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БОЛЕЗНЬ АЛЬЦГЕЙМЕРА И АМИЛОИДНАЯ ГИПОТЕЗА ЕЕ ПАТОГЕНЕЗА

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Болезнь Альцгеймера – это медленно прогрессирующее заболевание нервной системы, проявляющееся потерей когнитивных способностей, расстройствами памяти и повышенной утомляемостью. Существующие методы лечения способны замедлить развитие патологического процесса, но не обратить его. Ученым до сих пор не известна точная причина возникновения данной формы деменции, однако существует ряд гипотез, на основании которых ведется поиск эффективного метода лечения. На сегодняшний день, ведущей теорией является амилоидная гипотеза. Согласно ей, в мозге формируются амилоидные бляшки, оказывающие токсическое действие на нейроны и нейроглию.

Ключевые слова: деменция, амилоид, секретаза, процессинг, нейрон.

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ALZHEIMER'S DISEASE AND THE AMYLOID HYPOTHESIS OF ITS PATHOGENESIS

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Alzheimer's disease is a slowly progressive illness of the nervous system, manifested by loss of cognitive abilities, memory disorders and increased fatigue. Existing treatment methods can slow down the development of the pathological process, but not reverse it. Scientists still do not know the exact cause of this form of dementia, but there are a number of hypotheses on the basis of which an effective treatment method is being sought. Today, the leading theory is the amyloid hypothesis. According to her, amyloid plaques form in the brain, which have a toxic effect on neurons and neuroglia.

Key words: dementia, amyloid, secretase, processing, neuron.

Currently, neurodegenetic diseases are detected in 50 million people, and 10 million new patients are identified every year. According to statistics, Alzheimer's disease accounts for 60-70% of all cases of dementia. Huge amounts of money are spent on the maintenance of patients: in Russia this amount exceeds 74.8 billion rubles per year. Studying the features of the pathogenesis of this disease can make the search for a cure more effective. In addition, early diagnosis can slow down the onset of the disease, which is why it is so important to carry out educational activities of doctors among the population, especially in risk groups, which include people suffering from depression, senior generation, hypertension, smokers and diabetics.

The aim

To study various hypotheses of the origin of Alzheimer's disease, the molecular mechanisms of pathology development and the treatment methods being developed for this disease.

Material and methods

An analysis of various information sources containing the latest data on the pathogenesis of Alzheimer's disease, as well as a comparison of the information that was carried out.

Results and discussion

Alzheimer's disease (AD) is a severe age—related neurodegenerative disease characterized by a decrease in intellectual abilities up to a complete loss of cognitive skills. The onset of the disease proceeds imperceptibly, which practically eliminates the possibility of early diagnosis before the development of serious incorrigible changes in brain structures happens. BA is characterized by the following symptoms: absent-mindedness, memory problems, impaired concentration, disorders of written and oral speech, drowsiness [2,5].

Contemporary medicine still does not know the causes leading to the development of Alzheimer's disease. However, there are several theories of the pathogenesis of this disease, that are: the cholinergic hypothesis, the amyloid hypothesis and the tau hypothesis [4]. But most researchers tend to believe that the amyloid degeneration of the protein acts as a factor in the development of pathology.

This theory arose after a thorough examination of patients suffering from Alzheimer's disease. Amyloid plaques formed from accumulations of insoluble defective protein β-amyloid (Aß) that were found in the preparations of the brain tissues of such patients. At the same time, this β-amyloid peptide is a fragment of a larger transmembrane amyloid precursor protein (APP), which is normally part of the membranes of neurons and other cells [1]. The functions of the APP in the cell are not fully understood, but it is believed that it provides neuroplasticity. This polypeptide undergoes proteolysis by three types of enzymes: alpha, beta and gamma secretases. As a result of APP cutting by proteases and processing, soluble α- and insoluble β-amyloids are formed. Based on this, two ways of posttranslational modification of the precursor protein are distinguished: non-amyloidogenic and amyloidogenic.

In non-amyloidogenic processing, APP is cut by alpha and gamma secretases into a soluble α-amyloid consisting of an ectodomain and an intracellular C-terminal fragment [4]. The ectodomain is responsible for the adhesion of cells to the substrate and for the normal transmission of nerve impulses through synapses, and also, being the strongest neuroprotector, it provides the processes of memorization, learning, and promotes the survival of neurons. The intracellular fragment regulates the functions of the nucleus and gene expression.

The amyloidogenic path assumes APP being cleaved by beta and gamma secretases into β-amyloid peptides with different chain lengths. Aß 40 and 42 play a direct role in the formation of insoluble plaques. They are able to adhere to the surface of neuronal membranes and act as a toxic building fraction of Aß, which leads to blocking of ion channels, disruption of calcium metabolism in neurons, a decrease in glucose energy metabolism and activation of oxidative stress, leading to the death of cells of the nervous system.

However, normally the secretion of β-amyloid does not lead to pathology, since there is a balance between its synthesis and utilization [3]. Firstly, this protein is cleaved by proteinases, but

with age their activity decreases sharply, which is a prerequisite for AD. Secondly, the metabolism of copper and iron ions plays a crucial role in the development of the disease [3]. Furin protein activates alpha-secretase, while beta-secretase is competitively inhibited and the rate of synthesis of the soluble form of the protein increases. But with a raising in the concentration of iron, the activity of furin decreases and, accordingly, an accumulation of insoluble β-amyloid occurs.

Therefore, a violation of the relationship between the synthesis and breakdown of the insoluble form of protein leads to the formation of toxic amyloid plaques and destruction of the nervous tissue.

In addition, according to some scientists, there is a link between amyloid damage to the nervous system in Alzheimer's disease and the same damage as a result of the prion disease's development. If this hypothesis is confirmed by research, then the invention of medicine for these deadly illnesses will be greatly simplified.

Despite the prevalence of the amyloid theory, the cholinergic hypothesis of AD also has some advantages [3]. According to her, the disease develops due to a lack of acetylcholine in the brain, a neurotransmitter that transmits nerve impulses between cells. Based on this theory, drugs that prevent excessive destruction of acetylcholine in the brain have been used to treat this form of dementia. However, medications only slow down the progression of the disease without the complete cure.

The Tau hypothesis. Tau protein is a protein of central nervous system cells. Normally, tau protein participates in the assembly of microtubules and performs a stabilizing function. As a result of excessive phosphorylation, the structure of this protein is disrupted, which leads to a decrease in the functional ability of brain cells. Tau protein molecules stick together, form tangles, cease to perform their functions, and the process of biochemical signal transmission is disrupted in the affected neuron [1].

It is believed that amyloid brain lesions and hyperphosphorylation of tau protein develop in parallel, aggravating the course of Alzheimer's disease.

Currently, several strategies for the treatment of AD have been developed. Attempts to inhibit the synthesis of beta-secretases in the patient's body were being made, but the drugs had a strong hepatotoxic effect. Passive anti-Aß immunization is currently the main treatment strategy, but reducing the amyloid load on the brain did not prevent the development of dementia [3]. A truly effective treatment for Alzheimer's disease has not yet been developed.

Conclusion

Alzheimer's disease is a dangerous disease with a complex pathogenesis mechanism. Despite the ongoing research, none of the existing hypotheses explains the path of pathology development fully and reliably, taking into account all factors and features. Even the most common amyloid hypothesis cannot be accepted as the absolute truth, since treatment based on its mechanism did not

bring the expected positive results. Therefore, it is necessary to study the molecular and biochemical aspects of the pathogenesis of Alzheimer's disease in more detail using the possibilities of modern scientific technologies in order to eliminate all possible errors in the process of developing an effective treatment method.

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