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Mini Review

Adaptation of the Brain to Hypoxia

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Abstract

Hypoxia is a typical pathological process that develops as a result of a lack of biological oxidation, leading to a disruption in the energy supply of functions and plastic processes in the brain. Hypoxia of the brain is one of the main mechanisms of its damage in traumatic brain injury and acute cerebrovascular accident. With hypoxia, proteases are activated, including Ca2+-dependent (calpains). They are localized outside of lysosomes in membrane structures in the form of an inactive complex with inhibitory proteins (calpastatins). The main functions of calpains are: repair of the cytoskeleton and cell membranes, destruction of receptor proteins and their renewal, activation of enzymes. In this way, hypoxia causes structural and metabolic changes in the neurons of the central nervous system, triggers adaptation mechanisms implemented at the cellular, subcellular and molecular levels.

Keywords: Adaptation; brain; hypoxia

Introduction

Hypoxia is a typical pathological process that develops as a result of a lack of biological oxidation, leading to a disruption in the energy supply of functions and plastic processes in the brain. Hypoxia of the brain is one of the main mechanisms of its damage in traumatic brain injury and acute cerebrovascular accident. There are exogenic and endogenous reasons of hypoxia [1]. The exogenous type of hypoxia develops with decreasing of the partial pressure of oxygen in the inhaled air (less than 159 mm Hg). When barometric pressure is normal, normobaric hypoxia develops, with a decrease in barometric pressure, hypobaric hypoxia develops (ascent to a height at which PO2 decreases to 100 mm Hg). Endogenous hypoxic status as a result of pathological processes that give rise to disruption of gas exchange in the lungs (respiratory), insufficient oxygen transport to organs (circulatory) or to a violation of its utilization by the tissues (tissue hypoxia) [2].

The brain is most sensitive to hypoxia, especially the neurons of the cerebral cortex and the hippocampus. Functional and biochemical signs of neuronal damage are detected after 2 minutes of cerebral ischemia due to insufficient oxygenation of neurons, decreased energy production, impaired transport of potential-determining ions, changes in acid-base state, excitotoxicity, oxidative stress and apoptosis. The activity of neurons is associated with such energy-dependent processes as exo-and endocytosis of vesicles from presynaptic terminals, transmembrane transfer of K+, Na+, Ca2+ ions. That is why nerve cells are the most vulnerable to hypoxia. Oxygen shortage leads to violations of intracellular synthesis of proteins and amino acids. Free radicals are formed in mitochondria, inactivating phospholipids of their membranes, and thus one of the leading links of energy production is blocked, and due to a violation of the ion pump, intracellular potassium is replaced by sodium, tissue fluid enters damaged neurons and cytotoxic brain edema develops [3].

When hypoxia occurs, a dynamic functional system is activated to achieve and maintain an optimal level of biological oxidation in cells. This system realizes its effects by activating the delivery of oxygen and metabolic substrates to tissues and including them in biological oxidation reactions. Adaptive reactions can be divided into emergency and long-term adaptation reactions [4].

In case of emergency adaptation, an excess of metabolites with a vasodilating effect occurs in the brain: adenosine, prostacyclin, prostoglandins, kinins and others. They prevent the realization of the vasoconstrictor action of catecholamines, providing the extension of arterioles, which helps to strengthen the blood flow to the brain.

There is an activation of metabolism, including:

a) Increasing the efficiency of the processes of utilization of oxygen and oxidation substrates and their delivery to mitochondria due to morpho functional changes in the mitochondria of neurons, restructuring of mitochondrial enzyme complexes

b) Activation of oxidation and phosphorylation enzymes

c) An increase in the degree of conjugation of the processes of oxidation and phosphorylation of adenine nucleotides: adp, amp, creatine

d) Activation of the glycolytic oxidation pathway [5].

The basis of the mechanisms of long-term adaptation is the activation of the formation of mitochondria and the oxidation processes occurring in them. There is an increase in the synthesis of nucleic acids and proteins, the transport of O2 and metabolic substrates, and the efficiency of biological oxidation processes in mitochondria. Activation processes are most pronounced in the cerebral cortex, where the concentration of RNA increases by 50%, and protein synthesis increases by 2 times.

Metabolism acquires a number of characteristic features:

a) Economical use of oxygen and metabolic substrates in biological oxidation reactions and plastic processes. In general, energy consumption for the nervous tissue is reduced by 8.6 times. As a result, the reliability of oxygen homeostasis of neurons increases, which provides their greater survival.

b) High efficiency of reactions of anaerobic ATP resynthesis.

c) Dominance of the activity of anabolic processes over catabolic ones.

d) High power and mobility of transmembrane ion transfer mechanisms, which is ensured by the operation of membrane atpases.

There is hypertrophy of neurons and an increase in the number of synaptic terminals, the sensitivity of receptors to neurotransmitters increases. In addition, the following adaptation mechanisms occur at the cellular level: sprouting (regrowth of new processes from pericaryons of neurons), arborization (additional branching of dendrites) and changes in synaptic conduction [6]. For a long time, the formation of new neurons in the central nervous system was considered impossible. However, it was found that nerve stem cells are located in the subventricular zone of the lateral ventricles of the brain and the dentate gyrus of the hippocampal formation. After hypoxia, neurogenesis is activated, followed by migration and differentiation of the formed neuroblasts into the damaged areas of the brain [7]. One of the major adaptive mechanisms is the improvement of cerebral circulation. At its heart is an increase in NO synthesis and neovascularization, most prominent in the neocortex, striatum and hippocampus. At the electron microscopic level, there is an increase in the density of the arrangement of spikes on the dendrites of pyramidal neurons, complication of the spike apparatus and an increase in the number of active synaptic contacts. Stress-limiting brain systems (GABA-ergic, serotonin-ergic, endogenous opioid peptides system) are activated [8]. There is a restructuring of the sympathoadrenal system, which is expressed in hypertrophy of sympathetic neurons, an increase in the synthesis of catecholamines by the adrenal medulla the backup power of the sympathetic nervous system.

At the behavioral level, there is an acceleration of the development and an increase in the degree of preservation of conditioned reflexes, an improvement in the processes of information transition from short-term memory to long-term memory and an expansion in the resistance of the brain to the effects of extreme factors. The power of the antioxidant system boosts due to the activation of antioxidant enzymes (catalase, superoxide dismutase) under the action of melatonin epiphysis, the severity of lipid peroxidation of membranes loss. One of the forms of structural and functional adaptation of neurons to hypoxia is an expansion in the number and size of lysosomes. The formation of new primary lysosomes provides fast elimination of damaged structures by means of lysosomal auto phagocytosis and apoptosis. The activity of the key enzyme of the respiratory chain NADPH-cytochrome c-oxidoreductase increases. Its affinity for NADPH decreases, which increases the resistance of mitochondria to oxygen. With a decrease in the intensity of oxidative processes, a more efficient work of the respiratory chain was noted – the so-called “paradoxical effect” of adaptation to hypoxia [9].

An important part in neovascularization belongs to a specific regulatory protein – hypoxia-induced factor (HIF), the activity of which increases with a decrease in oxygen tension in the blood (see Chapter 8) [10]. Neuroglobin (Ngb) is a representative of the family of globin proteins of the nervous system participating in maintaining gas homeostasis of nerve cells. It serves to deposit and transfer oxygen to the mitochondria of neurons, and in pathology it can prevent neurodegeneration through antioxidant and anti-apoptotic mechanisms. Ngb plays a role in binding and neutralizing reactive oxygen and nitrogen species, the amount of which increases with the development of cerebral hypoxia, supports ionic homeostasis and energy metabolism of the cell, acting as a neuroprotector and regulator of cellular respiration [11]. In cerebral hypoxia, there is an increase in the expression of Ngb. The change in the conformation of Ngb provides neuroprotective signaling and control of mitochondrial respiration in hypoxia, supplying oxygen to neurons and contributing to the maintenance of their vital functions. Suppression of Ngb expression exacerbates ischemic and hypoxic damage to neurons. There is a suggestion that neuroglobin inactivates the enzyme of apoptosis p21-activated kinase Pak1 and

interacts with signaling molecules of the superfamily of Ras-like GTPases RhoGDI and RhoGTPase, inhibiting the distribution of the "death signal" induced by hypoxia. Hypoxia increases the activity of NF-kB (nuclear factor kappaB) and phosphorylated CREB (c-AMP response element binding protein), especially in the hippocampus and dentate gyrus.

Molecular neuroprotective mechanisms also include an increase in the expression of mitochondrial manganese-dependent superoxide dismutase (Mn-SOD). This enzyme is an antioxidant and catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide [12]. Heat shock proteins (HSP) are a class of functionally similar proteins whose expression increases with increasing temperature or other stress effects on the cell, including in response to cerebral ischemia (see Chapter 7) [13]. Matrix metalloproteinases (MMP) are a family of extracellular zinc–dependent endopeptidases which distribute the protein components of the extracellular matrix of connective tissue. They take part in tissue regeneration, angiogenesis, proliferation, migration and differentiation of cells, apoptosis. Brain hypoxia, both acute and chronic, is accompanied by an increase in the level of MMR, reflecting the degree of exposure to oxidative stress on the body. With hypoxia, cyclooxygenase-2 and catalase are overexpressed. Catalase destroys hydrogen peroxide and entails an increase in the expression of MMP [14]. With hypoxia, proteases are activated, including Ca2+-dependent (calpains). They are localized outside of lysosomes in membrane structures in the form of an inactive complex with inhibitory proteins (calpastatins). The main functions of calpains are:

a) Repair of the cytoskeleton and cell membranes

b) Destruction of receptor proteins and their renewal

c) Activation of enzymes [15].

In this way, hypoxia causes structural and metabolic changes in the neurons of the central nervous system, triggers adaptation mechanisms implemented at the cellular, subcellular and molecular levels.

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