DIABETIC NEUROPATHY

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Abstract. *The review summarizes the results of global studies and assesses contribution of hyperglycemia towards formation of neurologic complications in diabetic patients. Hyperglycemia is believed to play a leading role in the formation of neurological complications in diabetes mellitus. However, the achievement of normalization of glycemia level does not ensure the cessation of their development and progression, which indicates a lack of knowledge about the pathogenetic relationships in diabetic neuropathy. Limited understanding of these issues entails the absence of treatment options that effectively affect the course of this complication. Based on the analysis of experimental and clinical studies of recent years, data on the molecular-biological relationships of hyperglycemia with the formation of neurological complications in diabetes mellitus are summarized. The influence of the oxidative and nitrosative stress, advanced glycation end products, the activation of the polyol and hexosamine pathways on the state of the nerve fiber is analyzed. The data on molecular mechanisms of development of diabetic neuropathy are contradictory. On the basis of recent experimental and clinical data we review possibilities for pathogenetic therapy. The problem of oppositely directed effects of treatment is discussed. Clinical rationale is given for declared direction of further studies.*

Key words: *Diabetic neuropathy, hyperglycemia, pathogenesis, pathogenetic therapy.*

Diabetic neuropathy (DN) is one of the most frequent complications of diabetes mellitus, leading to a decrease in the quality of life and disability of patients with diabetes mellitus (DM) [1, 2]. In recent years,significant progress in understanding the pathogenesis of DN, while treatment options that effectively affect the course of DN and contributing to its reverse development, today is not enough. Numerous studies indicate on the polyetiological nature of DN [1, 3, 4]. In particular,attach great importance to genetic, metabolic and vascular factors [3, 4, 5]. However, not all experimental data obtained in vivo were reproduced in humans,

in connection with which they cause a lot of controversy about their role in the genesis of DN and the possibilities of using pathogenetic treatment [4].

The main etiological cause of DN today is day is considered hyperglycemia (both chronic and and episodic), triggering a cascade of cellular pathologicalogical processes through the activation of alternative active pathways of glucose oxidation, formation of oxide-tive and nitrosative stress, involvement of growth and vascular factors [1, 6]. Pathological processes ini- are induced by hyperglycemia, while even normalization blood glucose level does not stop their development tia and progression, which indicates the need further study of pathogenetic relationships in DN. Other independent risk factors include age, duration of carbohydrate metabolism disorders, smoking, arterial hypertension, hypertriglyceridemia, increased high body mass index, alcohol consumption, high cue growth [1].

Today it is believed that oxidative and nitrosative stress is a key pathogenetic mechanism in the formation of diabetic complications [1, 4, 6, 7]. Under physiological conditions, neurons have the ability to neutralization of reactive oxygen and nitrogen species. Since O2– and H2O2 are products of mitochondrial transport chain, the action of superoxide dismutazy, catalase and glutathione are sufficient to remove these metabolic products. Hyperglycemia increases mitochondrial activity and subsequent production O2– and reactive forms of nitrogen that contribute to the accumulation of these metabolites in a neuron with the formation of a progressive causing dysfunction of cell organelles, membranes and kernels [4]. In addition, free oxygen radicals induce protein kinase C (PKC) activation and lead to to an increase in PKC-mediated production of reactive oxygen species (ROS). In turn, glucose-stimulating activated activation of the RCS leads to an increase in the levels NADPH-dependent oxidase, which exacerbates oxidative stress and degenerative changes in the nerve fiber. However, at present, pathogenetic relationships between RCC and NAMs require clarification, since when checking research has produced mixed results [4,8]. During treatment with the RKS inhibitor ruboxytaurine in patients with DN showed no clinical improvement. Pre-It is believed that this circumstance may be related with poor passage of the drug through the hematoneural barrier [8]. In this connection, further research is required research.

Axons are the most sensitive structure-mi neuron to metabolic and vascular disorders in connection with the characteristics of the blood supply and a large content mitochondria, which play a critical role in cellular survival signaling pathways. Oxidative damage to mitochondrial DNA, proteins and membranes

initiate mitoptosis and apoptosis. Mitoptosis presents is a mechanism for ridding the cell of damaged mi- tochondria, which became such as a result of an increase in concentration of free radicals, mainly ROS, or inability to eliminate these radicals. In case of coverage the entire mitochondrial network superproduction of ROS cells enters apoptosis. As the dysfunction of the mitotichondria, axonal degeneration progresses [6, 7, 9].

In addition, hyperglycemia also contributes to treatment in the pathogenesis of DN and other metabolic pathways.The consequence of non-enzymatic glycation betweenreducing carbohydrates and free amino-groups of proteins, lipids and nucleic acids are the formation of glycation end products (AGEs), which that exert both intracellular and extracellular action [4].

Extracellular formation of protein AGEs is capable of disrupt cell adhesion, as well as activate receptor advanced glycation end products (RAGE), stimulation which is associated with the transcription of NF-kB, which regulates gene expression, inflammation and apoptosis. Mo-RAGE duplication in neurons induces NADPH oxidase activity, which is also associated with oxidative stresssom and cellular dysfunction [3, 4].

One of the pathways of glucose metabolism is its pre- rotation into sorbitol and fructose, called polyol way. To ensure the reactions of the polyol way in the cells, the enzyme aldose reductase (AR) is present, which converts glucose into sorbitol. Usually in this no more than 1% of glucose enters the reaction, and it is used to obtain fructose during the synthesis of glucosamines. The polyol pathway is activated in hyperglycemia when the flow of glucose into cells increases and the rate of synthesis sorbitol increases sharply [10]. accumulation of sorbitol in neurons inhibits the synthesis of cyclic alcohol myo-ino- zitol, which is part of phospholipids and is used during the transmission of a hormonal signal, and reduces the activity Na +, K + -ATPase, which disrupts the conduction of the nerve impulse. Excess in the cell of osmotically active sorbi- tol and fructose retains water, changes the shape of cells and their functional activity. Clinical Significance polyol pathway manifests itself in insulin-independent tissues nyah, in particular, in neurons. Excessive work of the AR leads to the consumption of NADPH in cells, which suppresses regeneration formation of glutathione used in the antioxidant cell system and metabolic processes, oxide synthesis nitrogen (NO), neutralization of ammonia in the reaction of reduction positive amination of α-ketoglutarate, microsomal ionic oxidation [4, 10]. A number of studies have shown that the use of antioxidants in the treatment of DN, in particular, preparations of alpha-lipoic acid (α-LA), promotes neutralization of hydroxyl and peroxyl radicals, superoxide, as

well as the reduction of glutathione [11].On background of intravenous administration of this drug at a dose 600 mg/day for three weeks confirmed improvement decrease in electromyographic parameters and decrease clinical manifestations in patients with DN [12, 13]. Therapy preparations of α-LA was recognized as safe and recommended approved by the American Diabetes Association for use in patients with DN [1]. However, a number of meta-a- analyzes and reviews of recent years have not revealed a significant improvement of neurological parameters during treatment this group of drugs. Modern Recommendations expert groups of specialists of the American Academy neurology and the European Federation of Neurological communities do not approve of the use of α-LA in drug tonic correction of RP [1, 14]. Due to the lack of a single consensus on this issue, it is necessary to clarify the pa- togenetic relationships and therapeutic effects α-LC in DN. One of the promising variants of pathogenic therapy of DN, correction is being considered today activity of enzymes that catalyze contributing to post-translational modification protein cations [15]. On models of DM in rodents, when administered poly(ADP-ribose) polymerase (iPARP) inhibitors or damage to the poly(ADP-ribose) polymerase (PARP) gene showed a protective effect against the development experimental DN. These models also show whether a decrease in the levels of superoxides and supernitrosines in epineural vessels, which indicates the relationship between oxidative stress and PARP [15, 16]. Works recent years describe the role of PARP activation in DN and discuss possible options for PARP-targeted therapy.

Some studies indicate a dose-dependent effect between degree of aldose reductase inhibition AR (AR) and regeneration of peripheral nerves. Data recent years demonstrate the positive impact of IAR on the course of autonomic neuropathy in DM in the form of a decrease reduction of manifestations of esophageal dysfunction, gastroparesis, an increase in the ejection fraction of the left ventricle [17]. Count- It is believed that the blocking of the AR, which contributes to the prevention depletion of NADPH, allows neurons to resist aggressive influence of ROS and nitrogen. Impact on polio Today, the fishing route is one of the main new pharmaceutical directions in the treatment of DN, however most results of double-blind placebo-con- controlled studies regarding efficacy the use of iAR in DN remains controversial. According to the Cochrane meta-analysis, published in 2006., only 4 studies out of 32 found significant differences in nerve conduction parameters in the group, treated with iAR, compared with the control group [4,18]. Although the majority of adverse reactions iAR were insignificant and were rare, negative dose-dependent effects were observed with the use sorbinil

(severe allergic reaction), zenarestat (increased creatinine levels) and tolrestat (impaired hepatic function) [18], in connection with which currently the possibility of widespread use of drugs of this groups in humans is discussed. The hexosamine pathway is an alternative oxidation pathway glucose, in which, under the influence of glutamine-fructo- zo-6-phosphate aminotransferase is converted fructose-6-phosphate to glucosamine-6-phosphate. Last converted to uridine diphosphate-N-acetyl glucosamine, involved in a number of reactions leading to disruption gene expression. Sp1 is one of the transcription factors modulated by uridine diphosphate-N-acetyl glucosamine. Sp1 regulates the expression of many genes that induce baths with hyperglycemia, in particular, an inhibitor of activating ra plasminogen-1 (PAI-1) and transforming factor growth of beta 1 (TGF-β1) [4, 19]. Particular interest in activating plasminogen py and PAI-1 is based on the assumption that fibrinolysis in small blood vessels nerve fibers contributes to nerve ischemia, association associated with oxidative stress and DN symptoms. In experimental animals, PAI-1 blocks the regeneration tion of nerve fibers. Modern research under-confirm the role of TGF-β and other TGF isoforms in DN [19]. Separately, I would like to note that a number of scientific works confirmed the role of short-term episodes of hyperglycaemia chemia in the formation of DN. In 25% of cases in patients with pain form of neuropathy with instrumental confirmation a daily loss of epidermal nerve fibers revealed but impaired glucose tolerance (IGT). Previously considered it was found that DN in individuals with IGT has a milder course compared with patients with diabetes, however, recent studies years confirm that these patients are characterized by electromyographic (EMG) signs such as axonopathy, and demyelination [1, 4, 20, 21, 22]. As an attempt restoration of the nerve fiber in violations of carbohydrate One exchange was suggested treatment with neurotrophins. Neurotrophins are proteins that support vitalityness of neurons by enhancing the morphological differentiation and regeneration, stimulation of ex-neurotransmitter depression [23, 24, 25]. Despite neuroprotective effect of neurotrophins, in patients with DN their action is ambiguous. in hybridization method situ demonstrates an increase in the expression of TrkA (NGF-re- receptor) and TrkC (NT-3 receptor) in the skin of patients with DM [24, 26]. The second phase of clinical trials showed her roprotective action of recombinant human nerve growth factor on the course of DN, however, the third phase this effect was not confirmed [27].Latest tests showed that the introduction of recombinant neurotrophic brain factor did not show significant significant improvement in electromyographic parameters and neuropathic symptoms in DN [4,28,29]. Besides, a number of studies have shown that C-peptide deficiency is

associated with the formation of microvascular complications in DM-1. Dockley Scientific studies have confirmed the effect of C-peptide on activity of Na+/K+-ATPase, endothelial NO-synthetase, expression of neurotrophins, regulation of molecular mechanisms underlying nerve degeneration in patients patients with DM-1 [27]. Small randomized double placebo-controlled study on 46 patients with DM-1 with satisfactory compensation, showed a significant improvement in the speed of the nerve of the sural nerve and the perception of vibration after 12-week subcutaneous administration of C-peptide. However the effectiveness of C-peptide in the treatment of DN in DM-1 in other works [28], as well as with SD-2 is doubtful and not proven [29], which requires additional research in this area.

Thus, hyperglycemia through the influence on metabolic, genetic, and vascular factors contributes to the formation of neurological falsehoods in DM. Despite the lack of a complete understanding mania for the mechanisms by which the effects are realized effects of hyperglycemia, its association with the formation and progression of DN is obvious. Ambiguity and non- the sufficiency of the results obtained so far research results require clarification of the mechanisms and conditions of realization of neurological effects of hyperglycemia in patients with DM. So far researched some types of pathogenetic therapy for DN, however, do-efficiency and safety indicators in the conducted randomized clinical trials are not enough but, in connection with which, it is necessary to carry out additional scientific research.

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