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DISRUPTED SYNTHESIS OF NEUROTRANSMITTERS IN THE PATHOPHYSIOLOGY OF DIABETIC ENCEPHALOPATHY (LITERATURE REVIEW)

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Abstract. This review provides a summary of data on the role of neurotransmitter synthesis abnormalities in the pathophysiology of diabetic encephalopathy (DE). It covers the key neurotransmitters that could be involved in the pathogenesis of DE: gamma-aminobutyric acid, glutamate, dopamine, acetylcholine and serotonin. The article describes the main pathophysiological mechanisms that may play a role in the development and progression of DE in the course of diabetes mellitus in a patient with disrupted release of key neurotransmitters. It provides data confirming the hyperreactivity of the GABAergic, glutamatergic and dopaminergic systems, along with the hypoactivity of the cholinergic and serotoninergic systems, as part of the pathophysiology of DE. Also provided are results of preclinical and clinical studies confirming that patients with type 1 and 2 DM have abnormalities in the synthesis of neurotransmitters, which could serve as early diagnostic markers of DE.

Keywords: diabetic encephalopathy, gamma-aminobutyric acid, glutamate, dopamine, acetylcholine, serotonin

НАРУШЕНИЕ ВЫРАБОТКИ НЕЙРОМЕДИАТОРОВ В ПАТОФИЗИОЛОГИИ ДИАБЕТИЧЕСКОЙ ЭНЦЕФАЛОПАТИИ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. В обзоре обобщены данные о нарушениях выработки нейромедиаторов в патофизиологии диабетической энцефалопатии (ДЭ). Рассмотрены основные нейромедиаторы, которые могут быть задействованы в патогенезе ДЭ: гамма-оксимасляная кислота, глутамат, дофамин, ацетилхолин, серотонин. Представлены основные патофизиологические механизмы, которые могут быть задействованы в формировании и прогрессировании ДЭ по ходу течения сахарного диабета (СД) при нарушении в выработке основных нейромедиаторов. Обоснована гиперреактивность ГАМК-эргической, глутаматергической (далее — глютамат) и дофаминергической систем, а также гипоактивность холинергической и серотонинергической систем

в патофизиологии ДЭ. Приведены данные доклинических и клинических исследований, доказывающие нарушение выработки нейромедиаторов при СД 1-го и 2-го типов, которые могут служить ранними маркерами в диагностике ДЭ.

Ключевые слова: диабетическая энцефалопатия, гамма-оксимасляная кислота, глутамат, дофамин, ацетилхолин, серотонин

INTRODUCTION

Diabetes mellitus (DM) is a chronic endocrine disease characterized by elevated glucose levels and insufficient insulin production or activity [1]. This endocrinopathy is associated with well-described and studied macrovascular and microvascular complications including diabetic retinopathy, nephropathy, cardiomyopathy and peripheral neuropathy [14]. Current scientific evidence suggests that DM can also have a negative impact on the central nervous system (CNS), causing a number of neurochemical, neurophysiological and structural disorders. Collectively, these disorders contribute to the formation of a specific complication and clinical symptom complex known as diabetic encephalopathy (DE) [2, 3, 12, 41]. In this regard, studying DE is an urgent area of modern endocrinology [1, 46]. It is well known that DE can manifest as cognitive dysfunction, amnestic disorders, decreased learning ability and speed of information processing in clinical practice [1, 41, 46]. However, pathogenesis of this complication in DM remains incompletely understood [46]. At present, there are a few contestants considered as possible triggers for DE development: decreased insulin secretion or activity, impaired regulation of glucose homeostasis, increased glucocorticoid levels, development of neuroinflammation, impaired neurotransmission, oxidative stress (OS), and mitochondrial dysfunction [29, 41].

At the same time, there is a concern that preventive measures and therapies for DE should be initiated as soon as possible in order to be most effective [46]. Until now, most cognitive disorders in DM have been clinically diagnosed by physical and neurological examinations using standard neuropsychological and cognitive tests [4]. However, it is known that DE progresses rather slowly over the course of DM, over several years, before the first obvious clinical symptoms appear [35]. Thus, early diagnosis of DE remains a major challenge during the long period of progression [46].

Evidence suggests that disorders in a neurotransmitter system may be the most early pathophysiological signs of cognitive dysfunction in DM, and several neurotransmitter systems can be used as early diagnostic markers of DE [23, 32]. It is believed that neurotransmission abnormalities on the background of DM occur much earlier than structural and functional changes in the brain on the background of DM [34]. However, there is still insufficient information on neurotransmitter disorders and their pathophysiologic role in the progression of DE [46]. Therefore, the aim of this review was to highlight possible mechanisms of impaired production of key neurotransmitters and to describe their possible use as early markers of DE. Due to the limited scope of this review, only key neurotransmitters that may play a key role in the pathophysiology of DE are considered: gamma-oxybutyric acid (GABA); glutamate (GT), dopamine (DA), acetylcholine (ACh), and serotonin (ST).

GABA

The GABAergic system is a major inhibitory neurotransmitter in the brain [40]. Numerous studies support the concept of cognitive function inhibition due to the activated GABAergic system [40]. Physiologic function of the GABAergic system is impaired in DM, and dysfunction of this system may be involved in the pathophysiology of DE [33, 45]. Dysfunction of the GABAergic system plays an important role in diabetic cognitive failure and CNS damage, impaired brain energy homeostasis, and enhanced oxidative stress [45]. An imbalance between excitation and inhibition due to dysfunction of GABAergic neurons has been shown to dramatically increase glucose toxicity in the brain [41]. Preclinical studies showed that GABA levels were significantly elevated in the hippocampus of rats with type 2 DM [16]. Elevated GABA levels have been reported in plasma from patients with type 2 DM, which correlated with the level of hyperglycemia and cognitive impairment [25]. Another study showed that patients with type 2 DM had marked insulin resistance and cognitive dysfunction, as well as increased concentration of GABA in the medial prefrontal cortex [37]. Van Bassel et al. showed that patients with type 2 DM exhibit higher concentrations of GABA in the occipital lobe of the brain, which was associated with poorer cognitive abilities [39]. It is no coincidence that drugs that modulate the GABAergic system have a positive effect on memory and cognitive abilities [9]. For example, GABA antagonists and some steroids that inhibit GABA, such as pregnenolone sulfate, show significant improvement in learning and memory [1]. Thus, it can be concluded that DE is characterized by hyperactivation of the GABAergic system, and high GABA levels may serve as early biomarkers of this complication.

GLUTAMATE

GT is one of the most important excitatory neurotransmitters in the brain [19]. Namely, low concentration of GT in neurons is necessary for optimal and physiological neuronal function [10]. Although GT is an important neurotransmitter, its pathologic accumulation causes this amino acid to become a potent neurotoxin [8]. This is mainly due to the activation of glutamatergic receptors, which leads to increased calcium entry into neurons and the formation of exitotoxicity processes [8, 27, 38]. In turn, excitotoxicity leads to degeneration and death of brain neurons [21, 30].

The excitotoxic cascade in DE begins with a marked disruption of oxidative metabolism, which leads to ischemia and depolarization of brain neurons [6]. This process disables neurotransmitter reuptake pumps, including GT, resulting in the activation of anaerobic metabolism processes in the brain [6]. As a result, GT begins to work extrasynaptically, stimulating opening of glutamatergic receptor channels, which leads to an excessive intake of sodium and calcium into brain neurons [6]. Against the background of high calcium concentration in neurons, endoplasmic reticulum is stressed. Mitochondrial dysfunction and OS activation occur, which are considered to be the leading pathophysiological mechanisms of DE formation on the background of excitotoxicity and excessive GT [31].

In addition, it has been shown that excitotoxic production of reactive oxygen species increases the activity of protein kinase C, which may contribute to the death of neurons on the background of DE [31]. Regarding clinical studies, the levels of GT in the brain were higher in patients with type 1 DM compared to controls, which suggests a potential role of GT as an early marker of cerebral complications caused by hyperglycemia in type 1 DM [43]. Consequently, activation of the glutamatergic system will occur in DE, and elevated GT levels may be considered as markers of cognitive impairment.

DOPHAMINE

DA is an important neurotransmitter of the CNS. It performs a number of important physiologic functions primarily related to cerebral activity (emotion processing, cognition formation, motor activity, and cognitive abilities) [36]. Alterations in dopaminergic signaling involve neurodegenerative diseases and encephalopathy of various genesis [5, 22]. Increased DA levels constitute a major factor in developing diabetic complications in type 2 DM. One of the most dangerous complications in DM is CNS damage, and the involvement of dopaminergic system dysfunction is no longer in doubt [26]. Insulin resistance in the brain may lead to changes in mitochondrial function, increased monoamine oxidase levels and increased DA clearance [18]. Thus, DA may represent a potential biomarker of cerebral insufficiency in DM on the background of dopaminergic system hyperactivation [13].

ACETYLCHOLINE

The cholinergic system is an important modulating neurotransmitter involved in cognitive processes. ACh itself plays a leading role in learning and memory [15, 28]. It was shown that synthesis and release of ACh were significantly reduced against the background of DM decompensation [42]. Decreased level of nicotinic acetylcholine receptors and increased apoptosis in the hippocampus was found in patients with type 2 DM [44]. It has also been reported that dysfunction of the cholinergic system is directly related to altered activity of crucial brain enzymes such as acetylcholinesterase (AChE), which may be one of the reasons for cognitive deficits in animals with DE [20, 24]. Notably, the same trend was observed in the serum of animals with DE, hence serum AChE can be used as an important biomarker to detect DE in the initial stages of DM [46].

SEROTONIN

In recent years, ST levels have been considered as powerful biomarkers of DM, including DE [17]. It has been shown that blood levels of ST were lower in patients with DM compared to controls [17]. Preclinical studies demonstrated that intranasal administration of ST reduces body weight in rats with DM and improves glucose tolerance and lipid metabolism [11]. In addition, ST restores hormonal modulation of adenylate cyclase activity in the hypothalamus and normalizes adenylate cyclase activation, which may improve cerebral activity [7]. Increasing ST content in the brain can be considered as an effective treatment for type 2 diabetes mellitus and its complications [11].

CONCLUSION

The pathophysiological aspects of DE are still far from being completely clear, and impaired neurotransmitter production can be considered as one of the possible hypotheses for the formation of this complication on the background of DM. DE will result in hyperactivation of the GABAergic, glutamatergic and dopaminergic systems, while the cholinergic and serotoninergic systems will be in a hypoactive state. Consequently, abnormally high values of such neurotransmitters as GABA, GT and DA, as well as low concentrations of other neurotransmitters, such as ACh and ST, may be early markers of DE formation, even at the preclinical stage

of DM. That is why the earliest possible diagnosis of DE by testing certain neurotransmitters will improve therapeutic approaches to manage this complication and improve the quality of life of patients with diabetes.

ADDITIONAL INFORMATION

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