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IMPROVEMENT OF AN EXPERIMENTAL MODEL FOR THE DEVELOPMENT OF DIABETES MELLITUS IN LABORATORY ANIMALS

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Abstract:
An urgent problem of evaluating the effectiveness of various therapeutic and surgical approaches in the treatment of any diseases occurring against the background of diabetes mellitus is the experimental formation of a diabetes model that would provide a stable increase in blood glucose levels and allow objective studies to assess the features of the course of various processes against the background of diabetes, and was not accompanied by a high mortality of animals in the stage of development of diabetes mellitus. The aim of this study was to develop a new method for modeling diabetes mellitus in an experiment, which will allow achieving an adequate, easily reproducible model of diabetes with damage to a significant part of beta cells, but the absence of high mortality in laboratory animals by reducing the damaging effect of alloxan. As a result of the research, it was possible to cause a persistent increase in blood sugar levels in experimental animals against the background of destructive processes in the endocrine glands of the pancreas. A new method for the formation of diabetes mellitus has reduced mortality to 5%, which is of great importance in further experimental studies to assess the effectiveness of various methods of treating diseases against the background of diabetes mellitus.

Keywords: diabetes mellitus; alloxan; purulent-necrotic process; liver abscess.

INTRODUCTION. Diabetes mellitus (DM) is one of the main global public health problems and the situation with it is gradually deteriorating, especially in developing countries. Against this background, an urgent problem of evaluating the effectiveness of various therapeutic and surgical approaches in the treatment of any diseases occurring against the background of DM is the experimental formation of a diabetes model that would provide a stable increase in blood glucose levels and allow objective studies to assess the features of the course of various processes against the background of diabetes, and also was not accompanied by a high mortality of animals in the stage of development of DM.

Animal models in diabetes research are very common, where rodents are the best choice due to the fact that they are smaller, easy to handle, omnivorous in nature and do not behave like wild ones. Typically, rodent models are divided into two main classes, namely: (1) genetic or spontaneously induced models and (2) non-genetic or experimentally induced models. Non-genetic models are more popular compared to genetic models due to lower cost, wider availability, easier to cause diabetes and, of course, easier to maintain compared to genetic models. Over the past three decades, a number of non-genetic models have been developed for diabetes research, including adult models with alloxan/streptozotocin (STZ), partial pancreatectomy model, high-fat diet (HF) models, high-fat diet models, HF diet models. Models with feeding STZ, models with nicotinamide-STZ, models induced by sodium glutamate (MSG), and models with intrauterine growth retardation (IUGR). The T2D model should have all the major pathogens of the disease commonly found in humans; however, none of the above models has limitations. This chapter provides a comparative assessment of most experimentally induced models of DM 2 in rodents, taking into account their limitations, advantages, disadvantages and the importance of development, in order to help diabetes research groups more correctly select animal models to work on their specific research question. HF-fed STZ models, nicotinamide-STZ models, monosodium glutamate-induced (MSG) models, and intrauterine growth retardation (IUGR) models [3, 10, 15].

Streptozotocin (STZ) is the most well-known diabetogenic chemical [4], which is widely used in animal experiments to create models of type 1 and type 2 diabetes [12]. Obtaining reliable data from STZ-based animal models of diabetes depends on proper

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preparation and use of STZ. Despite the long history and widespread use of STZ in diabetes research, some important points regarding the use of STZ (for example, its preparation, appropriate dose and abnormal composition) are not always taken into account. These problems prevent proper comparison of the results obtained in different studies and lead to losses in the translation of animal data to humans. Suboptimal preclinical data in animal models are one of the reasons for the limited success of drugs during clinical trials [14]. In this review, we offer practical guidelines on the use of STZ in diabetes research that can help researchers conduct better research.

Rats and mice are the preferred animals for diabetes research [7], which are mentioned in 94% of articles in the field of endocrinology [1], this is mainly due to their easy accessibility and short generation interval [15]. The rat model of diabetes is more similar to human disease, for example, in terms of the ability of agents to modify the disease [6].

The models of diabetes in rodents can be divided into genetic and experimentally induced ones. The latter has a lower cost and is easier to call, so it is widely used for research purposes [4, 7]. Experimentally induced models of diabetes in animals are created through surgery, dietary treatment, chemicals, or a combination of both. The most common types of diabetes are type 1 and type 2 diabetes, which are associated with absolute and relative insulin deficiency, respectively [10]. Chemicals used to induce diabetes in animal models include STZ, alloxan, vactor, ditizon, 8-hydroxyquinolone, and gold thioglucose [11, 16].

Alloxan diabetes is the most recognized model of the development of diabetes mellitus in rats. "Alloxan (2,4,5,6-tetraoxohexahydropyrimidine) is an unstable pyrimidine, a derivative of uric acid, with diabetogenic effect. In 1943, it was shown that the administration of this chemical compound to rabbits causes selective necrosis of the pancreatic islets, followed by the development of classic symptoms of diabetes mellitus [2]. Alloxan is a structural analogue of glucose, due to which it binds to the glucose transporter GLUT2 and selectively accumulates in the beta cells of the pancreas. Further study of the biochemical mechanisms of action of alloxan showed the presence of a mechanism of destructive action of the latter by generating reactive oxygen species in a cyclic reaction with dialuric acid, which initiate the destruction of β-cells with low antioxidant protection. Alloxan has a diabetogenic effect only with parenteral administration – intravenous, subcutaneous, intramuscular and intraperitoneal [5]. The effective dose depends on the type of animal, the method of administration, the nutritional status and the form of diabetes caused. However, as before, with all the availability of this technique, the disadvantage of the method is a fairly high mortality rate of animals, which reaches 30-70%.

In this regard, the purpose of this study was to develop a new method for modeling DM in an experiment, which will allow achieving an adequate, easily reproducible model of diabetes with damage to a significant part of beta cells, but the absence of high mortality in laboratory animals by reducing the damaging effect of alloxan.

MATERIALS AND METHODS. Experimental studies were performed in the laboratory of experimental surgery of the State Institution "Republican Specialized Scientific and Practical Medical Center of Surgery named after Academician V.Vakhidov" on 30 white mongrel rats of both sexes weighing 240-310g. The animals were kept in cages of 2 individuals in a vivarium equipped with supply and exhaust ventilation with an air temperature of 22-23 °C. Nutrition was carried out by eating a balanced meal with the inclusion of dry food and vitamins. Water was provided in unlimited quantities. Before performing the experiments, the animals were without food for 12 hours. All manipulations were performed in accordance with the requirements for the humane treatment of experimental animals (Strasbourg 1986).

The proposed method is performed as follows:

- Alloxan tetrahydrate is injected intraperitoneally with a syringe under anesthesia with ether vapor in a rat at the rate of 50 mg per 1 kg of animal weight in 0.4 ml of saline solution.
- After the introduction of alloxan tetrahydrate in the projection of the liver, percutaneous irradiation with low-energy laser radiation is performed using the Sogdiana apparatus with a wavelength of 0.89 microns, a pulse power of 3 W, a frequency of 1500 Hz, and a duration of 2 min.
- After the introduction of alloxan tetrahydrate in the projection of the liver, percutaneous irradiation with low-energy laser radiation is performed using the Sogdiana apparatus with a wavelength of 0.89 microns, a pulse power of 3 W, a frequency of 1500 Hz, and a duration of 2 min.
- Percutaneous irradiation with low-energy laser radiation in the projection of the liver of a laboratory animal using the Sogdiana apparatus with the above parameters - with a wavelength of 0.89 microns, a pulse power of 3 Watts, a frequency of 1500 Hz, a duration of 2 minutes - is carried out daily once a day for 7 days.
- 2 days after the first injection of alloxan tetrahydrate, this manipulation is repeated (alloxan tetrahydrate 50 mg / kg body weight intraperitoneally); the last similar dose is administered after another 3 days.

Thus, the scheme of administration of alloxan tetrahydrate 50 mg / kg of animal weight in 0.4 ml of

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saline solution intraperitoneally on an empty stomach: 1st, 4th, 8th day of the experiment. The scheme of percutaneous irradiation with low-energy laser radiation with the above parameters: 1st, 2nd, 3rd, 4th, 5th, 6th, 7th days of the experiment.

During the development of alloxan diabetes in animals, body weight and peripheral blood glucose were determined in dynamics.

Glucose and urea levels were determined in the blood plasma of animals using standard sets of reagents from Vital Diagnostics SPb and in whole blood the content of glycosylated hemoglobin was determined using a ready-made set of reagents from the Diabetes test company PHOSPHOSORB. Increased levels of glucose, urea and glycosylated hemoglobin are the main indicators and criteria for the development of diabetes mellitus. The optical density was measured using the SF-56 LOMO-Spectrum spectrophotometer.

To implement the method, a laser therapeutic device "SOGDIANA" (Uzbekistan) was used.

RESULTS AND DISCUSSION. The first signs of diabetes manifested themselves in the form of a sharp increase in water consumption to 120 ml, a sharp loss in weight, hair loss, Dynamics of blood parameters and morphology. For evaluation, the concentration of glucose, cholesterol, triglycerides and other biochemical parameters in blood serum was determined in the dynamics of the experiment, starting from the third day after the administration of alloxan. Rats were removed from the experiment by decapitation 14-60 days after administration of the drugs. Kidneys, thyroid gland, adrenal glands, retroperitoneal and epididymal fat, thymus were isolated, weighed and mass index was calculated as the ratio of organ mass to 100 g of body weight.

Unlike other methods, according to patent and patent-associated literature, in our method - after three times administration of an intraperitoneal alloxan tetrahydrate solution at a dose of 50 mg / kg of body weight lab. animal in 0.4 ml saline solution after 18 hours of fasting, and parallel percutaneous irradiation of the liver projection lab. Animal mortality was not observed by low-energy laser radiation using the Sogdiana apparatus with a wavelength of 0.89 microns, a pulse power of 3 Watts, a frequency of 1500 Hz, and a duration of 2 minutes, but the model of diabetes mellitus was fully formed.

Biochemical parameters of rat blood serum to the diabetogenic effect of alloxan are shown in Table 1.

Table 1
Biochemical parameters of rat blood serum to the diabetogenic effect of alloxan

Indicator	Control rats	Rats after Alloxan administration (Days of the experiment)						
		1st	3rd	5th	7th	14th	30th	45th
Albumin	33,2±0,02	34,7±0,03	32±0,5	30±0,05	29,8±0,02	29,5±0,2	29±0,03	33,5±0,02
Glucose	2,3±0,2	3,7±0,05	10,7±0,04	10,2±0,12	9,4±0,02	9,7±0,05	9,4±0,04	10±0,07
TSH	0,9±0,06	1,5±0,02	1,6±0,03	1,6±0,04	1,6±0,05	1,8±0,02	1,9±0,08	2±0,04
Urea	10,1±0,04	7,9±0,03	8±0,3	8±0,4	8±0,7	8±0,4	9±0,09	9±0,2
Cholesterol	2±0,02	1,9±0,05	1,3±0,07	1,3±0,05	1,4±0,04	1,6±0,05	1,7±0,07	2±0,07
HDL	0,7±0,02	0,9±0,07	1±0,04	1±0,08	1±0,02	1,2±0,03	1,4±0,01	1,7±0,02
LDL	0,6±0,03	0,6±0,03	0,5±0,05	0,5±0,02	0,5±0,04	0,3±0,05	0,24±0,04	0,2±0,03
ALT	46,6±0,2	45±0,25	54±0,5	50±0,3	47±0,21	40±0,31	38,3±0,4	84±0,5
AST	280,2±0,24	228±0,28	220±0,3	218±0,4	200±0,32	165±0,33	149±0,4	162±0,5
Bilirubin	1,4±0,03	0,9±0,04	1±0,03	1±0,02	1±0,01	1±0,01	0,9±0,02	3±0,03
Creatinine	66±0,22	60,2±0,2	62±0,23	64±0,31	60±0,32	55±0,09	53±0,4	60±0,5
Total protein	71,1±0,05	50±0,3	52±0,32	59,1±0,8	56±0,25	55±0,6	55±0,22	68±0,3

One of the directions that allow us to obtain valuable information for understanding the pathogenesis of DM, as well as managing the repair processes, is to study the degree of morphofunctional damage to pancreatic β-cells in alloxan diabetes.

HISTOLOGICAL CHARACTERISTICS OF THE PANCREAS. Pieces of pancreatic tissue were taken for histological examination. Next, the pieces of fabric were fixed in 10% formalin, passed through alcohols of increasing strength and poured into paraffin. Sections 5-6 microns thick were prepared from paraffin blocks. The sections were stained with hematoxylin and eosin.

According to the results of the study, intraperitoneal administration of alloxan to animals caused a change in the general condition of the animal and the appearance of clinical and biochemical signs characteristic of the development of diabetes mellitus (hyperglycemia, glucosuria, polyphagia, polydipsia, polyuria, weight loss). Histological examination of the

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pancreas of rats after administration of alloxan at a dose of 170 mg/kg revealed that the connective tissue capsule covering the gland is denser. The walls of the vessels are thickened, the inner layer is loose, the cells are enlarged in size with a sign of vacuolization. There is a pronounced fullness of blood vessels, especially in the area of the islets. There is swelling of the interlobular connective tissue. The contours of the endocrinocytes become indistinct. Vascular disorders: fullness of veins, stasis, diapedesis hemorrhages (Fig. 1).

In rats with alloxan diabetes, swelling of the interlobular connective tissue was observed. In pancreatic islets, lymphocytic infiltration can be traced in some places. Destruction was observed in some of the islands. Using morphometric studies, it was found that by the end of the experiment, the diameter of the pancreatic islets decreased by 1.4 times in relation to the intact ones. The glandular lobules of the pancreas are atrophied and deformed. In the stroma of the gland, there is an overgrowth of connective tissue and hyalinosis. Vascular disorders (fullness, hemorrhage stasis, stromal edema) were detected in the pancreatic parenchyma (Fig. 2, 3). The acinules of the gland are atrophied and deformed. Connective tissue overgrowth and hyalinosis are observed in the stroma. In animals sensitive to alloxan, diffuse venous fullness of the gland, multiple hemorrhages in the parenchyma and stroma of the gland were observed. In some cases, focal lymphocytic infiltrates were found in the pancreatic stroma.

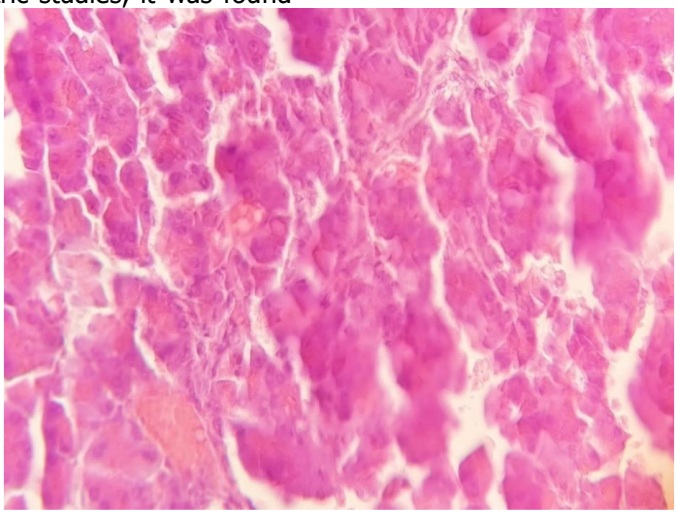

Fig. 1. The pancreas of a rat. Vascular disorders: fullness of veins, diapedesis hemorrhages. Staining: with hematoxylin and eosin. Magnification x 400

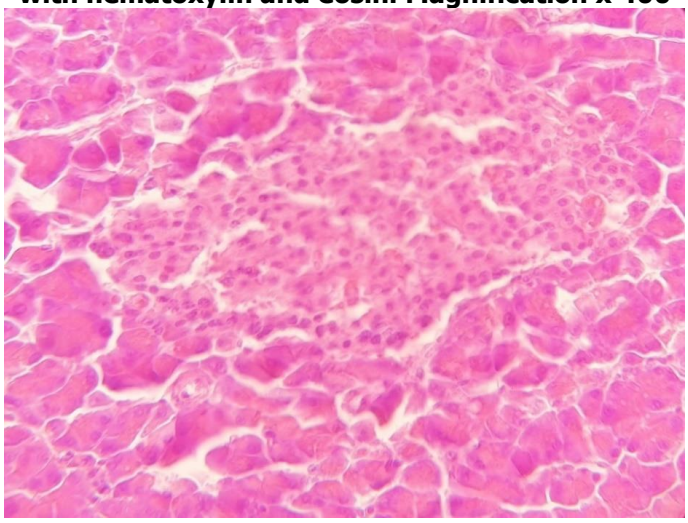

Fig. 2. Swelling of the pancreatic stroma. Staining: hematoxylin and eosin. Magnification x 400. Glandular lobules of normal size. Exocrinocytes of acinuses with dystrophilic changes. Accumulations of tissue fluid in the form of vacuoles are detected in the cytoplasm of cells, i.e. protein hydropic dystrophy develops

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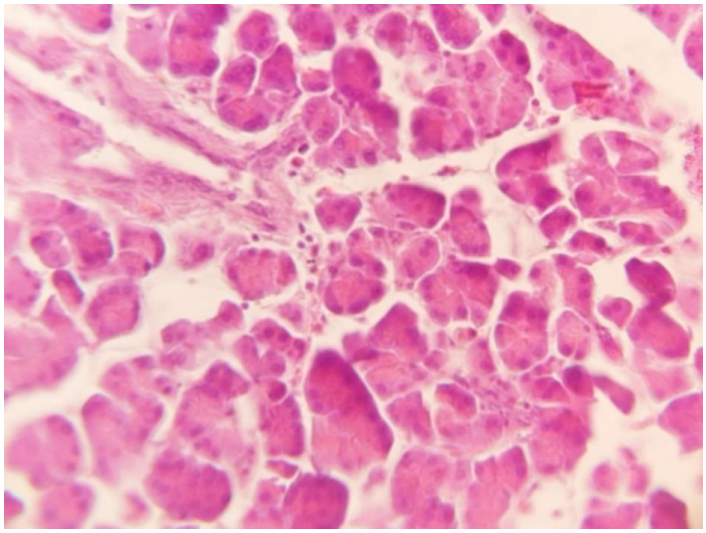

Fig. 3. Hydropic protein dystrophy of rat pancreatic exocrinocytes. Staining: hematoxylin and eosin. Magnification x 400. The pancreatic islets, reduced in size, are scattered throughout the parenchyma of the gland

Thus, highly alloxan-sensitive animals develop severe vascular disorders in the pancreas, pronounced interstitial edema, necrobiosis and necrosis of β-cells with emptying of the islets of Langerhans (Fig. 4).

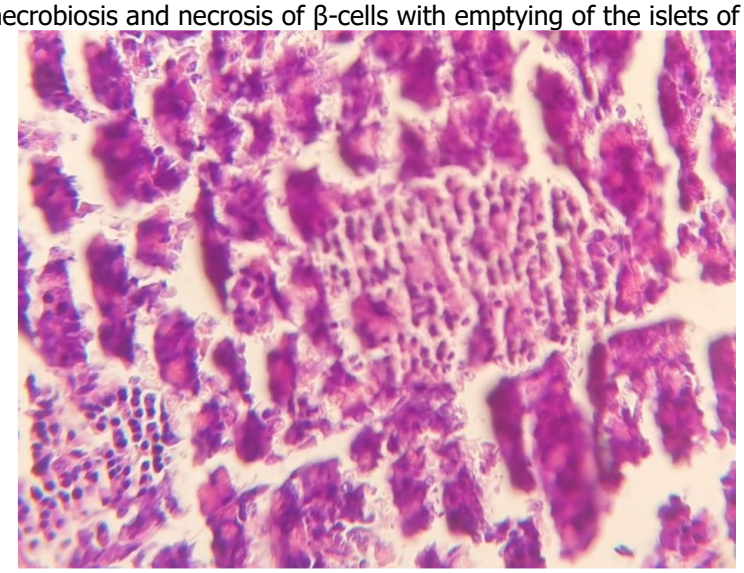

Fig. 4. Pancreatic islets of the pancreas reduced in size. Staining: hematoxylin and eosin. Magnification x 400

The advantages of the method are due to the following causal relationship between the distinctive features and the task being solved:

- The intervals between repeated injections of the drug are chosen in such a way as to create the best conditions for the body to adapt to pancreatic damage, which ensures a reduction in mortality after modeling alloxan diabetes in rats from 60% to 5% with the formation of a persistent increase in blood sugar levels;
- Laser radiation in these modes contributes to the additional release of insulin by secreting cells of the pancreas, thereby reducing the negative effect of alloxan;
- Laser radiation enhances microcirculation in the liver, reducing the damaging effect of alloxan;
- Laser irradiation improves the detoxification function of the liver, thereby reducing the toxic effect of alloxan;
- The method is simple to perform;

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- A persistent increase in blood sugar levels is formed;
- Morphologically proven selective damage to insulin-producing cells.

Consequently, the task was completely solved by the claimed method – an experimental model of diabetes mellitus was created, which made it possible to achieve an adequate, easily reproducible model of diabetes mellitus with damage to a significant part of beta cells, but the absence of high mortality in laboratory animals by reducing the damaging effect of alloxan by introducing small fractional doses of alloxan tetrahydrate and using percutaneous irradiation of the liver projection with low-energy laser radiation using the Sogdiana apparatus.

CONCLUSION. To develop new treatments for DM and its complications, it is important to be able to investigate their effectiveness in experimental conditions. To this end, we have tested a method for the formation of experimental diabetes mellitus in rats by administration of alloxan. The alloxan diabetes technique is a well-known and correct model for investigating the effectiveness of diabetic drugs. The problem of alloxan diabetes is the high mortality of animals after injection of the drug, which reaches 70% or more, depending on the dose administered and the time of formation of the pathological process. Taking into account the fact that the tasks of our research included modeling the complicated course of diabetes against the background of a purulent-necrotic process, the novelty of the research was the improvement of the methodology of alloxan diabetes with the possibility of preserving the immune system to preserve the viability of animals against the background of the formation of a purulent-necrotic process and septic intoxication. The novelty of the solution consisted in fractional intraperitoneal administration of alloxan with an interval of 2 days against the background of liver stimulation by percutaneous laser irradiation with an IR pulsed low-intensity laser with parameters: wavelength 0.89 microns, frequency 1500 Hz, pulse power 3 W with daily sessions of 1 minute.

Biochemical studies in rat blood serum against the background of alloxan diabetes showed that after three times administration of alloxan tetrahydrate at a dose of 50 mg/kg, several phases of changes in blood glucose were observed. The first phase is hyperglycemic, reaching a maximum during the first hours; the second is hypoglycemic, which mainly manifested itself during the first day, the third phase is a phase of persistent hyperglycemia, an increase in ALT and bilirubin levels. In animals, severe vascular disorders develop in the pancreas, pronounced interstitial edema, necrobiosis and necrosis of β - cells with the emptying of the islets of Langerhans.

As a result, it was possible to cause a persistent increase in blood sugar levels in experimental animals against the background of destructive processes in the endocrine glands of the pancreas. A new technique for the formation of diabetes mellitus has reduced mortality to 5%, which is of great importance in the development of methods for the treatment of acute liver abscesses or other experimental models for the formation of purulent necrotic processes in rats.

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