 75.5]
Albumin, g/l	36.5 [35.0; 37.0]	32.0 [31.5; 33.0]*
Urea, mmol/l	5.5 [5.0; 5.7]	15.8 [14.5; 17.8]*
Uric acid, mmol/l	165.0 [155; 182.5]	266.0 [236.0; 282.0] *
Total cholesterol, mmol/l	1.8 [1.6; 2.6]	13.6 [8.3; 17.3]*
Low-density lipoprotein cholesterol, mmol/l	0.6 [0.4; 0.7]	5.6 [3.8; 7.6]*
High-density lipoprotein cholesterol, mmol/l	1.0 [0.8; 1.2]	1.0 [0.8; 1.2]
Index of atherogenicity	1.0 [0.6; 1.5]	14.0 [8.9; 16.6]*
Free fatty acids, mM	0.7 [0.6; 0.8]	1.4 [1.3; 1.,8]*
Triacylglycerols, mmol/l	1.2 [0.7; 1.4]	5.1 [2.9; 7.0]*
Glucose, mmol/l	5.1 [4.8; 5.3]	16.9 [15.9; 17.6]*
Insulin, pg/ml	328.8 [229.1; 520.4]	355.9 [279.1; 521.2]
HOMA-IR	1.9 [1.2; 4.5]	5.4 [3.9; 8.4]*

* $p < 0.05$ comparing the experimental group with the control.

Thus, in this model it is possible to trace the main manifestations of carbohydrate, lipid, and protein metabolism disruptions, which are characteristic of the type 2 diabetes pathogenesis.

CONCLUSION

The obtained results indicate that rats fed with a high-fat diet (55% calories from fats) and administered with a single injection of streptozotocin in the low dose (35 mg/kg) reproduce the pathological processes of T2DM. The level of basal insulin does not change, but hyperglycemia is pronounced. This indicates the emergence of insulin resistance in peripheral tissues. Metabolic changes correlate with the results obtained during ITT and GTT and a higher HOMA-IR index. The created model can be used to study the pathogenesis of type 2 diabetes and to investigate the effects of potential hypoglycemic agents.

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Authors contribution

Kaydash O.A. – conception and design, review of publications on the topic, analysis of the obtained data, drafting of the manuscript. Ivanov V.V. – final approval of the manuscript for publication. Vengerovsky A.I. – critical revision of the manuscript for important intellectual content, approval of the manuscript for publication. Buyko E.E. – analysis of the obtained data, drafting of the manuscript. Shchepetkin I.A. – critical revision of the manuscript for important intellectual content, approval of the manuscript for publication.

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