

## Mice experimental model of diabetes mellitus type ii based on high fat diet

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### ABSTRACT

**Objective:** to develop and verify a high fat diet-induced type II diabetes mellitus model.

**Materials and methods:** C57BL/6 male mice were used as the object of study. We developed an experimental diet in which 59% of the total caloric content was from fat. The concentration of glucose in the blood was measured using a portable glucometer PKG-02.4 Satellite Plus (ELTA Company, Russia). Blood samples were obtained by puncture of the caudal vein. Insulin concentrations in the blood plasma of mice were determined by ELISA using the Ultra-sensitive mouse insulin ELISA kit (CrystalChem, USA). Statistical data processing was carried out using the statistical analysis package Statistica 8.0.

**Results.** Mice on a high-fat diet had a significant increase in body weight at week 3. At week 7, there was a significant increase in body weight in mice of the experimental group. The body weight of the experimental animals exceeded that of the control group by 18%. At week 8, the differences in weight rose to 32%. By the end of the experiment, the weight of mice on a high fat diet was 50% higher than the weight of the animals from the control group. It was shown that the applied fatty diet also led to impaired glucose tolerance, and the insulin concentration tripled.

**Conclusion.** The results suggest that the use of high-fat diet in mice leads to an increase in body weight and the formation of obesity, hyperglycemia, decreased glucose tolerance and hyperinsulinemia. All these facts confirm the adequacy of the experimental model for type II diabetes. The created model can be particularly useful in a wide range of studies on insulin resistance, diabetes and obesity, to provide a better understanding of the pathogenesis, as well as to test the effects of therapeutic interventions.

**Key words:** type 2 diabetes mellitus, model of diabetes mellitus, high fat diet, insulin resistance, hyperglycemia.

**Conflict of interest.** The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

**Source of financing.** The study was supported by the grant from the Russian Science Foundation No. 19-15-00118.

**Conformity with the principles of ethics.** The study approved by the local ethics committee under NR TSU (Protocol No. 11 of 24.09.2015).

**For citation:** Kapilevich L.V., Zakharova A.N., Dyakova E.Yu., Kironenko T.A., Milovanova K.G., Kalinnikova J.G., Chibalin A.V. Mice experimental model of diabetes mellitus type ii based on high fat diet. *Bulletin of Siberian Medicine*. 2019; 18 (3): 53–60. <https://doi.org: 10.20538/1682-0363-2019-3-53-60>.

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УДК 616.379-008.64-021.6:613.25]-092.9

<https://doi.org/10.20538/1682-0363-2019-3-53-61>

## Экспериментальная модель сахарного диабета II типа у мышей на основе диеты с избыточным содержанием жиров

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### РЕЗЮМЕ

**Цель исследования:** разработать и оценить адекватность модели сахарного диабета II типа у мышей на основе использования диеты с высоким содержанием жиров.

**Материалы и методы.** В качестве объекта исследования использовались самцы мышей линии C57BL/6. Мы разработали диету для экспериментальной группы, в которой 59% от общей калорийности приходилось на жиры. Измерение концентрации глюкозы в крови проводилось при помощи портативного глюкометра ПКГ-02.4 Сателлит Плюс (ООО «Компания ЭЛТА», Россия). Образцы крови получались пункцией хвостовой вены. Концентрация инсулина в плазме крови мышей определялась иммуноферментным методом с помощью набора Ultra sensitive mouse insulin ELISA Kit (CrystalChem, США). Статистическая обработка данных проводилась с использованием пакета статистического анализа Statistica 8.0.

**Результаты.** В ходе исследования показано, что у мышей, питающихся кормом с высоким содержанием жиров, на 3-й нед зафиксирован значительный прирост массы тела. К концу эксперимента масса тела выросла более чем в 2 раза. У мышей, питающихся нормальным кормом, к концу эксперимента масса тела увеличилась на 50%. Отмечено, что применяемая жировая диета также приводила к нарушению толерантности к глюкозе, при этом концентрация инсулина увеличивалась втрое.

**Заключение.** Полученные результаты демонстрируют, что использование высокожировой диеты у мышей приводит к увеличению массы тела и формированию ожирения, гипергликемии, снижению толерантности к глюкозе и гиперинсулинемии. Все это свидетельствует о высокой степени адекватности разработанной экспериментальной модели заболеванию диабетом II типа. Созданная модель может быть особенно полезна при исследованиях резистентности к инсулину, диабета и ожирения, чтобы обеспечить лучшее понимание патогенеза, а также для проверки эффектов терапевтического вмешательства.

**Ключевые слова:** сахарный диабет II типа, модель сахарного диабета, жировая диета, инсулинорезистентность, гипергликемия.

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

**Источник финансирования.** Исследование выполнено за счет гранта РНФ № 19-15-00118.

**Соответствие принципам этики.** Исследование одобрено локальным этическим комитетом Биологического института НИ ТГУ (протокол № 11 от 24.09.2015).

**Для цитирования:** Капилевич Л.В., Захарова А.Н., Дьякова Е.Ю., Кироненко Т.А., Милованова К.Г., Калинин Ю.Г., Чибалин А.В. Экспериментальная модель сахарного диабета II типа у мышей на основе диеты с избыточным содержанием жиров. *Бюллетень сибирской медицины*. 2019; 18 (3): 53–61. <https://doi.org/10.20538/1682-0363-2019-3-53-61>.

## INTRODUCTION

Type II diabetes mellitus, which accounts for at least 90% of diabetes cases, is associated with insulin resistance in tissues and elevated blood glucose levels [1,2]. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance [3-5].

Insulin sensitivity in tissues at the post-receptor level is reduced in type II diabetes mellitus. The defect in the signal transduction from  $\beta$  subunit of insulin receptor tyrosine kinase leads to a decrease in cell membrane permeability to glucose, due to reduced translocation to the plasma membrane of the glucose transporter protein GLUT 4. As a result, insulin resistance develops and in response to it, hyperinsulinemia occurs, which can compensate for insulin resistance and support normoglycemia for a certain time. Excess insulin by the feedback mechanism further reduces the sensitivity of the receptors to insulin. Glucose utilization by tissues decreases, gluconeogenesis increases in the liver, which leads to hyperglycemia. Also, in type II diabetes, the sensitivity of pancreatic  $\beta$ -cells to glucose stimulation is reduced, which leads to a decrease in insulin secretion. As a result, the first phase, the early phase of insulin secretion, is delayed or absent; gluconeogenesis increases in the liver and hyperglycemia develops. Type II diabetes may be associated with abdominal obesity, which results in insulin resistance [6].

Despite significant achievements, a number of molecular mechanisms of energy metabolism regulation in normal conditions and in pathology remain poorly understood, while new approaches to prevention and treatment of diabetes are needed [7].

An important and promising direction in thesearch fornew approaches to the treatment of this disease is the utilization of experimental models. To model obesity and diabetes in laboratory animals, several types of models are used, which can be divided into two groups: genetic and non-genetic.

To reproduce type II diabetes mellitus type 2 in rodents, chemical cytotoxic diabetogenic substances, streptozotocin, dexamethasone, etc., are most often used, or the combined effect of chemical and dietary factors [8]. Cytotoxic agents have different mechanisms of damaging effects on the beta cells in the pancreas, so their use can be very limited [9]. In addition, most well-known streptozotocin models develop diabetes with severe insulinopenia without obesity, dyslipidemia, and insulin resistance, which, as a rule, is not characteristic of type II diabetes [10].

One of the models for the development of diabetes is keeping animals on a high-fat diet. A high-fat diet can lead to obesity, hyperinsulinemia and altered glucose homeostasis due to inadequate compensation from the islets [11]. Since obesity in this case is caused by manipulations of nutrition, and not with cytotoxic substances, it is believed that such models are more similar to the disease in humans.

Objective: to develop and verify a high fat diet-induced type II diabetes mellitus model.

## MATERIALS AND METHODS

C57BL/6 male mice were used in the study. The mice were obtained from the animal facilities of the Tomsk National Research Medical Center of the Russian Academy of Sciences at the Research Institute of Pharmacology and Regenerative Medicine named after E.D. Goldberg. The age of the mice at the start of the experiment was 2 weeks. The regime of keeping animals was the following: day/night: 12/12, the sunrise is at 6:00, free access to food and water, the temperature in the room is 24°C.

Two groups were formed: 1) mice on a standard chow diet ( $n = 12$ ) – control group; 2) mice on a high fat diet ( $n = 12$ ) – experimental group.

The control group was fed with food for laboratory animals Prokorm (Biopro, privately-held company, Novosibirsk), in which fats accounted for 18% from the total calories intake. The composition of the feed was wheat, barley, bran, corn gluten, fish meat, protein feed, sunflower oil and soybean meal.

For the experimental group, we developed a diet that included the Prokorm feed described above (50%), animal (lard) (20%) and vegetable (sunflower oil) (10%) fat, sugar (15%) and dry milk (5%). Products were ground in a blender to a homogeneous mixture, after which the mass was formed into granules with a diameter of up to 10 mm and dried in an oven at 30°C. The feed was prepared for 5 days and stored at +4°C. The diet complied with the following criteria: 59% of the calories accounted for fats, including animal fats (2/3 of the specified amount) and vegetable fats (1/3 of the specified amount); the fatty acid composition is presented in table 1.

The experiment continued within 16 weeks. The body weight test was carried out every two weeks. The glucose tolerance test was conducted on the 1st and 16th week. Insulin concentration was measured at week 1 and 16 immediately after and 15 minutes after intraperitoneal glucose administration.

Table 1

Fatty acid composition of high fat diet (for the experimental group)			
Characteristics	Fatty acids	The content in grams per 100 grams of crude fat	
		Sunflower oil	Pork fat
C10:0	decanoic	–	0,06
C12:0	lauric	Δо 0,1	0,2
C14:0	myristic	Δо 0,2	1,1
C16:0	palmitic	5,0–7,6	19,5
C16:1	palmitoleic	Δо 0,3	2,7
C18:0	stearin	2,7–6,5	11,4
C18:1	olein	14,0–39,4	38,5
C18:2	linoleic	48,3–74,0	9,5
C18:3	linolenic	Δо 0,3	0,7
C20:0	arachidic	0,1–0,5	–
C20:1	gadoleic	Δо 0,3	–
C22:0	behenic	0,3–1,5	–
C22:1	erucic	Δо 0,3	–
C22:2	docosadiene	Δо 0,3	–
C24:0	lignoceric	Δо 0,5	–
C20:4	arachidonic	–	0,1

Table 2

Characteristics of diets for the experimental and control groups		
Characteristic	High fat diet	Chow diet
Calorie, kcal/kg	5 100	3 000
including of calories for fat, %	59	18
Composition		
Fat, %	33	6
including animal fats, %	20	–
Carbohydrates, %		
including sugar	15	–
starch	30	61
crude fiber	1,8	3,6
Squirrel, %	20	23,9
Lysine, %	0,8	1,5
Methionine + Cysteine, %	0,5	0,9

Окончание табл. 2  
End of table 2

Characteristic	High fat diet	Chow diet
Macronutrients		
Calcium, %	0,9	1
Phosphorus, %	0,7	0,8
Sodium chloride, %	0,24	0,34
Vitamins and trace elements	+	+
Antioxidants, Amino Acids	+	+

### INTRAPERITONEAL GLUCOSE TOLERANCE TEST

The concentration of glucose in the blood was measured using a portable glucometer PKG-02.4 Satellite Plus (ELTA Company, Russia). Blood samples were obtained by puncture of the caudal vein.

For the glucose tolerance test, the mice were fasted for 4 hours, maintaining free access to water, the animals were weighed in the morning and the glucose concentration in the blood was determined (0 min). Then, a solution of 40% glucose (2 g/kg body weight) (carbohydrate load) was injected intraperitoneally to the animals [12]. The concentration of glucose in the blood was determined at 15, 30, 60 and 120 minutes after carbohydrate loading [13]. The maximum achievable concentration, time to reach the maximum and time to return to the initial level were estimated, and the area under curve (AUC) was also calculated (Figure 2B).

### MEASUREMENT OF INSULIN CONCENTRATION IN BLOOD PLASMA

Blood samples were obtained by puncture of the caudal vein. Blood was collected in Microvette Sarstedt capillary tubes (Germany) 200 µl with K3EDTA.

The samples were centrifuged immediately after blood collection for 6 minutes at 10,000 rpm at 4 °C. Plasma was stored frozen at a temperature of -80 °C. Insulin concentration in the blood plasma of mice was determined by ELISA using the Ultra-sensitive mouse insulin ELISA kit (Crystal-Chem, USA). Measurement of the optical density of the samples was carried out using a microplate spectrophotometer Anthos. The calculation of the optical density of the samples was carried out at a wavelength of 450 nm and the reference wavelength was 620 nm.

To assess insulin resistance, we calculated the HOMA-IR Insulin Resistance Index (Homeostasis Model Assessment of Insulin Resistance), an indicator derived from Matthews D.R. et al., 1985, associated with the development of a mathematical homeostatic model for evaluating insulin resistance [14]. The calculation was performed according to the formula  $HOMA-IR = (\text{fasting glucose (mmol / l)} \times \text{fasting insulin (µED / l)}) / 22.5$ .

Statistical data processing was carried out using the statistical analysis package STATISTICA 8.0. The level of significance when testing the hypothesis that two samples belong to the same general population was estimated by the Kruskal-Wallis ANOVA test. The data were presented as  $X_{cp} \pm SE$ .

The study was approved by the local ethical committee of the Biological Institute of the TSU (protocol No. 11 of September 24, 2015).

### RESULTS

As a result of feeding mice with high fat diet, obesity developed in the animals. The dynamics of body mass change over 16 weeks in animals of the control and experimental groups is presented in Figure 1. The identified excess of body weight as opposed to the control can be interpreted as obesity. Many authors define obesity as an increase in body weight by more than 25% [8, 9, 10].

At week 7, there is a significant increase in body weight in the mice from the experimental group. The body weight of the experimental animals exceeded the weight of animals in the control group by 18%. At week 8, the differences in weight rose to 32%. By the end of the experiment, the weight of mice on a high fat diet had been 50% higher than the weight of the animals in the control group (Figure 1).

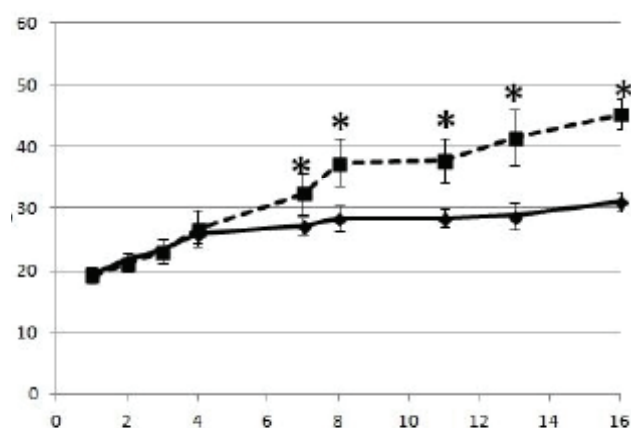
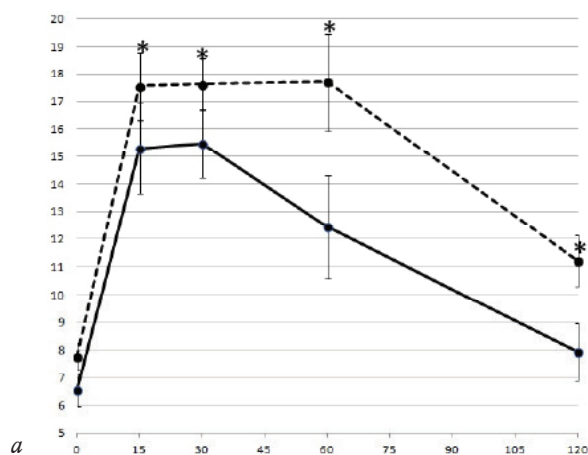


Fig. 1. The effect of a high-fat diet (59% calorie fat) on C57BL/6 mice body weight: on the abscissa axis – the weeks of keeping animals on a diet, on the ordinate axis – body weight (gram). The solid line is the control group,  $n = 12$ ; the dotted line is the experimental group,  $n = 12$ . \* versus the control group,  $p < 0.01$

Рис. 1. Влияние высокожировой диеты (59% калорийности – жиры) на массу тела самцов мышей линии C57BL/6: по оси абсцисс – время содержания животных на диете, нед, по оси ординат – масса тела, г. Сплошная линия – контрольная группа,  $n = 12$ ; пунктирная линия – экспериментальная группа,  $n = 12$ . \* достоверность различий с контрольной группой,  $p < 0,01$



Hyperglycemia in mice of the experimental group was observed from the 8th week of the study ( $6.63 \pm 0.91$  mmol/l versus  $4.4 \pm 1.3$  mmol/l in the control). By the end of the experiment in mice of the experimental group, the degree of glucose absorption decreased. After 15 and 30 minutes after the carbohydrate load in the mice of the experimental group, the level of glucose in the blood exceeded that of the control group by 13%. The same ratio persisted after 30 minutes. Within 60 minutes, the blood glucose level in the control group began to gradually decrease, whereas in the experimental group the index increased and the differences with the control were 41%. After 2 hours, the glucose level in the control group almost returned to the initial level, while in the experimental group it remained elevated by 57% (Figure 2A). In the control group, the maximum rise in the glucose concentration was observed at the 30th minute and was  $15.46 \pm 1.2$  mmol/l. In mice of the experimental group, the maximum concentration was reached at the 60th minute and amounted to  $17.7 \pm 2.3$  mmol/l. The area under the curve (AUC) in the control group was  $1424.6 \pm 218.7$  min \* mmol/l; in the experimental one it was  $1851.7 \pm 254.5$  min \* mmol/l ( $p < 0.05$ ) (Figure 2B).

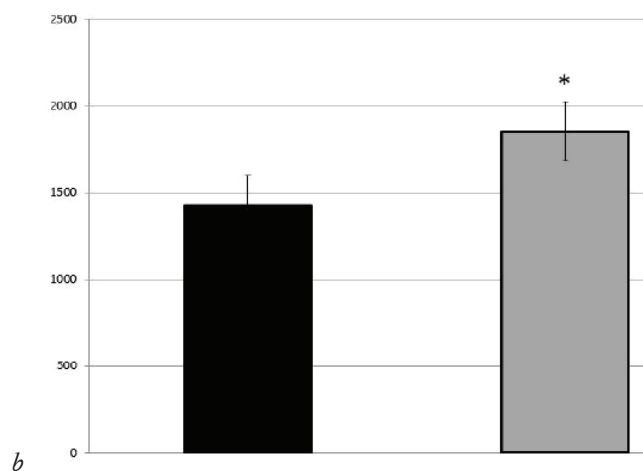


Fig. 2. The results of the glucose tolerance test in C57BL/6 mice after 16 weeks of high-fat diet feeding (59% calorie fat): a – dynamics of blood glucose concentration in mice of the control (solid line, 12 animals) and experimental (dashed line, 12 animals) groups after intraperitoneal glucose invasion (2 g/kg). The abscissa axis is the time after intraperitoneal glucose invasion, minutes, the ordinate axis is the glucose concentration, mmol/l; b – the area under the curve (AUC) in the control (dark bars) and experimental (light bars) groups, min \* mmol/l. \* versus the control group,  $p < 0.05$

Рис. 2. Результаты теста на толерантность к глюкозе у самцов мышей линии C57BL/6 через 16 нед содержания на высокожировой диете (59% калорийности – жиры): a – динамика концентрации глюкозы в крови у мышей контрольной (сплошная линия,  $n = 12$ ) и экспериментальной (пунктирная линия,  $n = 12$ ) групп после внутрибрюшинного введения глюкозы (2 г/кг). Ось абсцисс – время после внутрибрюшинного введения глюкозы, мин; ось ординат – концентрация глюкозы в крови, ммоль/л; b – величина площади под кривой концентрации глюкозы AUC при глюкозотолерантном тесте в контрольной (темные столбики) и экспериментальной (светлые столбики) группах, мин \* ммоль/л. \* достоверность различий в сравнении с контрольной группой,  $p < 0,05$

The decrease in glucose is called the hypoglycemic phase and indirectly reflects the rate of insulin production and the sensitivity of tissues to this hormone. Prolongation of this phase is characteristic of type II diabetes mellitus, which was observed in the experimental group of mice in this study.

Figure 3 shows the insulin concentration in the blood plasma of mice before and after the glucose administration. In mice of the experimental group, the insulin level exceeded 3 times the value in the control group both before and 15 minutes after the administration of glucose.

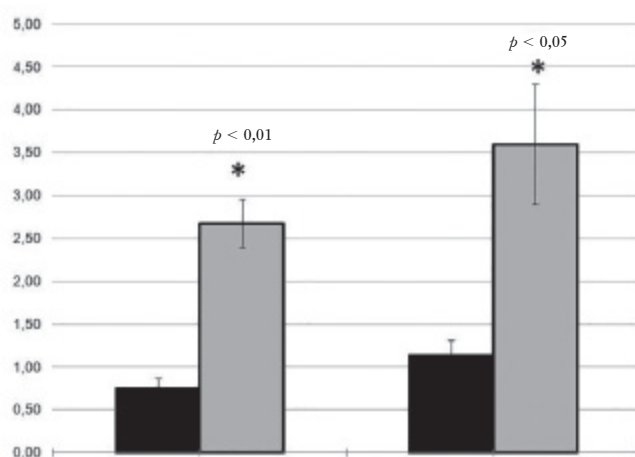


Fig. 3. The insulin concentration (ng/ml) in the mice blood plasma before and after 15 min glucose invasion; control group (dark bars,  $n = 12$ ), experimental group (light bars,  $n = 12$ ). \* versus the control group,  $p < 0.05$

Рис. 3. Концентрация инсулина (нг/мл) в плазме крови самцов мышей линии C57BL/6 до и через 15 мин после введения глюкозы; контрольная группа (темные столбики,  $n = 12$ ), экспериментальная группа (светлые столбики,  $n = 12$ ). \* достоверность различий с контрольной группой,  $p < 0,05$

The calculation of HOMA-IR gave the following results: in the control group at the 16th week of the experiment it was  $3.62 \pm 0.48$ ; and in the experimental one –  $19.85 \pm 3.07$  ( $p < 0.001$ ).

Typically, type II diabetes is characterized by insulin resistance. As the blood glucose concentration continues to rise, it promotes the release of more insulin.

## CONCLUSION

The results show that a high-fat diet in mice leads to an increase in body weight and development of obesity (body weight is more than 25%

higher than in the control group [8, 9, 10]), hyperglycemia, reduced glucose tolerance and hyperinsulinemia. All these facts confirm the adequacy of the developed experimental model of type II diabetes mellitus. The criteria for the adequacy of the model, therefore, are the following: the dynamics of body mass; hyperglycemia and glucose tolerance test results, including the area under the glucose concentration curve for the glucose tolerance test (AUC).

At the same time, a high concentration of insulin in the blood of animals of the experimental group indicates that the disorders were formed only in muscle tissue, while the sensitivity to glucose of pancreatic  $\beta$ -cells remains. This allows us to make a conclusion about the relative adequacy of the developed model: alterations in the muscular tissue, but not in the pancreas, are modeled. Perhaps, the formation of glucose resistance on the part of  $\beta$  – cells in the pancreas requires a longer period.

The created model can be especially useful in a wide range of studies on insulin resistance, diabetes and obesity. It will provide a better understanding of the pathogenesis of the diseases, and can also be used for experimental verification of the effects of therapeutic interventions.

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Received 15.04.2019  
Accepted 11.06.2019

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Поступила в редакцию 15.04.2019  
Подписана в печать 11.06.2019