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DIABETES MELLITUS – APPROACHES TO EXPERIMENTAL MODELING AND MOLECULAR MARKER

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Резюме

Objective. Generalization and systematization of literature data on the pathogenesis of diabetes mellitus, molecular markers and experimental models.

Methods. The basis of this study was a review of the literature on this topic.

Results. In most cases, the development of the autoimmune process plays a leading role in the pathogenesis of diabetes mellitus. This process usually lasts several years and is accompanied by the gradual destruction of the β-cells of the islets of Langerhans in the pancreas. A number of experimental models are used to model diabetes mellitus: surgical, dithizone, streptozocin, alloxan, dexamethasone. Insulin-like growth factor 1, protein S100β, basic myelin protein, neuroglobin protein, microRNA 23b-3p can act as molecular markers of diabetes mellitus.

Conclusion. The search for new molecular markers, the development of new adequate models of diabetes mellitus will serve as a fundamental basis for detailing the pathogenesis necessary to improve the methods of prevention, diagnosis and correction of diabetes mellitus.

Keywords: diabetes mellitus, experimental modeling, molecular markers

САХАРНЫЙ ДИАБЕТ – ПОДХОДЫ К ЭКСПЕРИМЕНТАЛЬНОМУ МОДЕЛИРОВАНИЮ И МОЛЕКУЛЯРНЫЕ МАРКЕРЫ

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Abstract

Цель. Обобщение и систематизация данных литературы о патогенезе сахарного диабета, молекулярных маркерах и экспериментальных моделях.

Методика. Основой данного исследования стал обзор литературы по данной теме.

Результаты. В большинстве случаев в патогенезе сахарного диабета ведущую роль играет развитие аутоиммунного процесса. Этот процесс обычно длится несколько лет и сопровождается постепенным разрушением β-клеток островков Лангерганса поджелудочной железы. Для моделирования сахарного диабета используется ряд экспериментальных моделей: хирургическая, дитизоновая, стрептозоциновая, аллоксановая, дексаметазоновая. В качестве молекулярных маркеров сахарного диабета могут выступать: инсулиноподобный фактор роста 1, белок S100β, основной миелиновый белок, белок нейроглобин, микроРНК 23b-3p.

Заключение. Поиск новых молекулярных маркеров, разработка новых адекватных моделей сахарного диабета, послужит фундаментальной базой для детализации патогенеза, необходимой для улучшения способов профилактики, диагностики и коррекции сахарного диабета.

Ключевые слова: сахарный диабет, экспериментальное моделирование, молекулярные маркеры

Introduction

Diabetes mellitus is a disease characterized by hyperglycemia as a direct consequence of insulin resistance, insufficient insulin secretion or excessive glucagon secretion.

Type I diabetes is an autoimmune disease that causes the destruction of the β-cells of the pancreas. Type II diabetes mellitus, which is much more common, is a problem of progressive dysregulation of glucose due to a combination of dysfunctional β-cells of the pancreatic islets of Langerhans and insulin resistance [16]. The number of people with diabetes has increased dramatically: from 108 million in 1980 to 422 million today (about 8% of the population in 2019), and it is projected that by 2025 this number may increase to 550 million [2]. According to the Ministry of Health, in Belarus there are about 18 thousand patients with type I diabetes (including almost 2.3 thousand children) and almost 315 thousand patients with type II diabetes (94% of all cases) [10].

There are such complications of diabetes mellitus as: cognitive, micro- and macrovascular ones, ketoacidosis, ketoacidotic coma, hyperosmolar coma, lacticidotic coma, diabetic rhinopathy, diabetic nephropathy, diabetic neuropathy, diabetic arthropathy, diabetic foot disease and encephalic foot disease. The main cause of death from diabetes mellitus is the neglect of the disease, namely: diabetic coma, hypoglycemic coma, chronic renal failure, gangrene complicated by sepsis [17].

Type II diabetes increases the risk of death from stroke by almost 3 times. Diabetes mellitus type II is also characterized by the development of diabetic macroangiopathy, the manifestation of which is atherosclerosis of the cerebral arteries. Some studies have established a high rate of detection of occlusion and pronounced atherosclerotic stenosis (atherosclerosis) of the extracranial parts of the internal vertebral and carotid arteries in patients with type II diabetes mellitus than in patients who do not have it [1].

The relationship between hyperglycemia and poor outcome after stroke is strongly pronounced in large cerebral infarctions and less pronounced in lacunar stroke. The negative effect of hyperglycemia on the outcome of stroke is explained by the need to take antihyperglycemic drugs in the acute phase [3]. Chronic hyperglycemia is the initiator of diabetic vascular complications. It leads to increased production of glycation end products, stimulation of the polyol pathway, activation of protein kinase C, vascular inflammation, an increase in free radicals, expression of genes for insulin-like growth factors and cytokines, activation of macrophages and platelets, and determines the progression of diabetic vascular complications. The main pathogenetic basis of cognitive impairment is chronic cerebral ischemia, cerebrovascular insufficiency or neurodegenerative process, and sometimes a combination of both. Type II diabetes mellitus is a risk factor for both cerebral vascular disease and Alzheimer's disease. Chronic cerebrovascular pathology is regarded as one of the characteristic manifestations of type II diabetes mellitus, which develops in parallel with disorders of carbohydrate metabolism. The combination of type II diabetes mellitus and arterial hypertension in persons under the age of 70, without a previous stroke, leads to a decrease in cognitive function. Arterial hypertension is currently considered the main risk factor for dementia and is an independent risk factor for cognitive dysfunction in any age group. Among other things, arterial hypertension is closely associated with the activation of the renin-angiotensin-aldosterone system (RAAS), biologically active components of the RAAS are involved in the physiological function of the regulation of cerebral blood flow and the regulation of behavioral reactions. Today, many scientists believe that hypoglycemia is the main cause of neurocognitive dysfunction [11].

The neurons in the brain are extremely sensitive to changes in blood sugar. The central nervous system has a rather limited store of glucose, and neurons have a very high level of glucose utilization. Decreased glucose availability leads to neuroglycopenia and severe brain damage. In patients with type II diabetes mellitus, deposits of tau-protein, amyloid, signs of activation of oxidative stress, manifested due to hyperglycemia and caused by the accumulation of glycated metabolic products, are detected in the brain tissues [11].

In diabetes mellitus, damage to the tissue of the nervous system occurs, which is explained by 2 mechanisms: the effect of angiopathies (both micro- and macro-) and the toxic effect of glucose metabolites on the tissue.

Dystrophic changes in the neurons of the spinal cord occur at the onset of the disease, pigment dystrophy prevails among them with a large accumulation of lipofuscin in the cytoplasm of the cell. In the later stages of the disease, neuronal death occurs. In the spinal ganglia at the initial stages of the disease, as a rule, unchanged neurons, cells of the shadow and cells in a state of acute swelling were found. Atrophy, manifested by deformation of the nerve trunks and the expansion of the endoneurium layers, was found in the sciatic nerve. At this stage of the disease, skeletal muscles were not atrophied, but their longitudinal cleavage was observed. The cross striation was retained. At a later stage of the disease, microangiopathy became much more common and pronounced, and there was also a significant thickening of the walls of the arterioles and a narrowing of their lumen. Microangiopathy leads to the appearance of foci of prolapse of neurons in the spinal cord, and can also cause cerebral ischemia. In the remaining neurons, the

formation of shadow cells, pigmentary dystrophy, and acute swelling are observed. In addition to neuronal damage in the spinal cord, there was also a massive lesion of the white matter manifested by axon and myelinopathy. At the moment when the damage to the brain substance occurred, hypertrophy of astrocytes and their processes could be noticed. In diabetes, a large number of rounded formations located subpially or perivascularly were found in the lumbar spinal cord tissue. The morphological features of diabetic polyneuropathy are pronounced axon- and myelinopathy and other degenerative changes in the neuropil [9].

Experimental diabetes mellitus

Diabetes mellitus is modeled in rats, mice, rabbits and dogs. In general, the smaller the animal, the more the model will be adapted to different conditions and, accordingly, the cheaper the cost of the experiment, therefore, rats and mice are often used. However, serious criticism of the use of rodents is based on the fact that the data obtained may inadequately reflect the disease in relation to humans, which is why larger animals are required, such as cats, dogs, pigs and primates [14].

Experimental diabetes mellitus also develops after the administration of counterinsular hormones. So, after prolonged use of hormones of the adenohypophysis (corticotropin, somatotropin), pituitary diabetes can develop. Due to the introduction of glucocorticoids, it is possible to achieve the development of steroidal diabetes mellitus. Spontaneous diabetes mellitus is observed more often in Chinese hamsters and some mice. Genetically determined disorders of the immune system in the form of an excess of T-effectors and a deficiency in the suppressor function of T-lymphocytes are more often observed in mice. All forms of experimental diabetes mellitus clearly prove that the base of its development is absolute or relative insulin deficiency. Absolute (pancreatic) insulin deficiency is explained by genetic or acquired disorders in the synthesis and secretion of insulin, relative (extrapancreatic) occurs with the normal formation of insulin under the influence of the factors that contribute to the suppression of its action or accelerate catabolism.

Surgical models of diabetes mellitus

In animals in which the regulation of carbohydrate metabolism was carried out with the help of insulin, it was possible to obtain a pancreatectomy form of diabetes mellitus. After a few hours, the rats, with the complete removal of the pancreas, developed diabetes mellitus. When the organ was removed, 96% of the diabetes mellitus developed only after two weeks, 93% – after 3-5 months, 80% – after 9 months. The main reason for the development of diabetes was insulin deficiency [8].

Dithizone diabetes

Otherwise known as "zinc diabetes". Zinc is a part of the catalytically active center of a number of enzymes - dehydrogenase, carboxypeptidase, transforylase. A certain amount of zinc ions is found in the pancreatic islets in humans, rabbits, cats, dogs, mice, rats and other animals, but not in guinea pigs. At the time of glucose administration, the amount of zinc in B cells decreases, and at a high glucose concentration it can disappear altogether. Doses of dithizone administration: the object of study is rabbits, rarely mice. Before the experiment, the animals should starve for about 1-2 days, after which they will be more sensitive to dithizone. After 2-5 minutes, dithizone enters into a chemical bond with zinc in pancreatic B cells, forming zinc dithizonate. Dithizone quickly and completely disappears from the vascular bed and after 15-20 minutes only traces of it can be found in the blood. On the first day after the introduction of the substance, a change in the concentration of sugar in the blood can be observed, moreover, it will be accompanied by structural changes in B cells [8].

Streptozocin diabetes

Models of rats with streptozocin diabetes mellitus are more often reproduced on male rats, while for modeling type I diabetes mellitus in sexually mature rats at the age of 8-10 weeks. Streptozocin dissolved in citrate buffer is injected intravenously (at a dosage of 60 mg/kg and 55 mg/kg, respectively). After 8 weeks after the onset of diabetes mellitus, a 3-4-fold increase in albuminuria is observed with a simultaneous decrease in the glomerular filtration rate by 1.5 times from the initial one, accompanied by the appearance of tubulointerstitial fibrosis and a 1.5-fold increase in the thickness of the glomerular basement membrane (according to electron microscopy). The duration of the experiment in this case is limited by the development of metabolic disorders due to severe hyperglycemia (more than 30 mmol/l) and insulinopenia. To accelerate the onset of specific diabetic changes in the renal tissue, surgical reduction of the mass of functioning nephrons is used. For this purpose, the rats preliminarily (3 weeks before the injection with streptozocin) undergo right-sided nephrectomy. In such cases, the first signs of diabetic nephropathy are detected already within the first month after the onset of diabetes, manifested by

hyperfiltration, a significant increase in blood pressure is noted at the 8th week, and after 8 months of diabetic status - a more than 30-fold increase in the level of albumin excretion in the urine relative to initial data, as well as morphological signs of diabetic glomerulosclerosis of varying severity. So, relatively recently, models of heminephrectomized rats with alimentary obesity (caused by the appointment of a high-fat diet) and the induction of diabetes by means of one or two administrations with a weekly interval of subdiabetic doses of streptozocin (30-35 mg/kg) have begun to be used. Diabetes mellitus type II is diagnosed 1 week after the injection with streptozocin by performing an oral glucose tolerance test, during which fasting blood glucose levels are measured in rats and 30, 60, 90 and 120 minutes after intragastric administration of 40% glucose solution at a dose of 3 g/kg, and a glycemic level from 9.0 to 14.0 mmol/l. In this case, the development of laboratory and morphological signs of late stages of diabetic nephropathy at 35-40 weeks of the experiment (proteinuria, diffuse glomerulosclerosis) [7].

The most sensitive rats are considered with a single intravenous injection of streptozocin at a dosage of 35 to 65 mg/kg. For mice, the average dosage is 100-200 mg/kg, for rabbits – 300 mg/kg. The likelihood of developing kidney or liver insulinoma directly depends on the duration of the experiment due to the oncogenic effect of streptozocin, and, as a consequence, spontaneous "recovery" is possible in the form of compensation for the diabetes pattern [7].

It is known that keeping rats on a high-fat diet leads to the development of insulin resistance in them. At the same time, it is known that low doses of streptozocin cause a moderate deterioration in insulin secretion, as in the later stage of type II diabetes mellitus. Therefore, the world began to actively develop models of non-insulin dependent diabetes, obtained by combining a high-fat diet and low doses of streptozocin. These models are of undoubted interest for pharmacological testing, since they make it possible to reproduce the metabolic characteristics of this disease characteristic of humans. After 2 weeks of keeping the rats on a high-fat diet, both groups were injected with streptozocin intraperitoneally at a low dose (35 mg/kg). In rats on a high-fat diet, in response to the injection of the diabetogenic agent streptozocin, pronounced hyperglycemia was found, in the control - a moderate increase in the level of plasma glucose. The plasma insulin content in the experimental group decreased only to the level in the control after streptozocin injection. In addition, in the rats of the experimental group, the concentrations of triglycerides and total cholesterol in the blood plasma remained elevated. In contrast, in rats of the control group fed by a diet with a normal fat content, streptozocin did not cause significant changes in plasma insulin, triglycerides, and total cholesterol. Thus, the authors concluded that this model (high fat diet/streptozocin) reproduces the natural progression of the disease and metabolic characteristics typical of people with an increased risk of developing type II diabetes mellitus due to insulin resistance and obesity, therefore it can be used for testing antidiabetic agents [12].

Alloxan diabetes

The model of alloxan diabetes, which occurs after the administration of alloxan to animals, is considered to be quite common. This substance damages the β-cells of the islets of the pancreas, due to which the secretion of insulin is significantly reduced. Diabetes mellitus in animals can also be reproduced with the help of antibodies to insulin. Such diabetes occurs in the case of both active and passive immunization.

The diabetogenic dose of alloxan in rats varies between 100 and 200 mg/kg. However, a single intravenous administration of alloxan at these doses is highly toxic and often ends in death in animals. Therefore, in order to reduce mortality and toxicity, it is recommended to reduce the dose of alloxan by 2-3 times. As part of the research, it was revealed that the most successful method for the induction of diabetes (with a mortality rate of 10 and 80%) is intraperitoneal single administration of alloxan at a dosage of 200 mg/kg. Hyperglycemia that occurs after alloxan destroys the β-cells of the islets of Langerhans in the pancreas is unstable and may turn out to be a reversible process, which, after a certain time, will lead to the normalization of blood glucose levels. The presence of GLUT2 receptors in the cells of the renal tubules and hepatocytes explains the high hepatotoxicity and nephrotoxicity, which in turn causes the development of uremico-diabetic syndrome in the first 5 days after surgery with an average mortality rate of 30% [14].

In rabbits with diabetes mellitus, left ventricular hypertrophy, increased interstitial fibrosis and atrial fibrillation, increased expression of markers of oxidative stress and fibrosis, and intracellular calcium were observed [23].

Dexamethasone diabetes

As a research of new drugs with antidiabetic activity, a model of dexamethasone non-insulin-dependent diabetes mellitus is used. High doses of glucocorticoids can lead to impaired secretory function of β-cells of the islets of Langerhans of the pancreas, as well as the development of insulin resistance. The model is

reproduced as follows: 18-month-old rats are injected subcutaneously with dexamethasone at a dose of 0.125 mg/kg body weight for 13 days. The animals develop moderate basal hyperglycemia, a twofold increase in the concentration of insulin and unsaturated fatty acids in the blood serum, a decrease in carbohydrate tolerance and sensitivity of peripheral tissues to the action of insulin. Subsequently, it was shown that a decrease in glucose utilization by adipocytes after administration of dexamethasone is associated with its direct effect on the expression of glucose transporters GLUT1 and GLUT4, which leads to insulin resistance. The inhibitory effect of dexamethasone on the secretory activity of pancreatic β-cells is possibly due to inactivation of mitochondrial FAD-glycerophosphate dehydrogenase, which is a key enzyme in glucose-induced insulin secretion. Thus, the dexamethasone model of type II diabetes mellitus in old rats, like the nicotinamide/streptozocin model, makes it possible to induce a violation of insulin secretion and action. This modeling of the state of prediabetes makes it possible to study new hypoglycemic substances, the mechanism of action of which may be associated with an increase in carbohydrate tolerance and the sensitivity of peripheral tissues to the action of insulin [12].

From which it follows that among the presented experimental forms of diabetes mellitus, the advantage remains with streptozocin diabetes. Since it is the simplest in terms of reproductiveness, it is possible to obtain diabetes of varying severity and duration thanks to this model, which makes it possible to simulate the constantly developing dysfunction of β-cells of the islets of Langerhans of the pancreas.

The overwhelming body of evidence from both experimental and clinical studies proves that oxidative stress plays an important role in the pathogenesis of type I and type II diabetes. It is assumed that it underlies the cellular changes that lead to diabetic complications. As a result of glucose oxidation, non-enzymatic glycation of proteins and subsequent oxidative degradation of glycosylated proteins in diabetes, free radicals are formed. An extremely high level of free radicals and a parallel decrease in antioxidant defense mechanisms often lead to damage to cell organelles and enzymes, an increase in lipid peroxidation and the development of insulin resistance. These consequences of oxidative stress can contribute to the development of complications of diabetes mellitus [20].

Lipid peroxidation is the main causative factor in the development of oxidative stress, which leads to diabetes and associated micro- and macroangiopathies. Thus, we conclude that the measurement of markers of oxidative stress can be one of the additional methods for the diagnosis and prognosis of diabetes [21].

In diabetes mellitus, there is a violation of the oxygen transport function of hemoglobin in chronic hyperglycemia, as well as the development of systemic hypoxia. As a result of hypoxia, the intensity of lipid peroxidation and the formation of reactive oxygen species increase. Several studies have demonstrated the hypoglycemic effect of gold nanoparticles. In the blood of rats with simulated diabetes, after the introduction of gold nanorods, the glucose level did not significantly decrease. Nevertheless, a significant decrease in the level of lipid hydroperoxides in the blood was noted, and in the serum of rats with combined pathology (liver cancer against the background of diabetes), a decrease in the number of average weight molecules. This indicates a possible decrease in the intensity of lipid peroxidation and the formation of toxic molecules of average weight [13].

Diabetes mellitus pathogenesis

In some cases, the pathogenesis of absolute insulin deficiency has a common link: the development of an autoimmune process. This process usually lasts several years and is accompanied by the destruction of β-cells of the islets of Langerhans in the pancreas. Symptoms of diabetes only appear when more than 75% of the β-cells of the islets of Langerhans in the pancreas are destroyed.

The chain of the mechanism of development of the autoimmune variant of diabetes mellitus includes the following facts - the introduction of a carrier of a foreign antigen into the body of persons genetically predisposed to diabetes mellitus. More often these are viruses, less often other microorganisms. Cells containing antigens are attacked by the body's immunobiological surveillance system, which perceives its own antigens as foreign. This phenomenon is called "cross-immune response". In the course of this reaction, the β-cells of the islets of Langerhans of the pancreas are destroyed, and the freely located proteins are denatured and become autoantigenic. Absorption, processing and presentation to lymphocytes of both foreign antigens and newly formed autoantigens of β-cells of the pancreatic islets of Langerhans by monocytes/macrophages. The autoimmune process is potentiated by the synthesis and transport of HLA class I and II antigens to the surface of damaged β-cells of the islets of Langerhans of the pancreas. These antigens stimulate helper T-lymphocytes and, as a consequence, the production of specific immunoglobulins and the differentiation of cytotoxic T-lymphocytes. Immune autoaggression against the pancreatic islets of Langerhans' own β-cells is enhanced. In this connection, the scale of damage to the insular apparatus is increasing. Migration to the regions of damaged and destroyed β-cells of the pancreas of phagocytes with the destruction of β-cells of the pancreatic islets of Langerhans with

the participation of lysosomal enzymes, reactive oxygen species and lipid peroxides, free radicals of organic substances, cytokines (γ-IFN, TNF-a, IL1). Release from the destroyed β-cells of the islets of Langerhans of the pancreas "foreign" proteins for the immune system (normally they are only intracellular and do not enter the bloodstream): heat shock, cytoplasmic gangliosides, proinsulin. Absorption by macrophages of the indicated cytoplasmic proteins of β-cells of the islets of Langerhans of the pancreas, their processing and presentation to lymphocytes. This triggers the next and recurring episode of immune attack with the destruction of additional β-cells of the islets of Langerhans in the pancreas. With a decrease in their mass to 75% of normal, clinical signs of diabetes mellitus immediately appear. As the β-cells of the islets of Langerhans of the pancreas die, the stimulus for the reaction of immune autoaggression also decreases. Thus, the level of antibodies to β-cell antigens significantly decreases 1-1.5 years after their first detection [15] [19] [22].

Based on the pathogenesis of diabetes mellitus, molecular markers can be used in experiments:
Insulin-like growth factor 1 (IGF-1), formerly called somatomedin C, is a polypeptide protein hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults. Human IGF1 is a 70 amino acid single chain polypeptide cross linked by 3 disulfide bridges with a calculated molecular weight of 7.6 kDa. The IGF1 gene, mapped to 12q22-q24.1, contains 5 exons. Exons 1-4 encode a 195 amino acid precursor (IGF1B) and exons 1, 2, 3 and 5 encode a 153 residue peptide (IGF1A). The structure of IGF1 is similar to that of IGF2. And the IGF1 and IGF2 genes have structures with many promoters. The expression of both genes is regulated at the levels of transcription, RNA processing, and translation. IGF-1 is produced by the liver as an endocrine hormone and in target tissues in a paracrine/autocrine manner. Moreover, approximately 97% of IGF-1 is always bound to one of 6 binding proteins (IGF-BP). Among other things, IGF-1 is a stimulator of cell growth and reproduction and a potent inhibitor of programmed cell death [18].

Protein S100 is often used as a marker of brain damage in various studies. Its increase is also noted in diabetes mellitus. S100β is also used as an assessment of the neuroprotective properties of anesthetics in conjunction with neuropsychological testing in studies aimed at assessing the effect of general anesthetics on cognitive impairment. 100β protein is the most convenient biochemical indicator due to its short (20-25 minutes) half-life, moreover, its concentration in serum will not depend on gender and age. Its serum concentration does not change with alcohol overdose, hemolysis, or moderate renal dysfunction. But the likelihood that the S100β protein can be released outside the brain will limit its use as a marker of brain damage. So, it is sometimes released during physical exertion, acute damage to muscle tissue, melanoma and sepsis-associated encephalopathy. Neuron-specific enolase (NSE) is a glycolytic enzyme 2-phospho-Dglycerate hydrolase, which belongs to the enolase family and is involved in the last stage of glycolysis - it catalyzes the transition of 2-phospho-D-glyceric acid to 2-phosphoenolpyruvate. It has a molecular weight of 78 kDa, a half-life of 24 hours, and exists in various variants of dimers, consisting of three subunits: α, β, γ. In this case, the α-subunit of enolase is secreted in various tissues, the β-subunit is found only in the heart and striated muscles. They were initially detected in high concentrations in neurons and endocrine cells, as well as in tumors that originated from these cells. Determination of the NSE level in diabetes mellitus makes it possible to judge the degree of neuronal damage and impairment of the membrane function of the blood-brain barrier. Today, this marker is used to diagnose acute conditions, namely, in cerebral ischemia and brain hypoxia, and is also used to study the pathogenesis of neurological diseases. It is very important in pathologies of the nervous system, such as epilepsy, Parkinson's disease, senile dementia, Alzheimer's disease, in perinatal brain damage, primary hypothyroidism, and brain tumors [6].

Protein S100B is a glial neurospecific biomarker. It contains glutamic and aspartic acids, phenylalanine and a small amount of tryptophan, tyrosine and proline. These proteins belong to Ca-binding proteins with low molecular weight up to 21 kDa and have three known subtypes, consisting of α- and β-chains. Various combinations of subunits divide the S100 family into homodimeric (α-α, β-β) and heterodimeric (α-β) forms. Protein S100β has a molecular weight of 10-12 kDa and consists of β-β, α-β forms. It is found in the cytoplasm of astrocytes, Schwann cells, adipocytes, chondrocytes, melanocytes. At low concentrations, S100β exhibits neuroprotective properties by blocking NMDA receptors and acting as a growth and differentiation factor for neurons and glia. At a very high concentration, it triggers the synthesis of proinflammatory cytokines and, therefore, leads to neuronal apoptosis [5].

Basic myelin protein is a marker of oligodendrocyte damage (a group of glial cells localized in the central nervous system and involved in the myelination of CNS axons). The oligodendrocyte winds its membrane around several axons of nerve cells, ensures their isolation, forming a multilayer myelin sheath, and the ability to quickly conduct a nerve impulse. It is with the destruction of this membrane in blood serum and cerebrospinal fluid that the concentration of basic myelin protein increases [5].

Of particular interest is the involvement of BNDF in the pathogenesis of depression. A decrease in the content of this neurotrophin in people suffering from depression and a return to normal after treatment with antidepressants have been revealed. The same results have been obtained in animal experiments. The receipt of these data is explained from the point of view of the neuroplastic theory, according to which depressive states are caused by a violation of the neuroplasticity of the hippocampus, which in turn leads to a decrease in the adaptive abilities of the brain. This is also supported by post-mortem studies in people with depression, showing a decrease in hippocampal volume and inhibition of hippocampal neurogenesis, in which BNDF is involved. Among other things, chronic stress leads to dysfunction of the hypothalamic-pituitary-adrenal system and the neurotransmitter serotonergic system. A study of cognitive dysfunction in patients with type II diabetes mellitus revealed a relationship between BNDF and HbA1c levels, which confirms the effect of the degree of compensation of this disease on the development and progression of cognitive dysfunction. An improvement in cognitive performance is observed with an increase in the level of cerebral neurotrophic growth factor in blood plasma [5].

Protein neuroglobin

Neuroglobin is a protein involved in neuroprotection that is highly specific to spinal nerves. At the moment, some studies have revealed its role in the formation of cognitive impairments during the development of various toxic and ischemic pathological processes in the central nervous system. The mechanism of action is to protect cells from hypoxia and oxidative stress by excreting nitric oxide. It is also known that this protein reduces the content of β-amyloid.

In patients with diabetes mellitus, neuroglobin was considered from the position of a biomarker of vascular complications of the disease in a model of retinopathy, and the significance of its expression for diagnosis was shown. A couple of years ago, a study was published that showed the relationship between neuroglobin and protein kinase B, namely, overexpression of this protein led to the activation of the insulin pathway, leading to a significant increase in central insulin resistance [6].

MicroRNA 23b-3p

Over the past few years, miRNAs have attracted attention as potential participants in the development of microvascular complications of diabetes mellitus, which affect the function of the kidneys, retina, and neurons, participating in the processes of fibrosis, apoptosis, inflammation, and angiogenesis. In an experimental study of the effect of microRNA-23b-3p on cognitive impairment in diabetes mellitus, it was found that overexpression of this RNA increased oxidative stress and apoptosis of neurocytes through the Sirt1/Nrf2 signaling pathway. At the same time, the Nrf2 pathway regulates the endogenous balance of oxidants and antioxidants; therefore, its activation may be associated with a potential protective effect in terms of correcting diabetic encephalopathy [6].

Genes Used to Diagnose Diabetes Mellitus

The following main groups of genes are distinguished in the gene network: genes of the major histocompatibility complex (HLA), which are responsible for the production, transport and presentation of the corresponding antigens on cell membranes (HLA, class II and III), genes that control the production of cytokines (IL1, IL1R1, IL1N1, TNFA), insulin gene - INS, genes that include the mechanisms of destruction, protection and repair of β-cells of the pancreatic islets of Langerhans (SOD2, HSP-70, NOS2), known and yet unidentified genes of IDDM loci, genes of the major histocompatibility complex MHC (HLA), also called IDDM 1. Traditionally, there are three classes of HLA genes and their products - I, II, III, moreover, HLA antigens of I and II classes - products corresponding genes. Studies have shown that the genes MIC-A and MIC-B are also associated with type I diabetes mellitus in various heterogeneous combinations. HLA class II genes, namely DRB, DQA, DQB, play the greatest role in susceptibility to type I diabetes mellitus. According to research, genes of both HLA classes are involved in the presentation of T-cell antigens. HLA I class present the antigen to cytotoxic T cells (CD8+), while T helper cells (CD4+) usually recognize the antigen by HLA class II. HLA II is able to present T antigens in part from the amino acid composition of their alpha and β chains. Substitutions at one or two critical positions can markedly increase or decrease the binding of the corresponding autoantigens and susceptibility to type I diabetes mellitus. More than 90 percent of patients with type I diabetes mellitus are carriers of either HLA-DR3, DR3-DQ2 or DR4, DR4-DQ8. In addition, about 30% of patients have the DR3/4 combined haplotype, which is associated with the highest disease susceptibility. A carrier of such a heterozygous genotype (DR3/DR3 and DR4/DR4) has a higher risk than a homozygous one. Among relatives of patients with type I diabetes, DR3/DR4 siblings are at greater risk than offspring [4].

TRPM7 gene belongs to the melastatin subfamily of the transient receptor potential ion channel families. Defects in this gene are the cause of amyotrophic lateral sclerosis — parkinsonism — dementia (Guam complex). The encoded protein is involved in the organization of the cytoskeleton, cell adhesion, cell migration, and organogenesis.

Among other things, the protein encoded by this gene is an ion channel whose kinase activity contributes to the regulation of magnesium ion homeostasis. It is also known that magnesium-containing supplements affect spatial memory by improving the processes of synaptic plasticity, as well as restoring the signaling pathway of the NMDA receptor.

The TRPM7 gene is associated with an increase in intracellular calcium levels, and when the channel is activated, the basal autophagy of Ca2 + is modulated, which reduces the deposition of β-amyloid and leads to an improvement in cognitive functions. Another mechanism is believed to be the effect of this channel on presenilins, a complex of proteins associated with the development of Alzheimer's disease.

In addition, the TRPM7 channel is known to play an important role in neuronal apoptosis and the response to cellular stress associated with hyperglycemia. It has been shown in models of type I diabetes mellitus that suppression of the TRPM7/miR-34a gene can improve spatial memory and increase the number of surviving neurons [4]. In this regard, the TRPM7 gene is responsible for the regulation of the metabolism of trace elements, which directly or indirectly affect the parameters of neuroplasticity in patients with diabetes mellitus [4].

Conclusion

Thus, in most cases, the development of the autoimmune process plays a leading role in the pathogenesis of diabetes mellitus. This process usually lasts several years and is accompanied by the gradual destruction of the β-cells of the islets of Langerhans in the pancreas. A number of experimental models are used to model diabetes mellitus: surgical, dithizone, streptozocin, alloxan, dexamethasone. Insulin-like growth factor I, protein S100β, basic myelin protein, neuroglobin protein, microRNA 23b-3p can act as molecular markers of diabetes mellitus. The search for new molecular markers, the development of new adequate models of diabetes mellitus will serve as a fundamental basis for detailing the pathogenesis necessary to improve the methods of prevention, diagnosis and correction of diabetes mellitus.

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