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Cellular Mechanisms of Damage and Compensation in the Brain in Cerebral Ischemia: Molecular Proteostasis Control Systems as a Target for Therapy

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Abstract

The relevance of the work is due to the wide spread of cerebrovascular pathology and ischemic strokes among the population. Most studies are devoted to the study of early brain damage in cerebral ischemia, while insufficient attention has been paid to the mechanisms of adaptation and long-term brain disorders. At the same time, delayed death of nerve cells in ischemia is not a predetermined and irreversible process, leaving opportunities for therapeutic intervention. There is a need to search for new data on the molecular and cellular mechanisms of damage development and compensatory processes in brain neurons in the dynamics of cerebral ischemia of varying severity. At the same time, the activation of compensatory mechanisms will reduce the severity of neurodegenerative disorders in the brain, increase the effectiveness of the treatment. An important role in the development of neurodegeneration is played by protein aggregates, which can be localized in nerve cells, in the intercellular space and cerebrospinal fluid. They are formed on the basis of damaged proteins, the violation of the structure of which can be caused by hypoxic and nitrosative stress, inflammatory processes provoked by ischemia, death of neurons. Therefore, an important role in preventing the development of secondary brain damage after ischemia can be played by cellular systems responsible for protein homeostasis, the protein synthesis apparatus, chaperones, the system of autophagy and elimination of damaged proteins ((ubiquitin, proteasome), as well as energy-intensive adaptation processes.

Keywords: cerebral ischemia, brain, neurons, proteostasis, damage, compensation, correction

The relevance of the project is due to the leading positions of cerebrovascular pathology in the structure of morbidity and mortality around the world. Famously, ischemic processes underlie 85% of all brain strokes (Lau et al., 2019; Esposito et al., 2021).

It is known that in cerebral hypoxia of ischemic genesis, such factors as energy deficiency, violation of intracellular calcium homeostasis, aspatrate-, glutamate-, and GABAergic signal transduction, inflammation with cytokine release and hyperproduction of oxygen radicals play an important role, which contributes to apoptosis of neurons. At the morphological level, there is a violation of microcirculation: stasis, plasma impregnation and necrobiotic changes in the walls of blood vessels of the brain, increased permeability, plasma output into the pericapillary space, edema (Lee et al., 2018).

The key links in the pathogenesis of cerebral ischemia are an acute lack of oxygen supply to the brain, inhibition of the aerobic and activation of the anaerobic glucose utilization pathway, changes in the acid-base state, electrolyte balance disorders, oxidative stress, inflammation, excitotoxicity, apoptosis (Lee et al., 2018; Shin et al., 2020).

Protein aggregates, which can accumulate in nerve cells, in the intercellular space, and even in the cerebrospinal

fluid, play an important role in neurodegeneration (including after ischemia). Such aggregates can be formed on the basis of denatured and damaged proteins, the violation of the structure of which can be caused by hypoxic nitrosative stress, inflammatory processes provoked by ischemic stroke. Finally, the death of nerve cells leads to the appearance of similar denatured proteins in the intercellular space, which are prone the formation of cytotoxic aggregates.

In the context of secondary injuries after cerebral ischemia the proteostasis maintenance system is extremely important. This system is based on three key components: chaperones, autophagy and proteolysis. At the same time, chaperones take part in the modulation of autophagy and proteolysis, being a kind of master regulator of the entire proteostasis system (Margulis et al., 2020). In general, it can be considered established that cerebral ischemia causes activation of all proteostasis maintenance systems (D etre et al., 1997; Wang et al., 2018). However, the published results allow us to speak only about short-term activation within a few days, while the duration of the development of secondary damage can be months or more (Catanese et al., 2017).

One of the key elements of the proteostasis system and the chaperone system in particular is the heat shock protein Hsp70 (heat shock protein 70 kDa, HSPA1A). Hsp70, prevents the formation of apoptosomes, binds apoptosis-inducing factor AIF and pro-apoptosis protein Bim and inhibits the maturation of caspases 3 and 7 (Guo et al., 2020). The inflammatory response, usually accompanying cerebral ischemia, is also regulated by Hsp70, which, through its association with TLR2, TLR4 and SREC receptors, is able to activate the innate immune system and/or reduce the response to pro-inflammatory cytokines (Gong et al. 2009). Another mechanism of action of Hsp70 is to protect cells from proteotoxic stress. On the one hand, Hsp70 is able to bind mutant, improperly folded proteins and prevent their oligomerization and aggregation (Duncan et al., 2015), on the other hand, if the native conformation of the protein cannot be restored, Hsp70 ensures their ubiquitinylation (Fernández-Fernández et al., 2017).

Another important chaperone blocking apoptotic cascades is the Hsp90 protein. It is believed that Hsp90 prevents the formation of apoptosis by binding Apaf-1, which inhibits the polymerization of the latter and the recruitment of caspase-9, necessary for the formation of apoptosis (Pandey et al., 2000).

In this regard, researchers have high hopes for the application of chemical inducers of heat shock proteins as therapeutic agents in the treatment of neurodegenerative conditions. Compounds capable of causing the accumulation of chaperones in cells have demonstrated their effectiveness in models of Parkinson’s disease (Ekimova et al., 2018), Alzheimer’s disease (Chow et al., 2013) and many others. In the context of cerebral ischemia, it was found that the administration of Hsp70 to rats on the eve of experimental ischemia contributes to the survival of neurons both immediately after carotid artery ligation and in the medium term. Moreover, it was shown that the purified drug Hsp70 can also be used as a therapeutic agent—intranasal administration of Hsp70 after cerebral ischemia improved the behavioral and histological parameters of animal rehabilitation (Shevtsov et al., 2014).

Despite the fact that in the world literature you can find about two dozen described various inducers of chaperones with neuroprotective effect, at the moment only one drug, the mechanism of action of which is based on the activation of the synthesis of chaperones, is used in the clinic. This is the drug Arimoclomol, which is used for the treatment of a rare disease—Niemann-Pick disease (Kierkegaard et al., 2016). At the same time, this drug has not yet been registered on the territory of Russia or on the territory of Belarus.

Summing up the above, most of the current studies are devoted to the study of the pathogenesis of early damage caused by cerebral ischemia (Liu et al., 2020; Meng et al., 2020; Xia et al., 2020), while insufficient attention has been paid to the mechanisms of long-term damage and compensation of the brain. At the same time, activation of adaptive mechanisms in the brain, in our opinion, will increase the effectiveness of the therapy. There is a need to search for new data on the molecular and cellular mechanisms of the development of degenerative and compensatory processes in the brain with ischemia of varying severity, while developing effective ways of neuroprotection. In addition, the processes of ischemic brain damage were evaluated on the basis of one of the models of ischemia, usually simultaneous.

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