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MORPHOFUNCTIONAL STATE OF PANCREAS IN RATS WITH DIABETES MELLITUS

O.R. Ivantsiv[1], V.M. Fedorak[2], I.I. Bilinskyi[3], Yu.I. Popovych[4], V.V. Fedorak[5]

Ivano-Frankivsk National Medical University, department of pediatric surgery with a course of clinical anatomy and operative surgery; department of pharmacology, Ivano-Frankivsk, Ukraine
[1]ORCID ID: 0000-0002-4366-6406, e-mail:oivantsiv@ifnmu.edu.ua
[2]ORCID ID: 0000-0003-4607-0496, e-mail:fedorak@ifnmu.edu.ua
[3]ORCID ID: 0000-0001-5106-0095, e-mail:ibilinskuy@ifnmu.edu.ua
[4] ORCID ID: 0000-0002-2401-4699, e-mail:yupopovych@ifnmu.edu.ua
[5]ORCID ID: 0009-0009-2688-3490, e-mail: fedorak_vl@ifnmu.edu.ua

Abstract. Goal. To analyze the literature sources concerning morphofunctional state of a pancreas in case of diabetes mellitus and treatment in white laboratory rats.

Materials and methods. Generalisation of ukrainian and foreign literature data, results of meta-analyses and randomized studies.

Results. Characteristics of main mechanisms of diabetes mellitus modeling was conducted in experimental animals. Literature data regarding the peculiarities of pancreatic islets in normal conditions, in case of diabetes mellitus and pharmacological correction of this disease were intensified.

Anatomically, pancreas is divided into three regions: duodenal, gastric and splenic. This division in rats is somewhat conditional due to small size of organ. In some cases, highest concentration of endocrine islets is found in splenic region of gland. Islets are formed by endocrinocytes. There are four types of endocrine cells in rats: insulinocytes, glucagonocytes, somatostatinocytes and pancreatic polypeptide cells. In rats with diabetes, morphofunctional state of pancreas worsens. Numbers of insulinocytes and area of islets are decreases, level of glucose and glycosylated hemoglobin increases.

Review of literature sources shows social significance of conducted research, as experimental diabetes mellitus creates discomfort and reduces the quality and lifespan of experimental animals. Prolonged uncorrected hyperglycemia creates the background for micro- and macroangiopathies development. Pharmacotherapy for diabetes primarily aims to achieve normoglycemia through dietary correction in combination with pharmacological agents. This not only slows down the progression of diabetic micro- and macroangiopathies but also extends the lives of rats. In context of absolute insulin deficiency, a priority for correcting streptozotocin-induced diabetes remains using of insulin therapy with exogenous insulin drugs and enhancing reparative processes in the gland due to improved regeneration of endocrinocytes.

The priority task for scientists still remains the development of medicines capable of promoting regeneration processes of islets. According to literature sources, polytherapy of diabetes mellitus using pharmacological antidiabetic drugs can be more effective as compared to monotherapy. Several authors have studied the combined effect of insulin and exenatide (an incretin mimetic), finding that exenatide enhances the regenerative capabilities of pancreatic islets in diabetes mellitus. However, the use of incretin mimetics in type I diabetes mellitus remains controversial and requires further study.

Expediency of experimental diabetes mellitus modeling is based on developing new methods for type I diabetes mellitus correction. This will promote prolonged functioning of endocrine cells, enhance regeneratory and compensatory processes in pancreas and optimize the therapeutic effect of antidiabetic drugs in experiment.

Conclusion. The presented data establish the peculiarities of morphological changes in pancreatic islets in pathogenesis of diabetes, confirm the necessity of pharmacological correction of streptozotocine-induced diabetes in experimental animals by normalizing carbohydrate metabolism, activating compensatory-recovery processes and regenerations of islets with the help of nutrition and treatment. Comprehensive polytherapy and normalization of nutrition allow for the slowing of the development of diabetic micro- and macroangiopathies and cardiovascular events in the context of diabetes.

Keywords: pancreas, morphofunctional state, exocrine cells, pancreatic islets, diabetes mellitus, animals, regeneration, carbohydrate metabolism.

Introduction. For a long time, understanding of morphofunctional state of the pancreas in individuals with type 1 and type 2 diabetes has necessitated the search for effective methods of correcting these pathologies. Experimental research methods on rats have yielded numerous conclusions that explain the genetic mechanisms of disease development, metabolic restructuring of the body during endocrinocyte dysfunction, have introduced new technological achievements regarding the possibility of cultivating the pancreas in vitro using a pool of stem cells, and research on possibility of gland transplantation is also being conducted. Despite this, many studies are subject to doubt. In this article, we will consider researchers' data on morphological state of the pancreas in intact rats, in experimental diabetes, and methods of its correction.

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Materials and methods. Generalisation of ukrainian and foreign literature data, results of meta-analyses and randomized studies.

Results. The pancreas, as a component of endocrine system, belongs to the glands of mixed secretion. Combining two different functions: exocrine and endocrine, it ensures homeostasis in carbohydrate metabolism, participates in the processes of food digestion, etc. A large cascade of morphofunctional, biochemical, and metabolic changes in parenchyma, often have a systemic impact on metabolism in general, can be trigger factors for various pancreas diseases. A significant number of scientific publications are dedicated to morphofunctional restructuring of pancreas in norm, in pathology, including presence of diabetes. Using of different methods of research (histological, electronmicroscopic, immunohistochemical, morphometric, and biochemical, 3-D reconstruction of biological objects), the possibilities for studying the morphological peculiarities of pancreas structure in both normal and pathological states in experiments have increased today.

Morphology of pancreas in intact animals. In white laboratory rats, the pancreas is externally covered by a connective tissue capsule. Interlobular septa branch of pancreas into lobules. The lobules comprise acini with centroacinar cells. It is known that acini contain from eight to twelve exocrine cells. These cells have a conical shape, and their cytoplasm is divided into two zones: apical and basal. Zymogen granules accumulate in apical zone and cell nucleus with membranous organelles is located in basal zone. Plasmalemma of exocrine cells forms internal folds in basal zone and microvilli in apical zone. Intercellular contacts are formed between neighboring exocrine cells [2]. Results of studies of pancreas in animals can often be extrapolated to humans due to similarity of their structural organization [3].

Exocrine cells of pancreas produce proenzymes and enzymes that are secreted into the pars descendens duodenum through the system of excretory ducts. Intercalary ducts are formed in terminal parts of pancreas, lined with cubical epithelium and then merge into intra-lobular and interlobular ducts, which are covered with a single layer of prismatical epithelium. Exocrine cells produce a different enzymes (amylase, lipase, carboxypeptidase, ribonuclease, deoxyribonuclease, etc.) and precursors of protein peptidases – proenzymes (trypsinogen and chymotrypsinogen), which break down polysaccharides into monosaccharides, proteins into amino acids and fats into glycerol with fatty acids in the digestive tract [4]. In studies by Fujivara S. on the effect of zinc on structure of pancreas, it was proven that excessive zinc loading induces atrophy of the acinar cells of the gland and increases the number of duct-like structures. Interstitial fibrosis and macrophage infiltration also correlated with the degree of acinar atrophy. The electron microscopic method allowed diagnosing the loss of zymogen granules in apical zone of acinar cells, proliferation of collagen fibers in the gland capsule, and an increase in number of fibroblasts, which could subsequently lead to fibrous restructuring of pancreas parenchyma under zinc loading [5].

Anatomically, human pancreas is divided into three regions: duodenal (head of pancreas), gastric (body) and splenic (tail) [2, 4]. This division in rats is somewhat conditional due to small size of organ. Duodenal part is located in V-shaped bend of duodenum, caudally from common bile duct. In some cases, highest concentration of endocrine islets is found in splenic region of gland in both humans and white laboratory rats [3]. Several studies over the last decade have shown that pancreas of patients with type 1 diabetes was smaller, than in the healthy patients. Researchers have attributed development of interlobular fibrosis, atrophy of acini, apoptosis of exocrine cells, leukocyte infiltration of parenchyma, presence of inflammatory changes in parenchyma and slight fatty infiltration of capsule over time as histological anomalies of exocrine part of the gland in context of diabetes. Diabetes researchers noted biochemical changes in the levels of insulin, glucagon, somatostatin and the secretion of pancreatic polypeptides [6-7].

Endocrine part of pancreas is represented by islets, total number of islets can be from 1.0 to 1.5 million. Islets are formed by endocrinocytes. These cells produce hormones and play an important role in carbohydrate metabolism. In humans, many types of endocrinocytes are distinguished, including A, B, D, EC (enterochromaffin cells), PP (pancreatic polypeptides), PYY, pancreatic gastrinocytes, and ghrelin-producing endocrinocytes [8-9]. There are four types of endocrine cells in rats: insulinocytes (B), glucagonocytes (A), somatostatinocytes (D) and pancreatic polypeptide (PP) cells [10]

Many researchers have studied the application of stem cells for differentiation into exo- and endocrinocytes. Mesenchymal stem cells have a high potential for regeneration. These cells migrate and return to the damaged site, restoring cells and tissues. Often, oxidative stress and inflammation hinder stem cell transplantation. In study by Farid A. et al., the introduction of grape seed extract during stem cell transplantation in streptozotocin-induced type I diabetes was conducted, noting an improvement in the level of pro-inflammatory cytokines, a reduction in markers of oxidative stress, which facilitates the regeneration of the insulinocyte pool [9].

At electronmicroscopic level, Miskiv V.A. studied the changes in the qualitative and quantitative composition of four types of endocrine cells: insulinocytes, glucagonocytes, somatostatinocytes and pancreatic gastrinocytes in animals of different age groups. It was noted that regenerative processes in islets significantly slow down with age, while in young rats, the highest regenerative changes in the islets were observed [11]. The number of islets depend on influence of exogenous and endogenous factors. It has been proven that with age and due to the toxic effects of certain medicinal agents, the number of islets decreases [12].

Islets can be of various shapes (oval, round, star-shaped), sizes, areas, and diameters. Firstly, we detected an islet of triangular shape during staining with aniline blue-orange G [13]. Tkachuk O. and co-authors [14] distinguished the following types of islets based on area: small (100 – 1500 cm^2), medium (1500 – 3500 cm^2), large (3500 – 7500 cm^2) and giant (more than 7500 m^2). The ratio of endocrine to exocrine parts of the pancreas changes with age towards a decrease in the number of islets. In addition to endocrinocytes, the islets include hemomicrovessels, nerve endings, neurons, and neuroglial cells. In the context of diabetes, the nervous apparatus of not only the pancreas but also other organs of gastrointestinal tract, including duodenum, undergoes restructuring [15].

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Primary cell pool of islets is occupied by insulinocytes. These polygonal-shaped cells, located at the center of islets, have secretory granules with a clear halo and synthesize of insulini, proinsulini, C-peptide and GABA. Glucagonocytes make up to 30% of the total cell population of islet. They are located on periphery of islets, contain secretory granules without a halo and synthesize the hormones glucagon and pancreastatin. Some authors distinguish so-called acino-islet cells, in cytoplasm of which have many zymogen granules together with secretory granules of endocrinocytes. Electron microscopic studies have shown the absence of a clearly defined cytoplasmic membrane in acinar-islet cells. Some researchers found so-called "ductal" insulinocytes in the ducts. Cambial "ductal" endocrinocytes and acino-islet cells are considered as possible sources of regeneration [13]. In several studies, it has been noted that proliferative processes of cells accelerate under hyperglycemia, as indicated by the detection of cytokeratin – a marker of differentiation and neogenesis of endocrine cells. Sometimes, so-called "buds" are formed, which are local protrusions of endocrinocytes, that can further "pinch off" from the duct, and their cytoplasm begins to contain secretory granules characteristic for insulinocytes. It has been established that with age, the amount of cytokeratin in endocrinocytes decreases [16].

Distribution and number of endocrine cells depend on the type of blood supply to islets. In small islets of isolated endocrine cells, small clusters of mantle-type islet endocrinocytes form, where glucagonocytes are located peripherally, so blood capillaries do not penetrate into the middle of islet but pass over its surface. In islets of medium and large sizes, glucagonocytes are located both in the peripheral and central zones of the islet along the blood vessels that permeate the islet. In large islets, insulinocytes form central clusters, surrounded by glucagonocytes and hemomicrovessels. Knowledge of gland's blood supply mechanisms is of great importance in organ transplantation [17].

In context of development of type I diabetes, an autoimmune destruction of insulinocytes is observed, with activation of cellular and humoral immunity, plasma cells begin to secrete autoantibodies to various antigens of insulinocytes and as a result, an inflammatory process called insulitis develops. This condition is a cell-mediated autoimmune reaction against one's own endocrinocytes with mononuclear infiltration of islets. Often, exocrine disorders of pancreas cause or precede the appearance of diabetes, which in this context is referred to as pancreatogenic diabetes of type II [18].

Experimental models of diabetes in rats. Similarity of histological organization of pancreas in humans and rats allows for modeling pathological processes, studying their treatment effects. Necessity to introduce indications for clinical research of hypoglycemic agents used in context of diabetes necessitates the study of various models of insulin-dependent and insulin-independent diabetes in animals at preclinical stage, which replicate the leading links in development of disease in humans. The most common experimental models of animal diabetes include surgical models, chemically induced or genetically determined forms of disease [19]. Latter develop in rats due to mutations in certain genes through selection. Type I diabetes is induced of the NODM (non-obese diabetic mouse) hybrid line and Wistar rat populations. With a long latent period of diabetes development, it is convenient to study the properties of antidiabetic drugs that inhibit the destruction of insulinocytes and stimulate their regeneration. Experimental type II diabetes is modeled in obese animals. In such homozygotes for the diabetes-fat gene, a diabetic syndrome and characteristic clinical manifestations of the disease can develop: hyperglycemia, polydipsia, hyperphagia, polyuria, progressive insulin deficiency, changes in fur and skin, animal hyperactivity, etc. [20-21].

Chemically induced forms of diabetes are modeled by the administration of highly toxic pharmacological chemotherapeutic agents or hormones (alloxan, streptozotocin, dexamethasone, oxihinoline, etc.). Chemical models of diabetes are reproduced not only in rats but also in dogs, rabbits. Some authors used alloxan for diabetes modeling. Diabetogenic effect of alloxan depends on method, speed of administration, concentration of solution; species, body mass of the animals. Toxic effect of high-dose alloxan administration appears within a few hours, and insulin deficiency – within a few days. A drawback of this model is the lack of selective impact on the islets. Toxic changes not related to the development of the disease occur in other organs as well. To induce alloxan diabetes, some authors investigated the effect of phytoprotectors on the functioning of liver enzymes in alloxan diabetes. The development of alloxan diabetes in rats was accompanied by an increase in the activity of liver NAD^+- and $NADPH^+$-dependent enzymes, associated with an increase in the transcription rate of genes encoding these enzymes. Oral intake of aqueous extracts of Jerusalem artichoke and olive by rats with diabetes caused a noticeable reduction in blood glucose levels and enhanced antioxidant properties [22].

Dexamethasone diabetes is induced by oral, subcutaneous or intramuscular prolonged administration of drug. Prolonged high-dose administration to 18-month-old Wistar rats led to increased levels of basal hyperglycemy, decreased sensitivity of peripheral tissues to insulin action and created predispositions for development of metabolic syndrome, manifested by obesity, hypodynamy, hyperglycemy [23].

Streptozotocin has gained widespread use in animal experiments. It is important to remember that high single doses of drug induce absolute insulin deficiency. Establishment of stable hyperglycemia lasts about two weeks. In our observations, 6% of rats die from pancreonecrosis or hypoglycemic coma after drug injection, in most (80%) animals, hyperglycemia develops, however, 14% of Wistar rats were insensitive to the drug's action, such animals are excluded from experiment due to absence of disease onset. Relative insulin deficiency can be modeled with low subdiabetogenic doses of streptozotocin. Upon repeated intraperitoneal administration of drug over 5 days, intensive infiltration by macrophages and lymphocytes is noted in islets of rats, insulitis develops, with is maximum expression forming 12-14 days after injections. Experimental studies have shown that cytogenetic effects in insulinocytes are realized in different ways of disease due to formation of free radicals, active forms of oxygen, and hydrogen peroxide with damage of cell DNA, oxidation of SH-groups of aminoacids and activation of TRAIL-mediated apoptosis mechanisms. Against background of administering animals with streptozotocin-induced diabetes with an alcoholic extract of Alhagi camelorum, some

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authors identified a significant reduction in levels of hyperglycemia and hyperlipidemia associated with diabetes [24].

Against the backdrop of development of streptozotocin-induced diabetes, pathways of diabetic microangiopathy and macroangiopathies have been identified [25]. Specifically, presence of endothelial dysfunction, hemorheological disorders (stasis, sludge of blood formed elements), narrowing of lumen arterioles and precapillaries, dilation of lumen of postcapillary vessels and venules have been established. It has been found that in conditions of streptozotocin-induced diabetes, these changes are manifested not only in hemomicrovessels of pancreas, but also in other organs, including the hypothalamo-hypophisary system, liver, salivatory, adrenal glands and spleen.

Features of experimental diabetes development. Many researchers have studied the impact of various factors and pharmacological agents on morphofunctional state of pancreas in experiments. In pathogenesis of development of experimental type 1 diabetes, main mechanism for reduction in number of insulinocytes is apoptosis. This process is characterized by an increase in electronic density of cytoplasm, formation of apoptotic bodies in endocrine cells and their phagocytosis. Average term of cell apoptosis is about 15-20 minutes. This mechanism is implemented with the involvement of plasma membrane receptors and mitochondrial cytochrome-C. Surface cell receptor CD-95 interacts with the ligand of the transmembrane protein, activating a cascade of specific reactions involving cysteine proteases. The viability of cells depends on the ratio of activator and inhibitor proteins of apoptosis (Bax and Bcl proteins) [26].

An application of gene therapy with introduction of PEI-pDNA (a complex carrying the proinsulin gene) to animals (40 mg/kg of streptozotocin) allowed reducing of intensity apoptosis and activating compensatory-adaptive mechanisms in islets of pancreas. To assess the degree of apoptosis, the immunohistochemical TUNEL- method was used. The number of TUNEL-positive cells in islet under gene therapy conditions was 1.22[27]. In histological sections of pancreas from a patient with a long, progressive course of type 1 diabetes, it was found that endocrine part of human pancreas, unlike in animals, presents a mosaic pattern with areas containing only insulinocytes and, conversely, areas of islets without insulinocytes. These results indicate the heterogeneity of disease and are evidence of high frequency of a latent autoimmune course in humans [28].

Several scientists have studied the impact of cell culture transplantation on course of diabetes in experiments. It was proven that transplantation of stem cell cultures led to a gradual reduction in glycemia levels and normalization of HOMA- index. The ability of stem cells to differentiate into insulinocytes remains a matter of debate. Through directed differentiation, insulin-like cells can be obtained, which begin to synthesize secretory granules. Stem cells enhanced regeneration by synthesizing stimulating factors (cytokines, growth factors, adhesion molecules, integrins), locally suppressing apoptosis and collagen formation, improving vascularization and cell differentiation (so-called "trophic" effect of stem cells). Multipotent precursors of insulinocytes and oligopotent cells possessed high regenerative potential and their pharmacological stimulation into insulin-secreting cells could become an alternative to pancreas transplantation. However, transplantation leads to a relatively high level of surgical complications. Patients with excessive weight more often require a robotic approach to pancreas transplantation, which, moreover, currently has more disadvantages than advantages [29].

Impact of stress of bodies of laboratory animals is adequately reflected in scientific studies. Under chronic stress, concentration of adenylatecyclase and glucose in the blood of rats decreases, but insulin level does not change significantly. The stimulation of anaerobic glycolysis in insulinocytes is a manifestation of compensatory restructuring under enhanced ATP-dependent processes. Using of immunomodulators under conditions of preslaughter stress in animals did not observe significant changes in morphostructure of pancreas. Restructuring of endocrine apparatus under chronic stress characterized by degenerative changes in nuclei of endocrinocytes, an increase in volume of stroma, damage to insulinocytes. Therefore, prolonged stress can become a precursor to development of diabetes in experiments [30].

Using of exenatide and insulin glargine in diabetes correction. Pharmacotherapy for diabetes primarily aims to achieve normoglycemia through dietary correction in combination with pharmacological agents. This not only slows down the progression of diabetic micro- and macroangiopathies but also extends the lives of patients. Given the multifactorial nature of hyperglycemia development (absolute or relative insulin deficiency), modern hypoglycemic drugs should exert their glucose-lowering effect through various pathways. Thus, in the context of absolute insulin deficiency, the priority for correcting streptozotocin-induced diabetes remains the use of replacement insulin therapy with exogenous insulin drugs and enhancing reparative processes in the gland due to improved regeneration of endocrinocytes [31].

Traditional short and intermediate-acting insulin drugs, administered by injection in various regimes, are not fully capable of normalizing the daily insulin profile and require multiple administrations throughout the day. Currently, one of "peakless" long-acting insulin drugs is insulin glargine (Lantus), a biosynthetic analogue of human insulin. It is synthesized through three DNA modifications of human insulin: a) attaching two molecules of arginine to B-chain of insulin (shifting isoelectric point pH, thus reducing its solubility at the physiological pH of subcutaneous adipose tissue); b) replacing asparagine with glycine in the A-chain (the molecule acquires a neutral charge, which increases the bioavailability of insulin); c) adding Zn^{2+} to stabilize contacts between hexamers. These modifications of insulin glargine result in prolonged absorption at injection site, a peakless action profile, and a consistently reproducible glucose-lowering effect for at least 24 hours, reducing the frequency of nocturnal hypoglycemias [32].

Regeneration is an ability of cells, tissues, organs, and the organism as a whole to recover after damage, given favorable external or internal factors. Ongoing research seeks medicinal forms capable of activating intracellular regeneration mechanisms in type 1 diabetes. Many studies focus on finding means to activate regeneration of insulin-producing islet cells and inhibit their apoptosis. An ability to enhance plastic processes in pancreatic islets and adapt the number of insulinocytes to insulin requirement by

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reducing their damage or restoring functional volume of islets becomes the main goal of diabetes therapy [33-34].

In recent years, a new group of drugs, incretin mimetics, has been used for treating type 2 diabetes. Incretins are endogenous insulinotropic peptides involved in physiological regeneration of glucose homeostasis. This group includes glucagon-like peptide-1 (GLP-1), produced by intestinal L-cells in response to food intake and stimulates glucose-dependent insulin secretion, enhancing the regeneration of pancreatic endocrinocytes. However, native GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), leading to development of its analogue, exenatide (Byetta, Eli Lilly, USA), resistant to DPP-4 action. Exenatide is a synthetic form of the hormone exendin-4, derived from the saliva of the Gila monster lizard. Clinical studies have shown that exenatide increases the HOMA-β index, indicating enhanced secretory capacity of insulinocytes. For this reason, the drug is recommended for patients with type 2 diabetes whose level of glycated hemoglobin is more than 7.1%. The application of this drug in type 1 diabetes, where preserving the ability of undamaged insulinocytes to synthesize the amount of insulin that would optimally maintain glucose levels in the compensation stage, remained unexplored [35, 41].

A mechanism of action of incretin mimetics involves stimulating glucose-dependent insulin secretion, enhancing insulinotropic activity of glucose, slowing down transit rate of substances through gastrointestinal tract, reducing gastric secretion. Effect of incretin mimetics in regulation of digestion through medulla oblongata has been proven. Pharmacological mechanisms of exenatide action are realized through modulation of drug's activity, enhancing the secretion and release of insulin; however, the normalization of insulin levels occurs not due to hypertrophy of endocrine cells but due to an increase in GLP-1 levels and regeneration. Several studies have focused on effect of GLP-1 on course of immunological reactions in type 1 diabetes. GLP-1 has ability to influence number of circulating T-killers and modulate secretion of monocytes, which reduces autoimmune damage to pancreatic islets in diabetes. In mice receiving exenatide for type 2 diabetes, a decrease in body weight and blood glucose levels was observed, along with reduced local motor activity and stress levels [36].

Besides of it the proven favorable effect of exenatide on carbohydrate metabolism parameters, along with using of insulin therapy, this drug can also provide indirect positive effects on different metabolic indicators. Exenatide is a synthetic peptide, allowing it to act as a potent agonist of GLP-1 receptors in humans. Animal studies have shown that GLP-1 is one of important regulators of food intake, enhances the feeling of satiety, and reduces the sensation of hunger [37]. At the same time, an analysis of results of long-term treatment with exenatide within the framework of randomized studies showed a statistically significant improvement in blood lipid profile indicators, manifested by a reduction in triglycerides, total cholesterol and low-density lipoproteins, an increase in high-density lipoproteins. In the group of patients receiving exenatide treatment, a reduction in total cholesterol was noted. It's important to highlight that the improvement in blood lipid profile indicators occurs not only with significant weight loss but also in patients without significant body mass loss. Thus, long-term therapy with exenatide allows for an improvement in blood lipid profile in patients with diabetes [38].

Considerable attention by researchers has been devoted to studying effect of exenatide on blood pressure indicators in type 2 diabetes. Long-term studies of exenatide use in patients with type 2 diabetes noted a favorable effect of the drug on systolic and diastolic blood pressure indicators. Insulin administration did not cause changes in blood pressure. Therapy with exenatide for 82 weeks as part of an open study following patients' participation in phase III double-blind placebo-controlled studies led to a statistically significant reduction in diastolic blood pressure by 2.7 mm Hg. The effect of exenatide on blood pressure indicators in patients with type 1 diabetes and arterial hypertension requires further study [39].

Therefore, long-term therapy with exenatide has a beneficial effect not only on glycemia indicators but also on all other risk factors for cardiovascular pathology present in most patients with type 2 diabetes (excess body weight, dyslipidemia, arterial hypertension). However, the application of exenatide in the development of type 1 diabetes remains a relevant issue in contemporary diabetology [40, 41].

Conclusion. The presented data establish the peculiarities of morphological changes in pancreatic islets in pathogenesis of diabetes, confirm the necessity of pharmacological correction of streptozotocine-induced diabetes in experimental animals by normalizing carbohydrate metabolism, activating compensatory-recovery processes and regenerations of islets with the help of nutrition and treatment. Comprehensive polytherapy and normalization of nutrition allow for the slowing of the development of diabetic micro- and macroangiopathies and cardiovascular events in the context of diabetes.

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МОРФОФУНКЦІОНАЛЬНИЙ СТАН ПІДШЛУНКОВОЇ ЗАЛОЗИ У ЩУРІВ ІЗ ЦУКРОВИМ ДІАБЕТОМ

О.Р. Іванців[1], В.М. Федорак[2], І.І. Білінський[3], Ю.І. Попович[4], В.В. Федорак[5]

Івано-Франківський національний медичний університет, кафедра дитячої хірургії з курсом клінічної анатомії та оперативної хірургії; кафедра фармакології, м. Івано-Франківськ, Україна

[1]ORCID ID: 0000-0002-4366-6406, e-mail: oivantsiv@ifnmu.edu.ua
[2]ORCID ID: 0000-0003-4607-0496, e-mail: fedorak@ifnmu.edu.ua
[3]ORCID ID: 0000-0001-5106-0095, e-mail: ibilinskuy@ifnmu.edu.ua
[4]ORCID ID: 0000-0002-2401-4699, e-mail: yupopovych@ifnmu.edu.ua
[5]ORCID ID: 0009-0009-2688-3490, e-mail: fedorak_vl@ifnmu.edu.ua

Резюме. Мета. Проаналізувати наукові джерела про морфофункціональний стан підшлункової залози при цукровому діабеті та лікуванні у білих лабораторних щурів.

Матеріали і методи. Узагальнення інформації української та зарубіжної літератури, результатів метаналізів і рандомізованих досліджень.

Результати. Проведено характеристику основних механізмів моделювання цукрового діабету. Узагальнено літературу щодо будови острівців підшлункової залози в нормі, при цукрому діабеті і лікуванні.

Огляд наукових праць підтверджує соціальне значення досліджень, оскільки цукровий діабет призводить до розвитку мікро- і макроангіопатій.

Важливим завданням науковців є створення лікарських засобів, які посилюватимуть процеси регенерації в острівцях. За науковими джерелами, політерапія цукрового діабету з використанням кількох фармакологічних антидіабетичних препаратів зарекомендувала себе краще, ніж монотерапія. Багато авторів вивчали комплексний вплив інсуліну та ексенатиду (міметика інкретину) і встановили, що ексенатид підвищує регенераторні можливості острівців в умовах діабету. Проте питання застосування препаратів з групи інкретиноміметиків за умов цукрового діабету I типу залишається дискусійним і потребує подальшого вивчення.

Доцільність експериментального моделювання діабету ґрунтується на необхідності розробки нових підходів до корекції діабету I типу. Це сприятиме максимально тривалому збереженню функцій ендокринних клітин, посиленню регенераторних, компенсаторно-відновних процесів у підшлунковій залозі, а також оптимізує терапевтичний ефект антидіабетичних препаратів в експерименті.

Висновок. Наведена інформація підтверджує функціональні зміни підшлункової залози при цукровому діабеті, акцентує на важливості його лікування в експериментальних тварин для нормалізації вуглеводного обміну, компенсаторно-відновних процесів і регенерації підшлункової залози при харчуванні та лікуванні.

Ключові слова: підшлункова залоза, морфофункціональний стан, екзокриноцити, острівці, цукровий діабет, тварини, регенерація, вуглеводний обмін.

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