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CURRENT ISSUES IN THE DEVELOPMENT OF NEUROPROTECTIVE THERAPY IN ISCHEMIC STROKE

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Abstract
The article demonstrates the world experience in the use of metabolic therapy in the treatment of ischemic stroke. The question is resonant. The feasibility of prescribing metabolic drugs is not completely clear, the effectiveness has not been definitively proven, despite numerous studies that only show trends. The article presents a review of the most popular drugs from different pharmacological groups with metabolic action that affect different links of the ischemic cascade.

Keywords. Stroke, neuroprotectors, cytokines, reperfusion., neuroprotective agents, metabolic therapy.

Introduction

The use of metabolic therapy in the treatment of patients with acute cerebrovascular accidents is a controversial issue and is actively discussed in the literature. The results of a number of clinical studies show that only with the help of metabolic therapy the best results are achieved in the treatment of acute cerebrovascular accident [1], but some authors question the effectiveness of additional drug therapy [2, 3]. With the development of cerebral infarction, a complex ischemic cascade of sequential interrelated reactions occurs. Due to hypoxia, glucose breakdown occurs along the anaerobic pathway, which causes lactic acidosis. Dysfunction of the enzyme system and transport proteins leads to the release of potassium ions from the cell into the extracellular space and the movement of sodium and calcium ions into the cell. An excess of excitatory neurotransmitters leads to the opening of the calcium channels they control and an additional influx of calcium ions into neurons. Excessive calcium accumulation inside the cell activates enzymes, overloads mitochondria with uncoupling of oxidative phosphorylation and enhances catabolic processes. The breakdown of

phospholipids in the outer cell membrane, as well as the membranes of intracellular structures, enhances lipid peroxidation and the formation of free radicals. The set of reactions leads to the death of nerve cells. Medicines have been developed to influence each stage: succinate-containing substances, derivatives and analogs of gamma-aminobutyric acid, amino acids and their combinations, acetylcholine precursors, polypeptides and neuropeptides, hemoderivates, pyridoxine, carnitine, pyrrolidine derivatives, anticholinesterase and complex preparations.

The development of acute cerebral ischemia triggers pathobiochemical cascade reactions, the outcome of which is cerebral infarction (MI), which is formed by two mechanisms: necrotic cell death and apoptosis - programmed cell death [2,7]. These modern pathogenetic concepts have made it possible to propose a sequence of stages »Based on their causal relationships. [9] Each stage of the cascade is a target for the therapeutic effect of drugs, primarily with neuroprotective effects. The earlier the cascade is interrupted, the greater the effect can be expected from therapy (6).

There are two main areas of neuroprotective therapy. Primary neuroprotection is aimed at interrupting the rapid mechanisms of cell necrosis - the reactions of the calcium glutamate cascade. This type of neuroprotection should begin from the first minutes of ischemia, especially actively in the first 12 hours. Secondary neuroprotection is aimed at reducing the severity of the long-term effects of ischemia: blockade of pro-inflammatory cytokines, inhibition of prooxidant molecules, interruption of apoptosis, is effective in the first 72 hours, when the focus is re-formed. Despite numerous studies, currently, unfortunately, the issue of the effectiveness and absolute evidence of neuroprotection in cerebral ischemia in humans remains controversial. A fairly large number of drugs with different mechanisms of action have been proposed as neuroprotectors. The effectiveness of most of them has been demonstrated experimentally, but has not been confirmed in the clinic. [4]

It is believed that the failure of the clinical application of most neuroprotective agents is due to a number of objective reasons. First, the terms from the beginning of therapy in the clinic, in contrast to the experiment, are mostly outside the "therapeutic window". Also, one of the features of cerebrovascular accident is the contribution of reperfusion both to the process of cell preservation and to their damage. The absence of reperfusion suggests that the focus will occupy the maximum volume, moreover, in the absence of blood flow, it is difficult or impossible to deliver the drug to the site of the event, and the restoration of blood flow includes new and enhances old damage mechanisms [1]. The drugs proposed

for neuroprotection may be far from ideal in their properties - they poorly penetrate the blood-brain barrier, do not enter the penumbra zone, do not develop their effect at the level of the vascular wall [11]. Some neuroprotective agents are not effective in humans, in contrast to animals. In addition, brain damage preceding ischemia could create conditions under which the effect of neuroprotection could be minimal (diabetes mellitus, high arterial hypertension). And finally, ischemic stroke is a heterogeneous state, not only in pathogenesis, but also in localization and size of the lesion, which suggests some difference in the metabolic and hemodynamic conditions created during ischemia. A particular difficulty for assessing the effectiveness of neuroprotective agents in the clinic, in contrast to the experiment, is the standardization of the groups of patients under study and the choice of outcome assessment (8).

However, to date, based on an understanding of the pathobiochemistry of ischemia, the study of the neuroprotective effects of drugs that interfere with the mechanisms of excitotoxicity, the development of oxidative stress, as well as drugs with neurotrophic action is considered a promising direction. (5). And, despite the presence of many unresolved problems and contradictions regarding the drug therapy of stroke, an increase in its effectiveness in the appointment of patients with various drugs with different mechanisms of action, points of application and their combination, aimed at correcting pathological processes in stroke, both for theoretical and and for practical medicine is an urgent problem. There is a constant search for drugs that can interrupt the pathological processes of ischemia. In this regard, amantadine sulfate is of great interest, the mechanism of action of which is aimed at blocking both dopamine and NMDA receptors, which play an important role in the induction of the ischemic cascade. This provides a theoretical basis for the possibility of a neuroprotective effect of this drug in ischemic brain lesions. And the first pilot studies of amantadine sulfate showed positive results in terms of the effectiveness of the treatment of cerebrovascular accident (CMB) (6). This motivated the study of the neuroprotective potential of this drug.

Stroke continues to be one of the urgent problems of modern medicine, being the main reason for the disability of the population [10]. In recent years, the number of people with disabilities after a stroke has been steadily increasing. Thus, in Uzbekistan, no more than 3-23% of stroke patients return to work, 85% of patients require constant medical and social support, and 20-30% of patients experience profound disability until the end of their life [8].

Over the past 5 years, 1.4 million people have died from diseases of the circulatory system in Uzbekistan, of which 18.9% are people of working age [3]. In this regard,

the search for optimal and highly effective methods of treating stroke in order to reduce the risk of occurrence and the degree of post-stroke disability is one of the priority tasks of the healthcare system as a whole. [9.12]

Along with the use of specialized treatment technologies in vascular centers, according to the standards, all patients undergo neuroprotective therapy from 1 hour after admission to the intensive care unit in order to reduce the consequences of hypoperfusion in ischemic stroke and perifocal changes in intracerebral hematomas, reperfusion injury when using recanalizing technologies and multiple organ violations. [11] Of the group of drugs recommended by the standards for the treatment of stroke, the most commonly used are those that have a multimodal effect, are safe for all types of stroke, and also improve regenerative-reparative processes with an effect on neuronal plasticity

Conclusion, it should be noted that neuroprotective therapy for ischemic stroke should begin as early as possible and continue during the recovery period, which will reduce the number of complications, reduce mortality, improve recovery of neurological functions and the quality of life of patients.

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