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EFFECT OF HYPOXIA ON MORPHOFUNCTIONAL CHARACTERISTICS OF BRAIN NEURONS AND MOLECULAR MARKERS OF ISCHEMIC HYPOXIA

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Abstract

Objective. Generalization and systematization of literature data on the effect of hypoxia on morphofunctional characteristics of brain neurons and molecular markers of ischemic hypoxia.

Methods. The basis of this study was a review of the literature on this topic.

Results. Ischemic hypoxia causes similar structural and metabolic disorders in neurons in different parts of the cerebral cortex, the severity and rate of development of which depends on the phylogenetic age of the formation. To a greater extent, violations are expressed in the neocortex, the neurons of which are most sensitive to a lack of oxygen due to the high level of energy consumption. Hyperchromic wrinkled neurons – cells with an abnormal shape and size can act as a marker of the severity of dystrophic processes. Violations of their ultrastructure (swelling of mitochondria, disorganization of the cisterns of the endoplasmic reticulum and the Golgi complex) also indicate ischemic damage. A number of molecular markers, such as neuron-specific enolase, neuroglobin, heat shock proteins, make it possible to assess the depth and severity of hypoxic damage.

Conclusion. Further study of the pathogenesis and consequences of cerebral ischemia will serve as a fundamental basis for improving methods of diagnosis, prevention, treatment and assessment of the effectiveness of the methods used to correct this pathology.

Keywords: hypoxia, brain neurons, molecular markers

ВЛИЯНИЕ ГИПОКСИИ НА МОРФОФУНКЦИОНАЛЬНЫЕ ХАРАКТЕРИСТИКИ НЕЙРОНОВ МОЗГА И МОЛЕКУЛЯРНЫЕ МАРКЕРЫ ИШЕМИЧЕСКОЙ ГИПОКСИИ

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Резюме

Цель. Обобщение и систематизация данных литературы о влиянии гипоксии на морфофункциональные характеристики нейронов мозга и молекулярных маркерах ишемической гипоксии.

Методика. Основой данного исследования стал обзор литературы по данной теме.

Результаты. Ишемическая гипоксия вызывает сходные структурные и метаболические нарушения в нейронах разных отделов коры головного мозга, выраженность и скорость развития которых зависят от филогенетического возраста образования. В большей степени нарушения выражены в неокортексе, нейроны которого наиболее чувствительны к недостатку кислорода из-за высокого уровня энергозатрат. Гиперхромные сморщенные нейроны – клетки аномальной формы и размера могут выступать маркером тяжести дистрофических процессов. Нарушения их ультраструктуры (набухание митохондрий, дезорганизация цистерн эндоплазматического ретикулума и комплекса Гольджи) также указывают на ишемическое поражение. Ряд молекулярных маркеров, таких как нейронспецифическая енолаза, нейроглобин, белки теплового шока, позволяют оценить глубину и тяжесть гипоксического повреждения.

Заключение. Дальнейшее изучение патогенеза и последствий церебральной ишемии послужит фундаментальной основой для совершенствования методов диагностики, профилактики, лечения и оценки эффективности методов коррекции данной патологии.

Ключевые слова: гипоксия, нейроны головного мозга, молекулярные маркеры

Introduction

Cerebral hypoxia is a universal mechanism of death of the body both in local circulatory disorders (ischemic or hemorrhagic stroke) and due to other causes of exogenous (deficiency or excess of oxygen in the atmosphere) and endogenous nature (cardiovascular, respiratory pathology, anemia and hemoglobin inactivation, violation of oxygen utilization by enzymes). Brain hypoxia occurs with various intoxications – alcohol dependence and tobacco smoking (due to the pathology of mitochondrial respiration), encephalitis, meningitis (due to circulatory disorders). The most common type of cerebral hypoxia is ischemic hypoxia, which is a variant of circulatory hypoxia. Ischemic brain lesions are leading not only as the causes of its pathology (85% of all strokes are due to cerebral ischemia), and as one of the leading causes of death (about 6 million people in the world annually) and disability [28]. Even short-term cerebral ischemia leads to deep damage to the nervous tissue due to insufficient oxygenation of neurons, decreased energy production, impaired transport of potential-determining ions, changes in the acid-base state, excitotoxicity, oxidative stress and apoptosis [1, 3, 10-12, 31].

The leading links in the pathogenesis of cerebral ischemic hypoxia are energy deficiency and excess metabolic products accumulating in the ischemic zone. These processes lead to a decrease in plastic processes, the development of degenerative, atrophic and necrotic changes in neurons. The neurons of the brain are most sensitive to the lack of oxygen, but the severity of the changes depends on the phylogenetic age of the formation. The leading role in neurodegenerative processes in the brain during its ischemic hypoxia is played by such factors as disturbance of intracellular calcium homeostasis, aspartate, glutamate, and GABAergic signal transduction, inflammation with the release of cytokines and overproduction of oxygen radicals. Their combined action leads to neuronal apoptosis [3, 5, 6, 9, 12, 14, 21, 26].

The aim of this work was to analyze and summarize the literature data on the effect of ischemic hypoxia on the morphological and metabolic characteristics of neurons in phylogenetically different parts of the brain, as well as to provide an overview of molecular markers of hypoxia.

Morphological disorders

At the morphological level, with cerebral hypoxia, edema is observed. An early manifestation of edema is the appearance of signs of impaired microcirculation: stasis, plasma impregnation and necrobiotic changes in the walls of blood vessels of the brain, an increase in their permeability, and the release of plasma into the pericapillary space [5, 8]. When modeling ischemic hypoxia in rats, degenerative processes in the white matter of the brain were revealed. The most pronounced disorders were noted in the temporoparietal region of the neocortex, internal capsule, caudate nucleus, and thalamus. These results are similar to those obtained in the clinic when studying the consequences of ischemic stroke in humans. Abnormal white matter includes microglial infiltration, astrocytosis, neuronal and axonal degeneration, and demyelination. The destruction of white matter entails necrosis of the neuronal bodies [3, 13, 24].

At the same time, there is also feedback. When the perikarion of a neuron is damaged under the influence of the resulting decay products, the microtubules of the dendritic-spiny apparatus disappear. Dendrites undergo dystrophic changes and exhibit enhanced endocytosis, capturing fragments of neural structures in contact with them. Such endocytosis is interpreted as phagocytosis, which is an expression of biological disinhibition and aimed at replenishing the trophic deficit in damaged nerve cells and their processes. Phagocytosis is not only parts of destroyed, but also dendrites of reversibly altered nerve cells. At the same time, excessive phagocytosis leads to degeneration of dendrites, and then neurons due to the accumulation of a large amount of phagocytized material in them. This is also facilitated by insufficient supply of trophic factors to neurons through damaged dendrites, antegrade supply of pathogenic substances from the axons of pathologically altered neighboring neurons and retrograde supply from altered dendrites (transneuronal degeneration). When neurons are damaged, microglia and lemmocytes are disinhibited and the properties of macrophages appear in them in relation to the degenerating neuron and its processes.During cerebral ischemia in rats in the neocortex, a decrease in the size of neurons, a change in their shape (polygonal, elongated, expansion and tortuosity of the apical process), the appearance of satellitosis and neuronophagy were revealed. Disorganization of the cell layers and a significant increase in the size of the perikaryons of neurons, the loss of the clarity of their contours and deformation are also noted in the field cortex. Chromatolysis, karyopycnosis, swelling of nuclei and their displacement to the periphery of the perikarion, apoptotic changes are observed [15-17, 22, 23, 25, 32].

In the subcortical nuclei of the brain, wrinkling of neurons, changes in the size and shape of their nuclei, perikarions and neuropil are noted.In general, histological changes are similar in phylogenetically different parts of the brain, but their degree and time of appearance vary. There is a direct relationship between the metabolic rate and the sensitivity of the brain region to hypoxia [18, 19].

At the electron microscopic level, changes are noted in the mitochondria of neurons: swelling, destruction of their cristae, uneven distribution in the cytoplasm, which indicates a violation of the energy supply of neurons. A decrease in the number of mitochondria is caused by a violation of the integrity of the outer and inner membranes due to a violation of the permeability to cations, which leads to edema and rupture. Active swelling of mitochondria is associated with the work of the electron transport chain. There is an expansion of the tubules of the granular and smooth endoplasmic reticulum, a change in their structure, disintegration into small granules, the appearance of large vacuoles and loops. Free ribosomes predominate, forming extensive clusters. This is one of the manifestations of the energy deficit that forms in the cell, since the fixation of ribosomes to the membranes of the rough endoplasmic reticulum with the participation of the riboforin protein is an energy-dependent process. Under conditions of ischemic action, the neuron reduces the export of protein and seeks to direct it for internal needs. Disorganization of the granular endoplasmic reticulum leads to the accumulation of newly formed proteins in the cytoplasm. As cell hypoxia and acidosis increase, their denaturation increases.In the Golgi complex, the expansion of cisterns due to water accumulation and their partial fragmentation are noted. The total number of lysosomes increases, and their sizes increase. There is an exit into the cytoplasm and activation of hydrolytic enzymes of lysosomes – cathepsin, ribonuclease, acid phosphatase, deoxyribonuclease, hyaluronidase and other enzymes, which leads to autolysis [17-19, 22, 23, 25, 32].

Cerebral ischemia is characterized by the appearance of hyperchromic and hyperchromic shriveled neurons. Although hyperchromic shriveled neurons have been studied by many authors, nevertheless, information about them is very contradictory and it is rather difficult to judge the essence and functional significance of this phenomenon from them, especially since similar changes in cells can sometimes occur as artifacts. So, posthumous shriveling of ganglionic elements can be the result of improper fixation and autolysis of nervous tissue, as well as a consequence of drying out or mechanical compression of the material during its extraction. Under normal conditions, only a few hyperchromic and hyperchromic shriveled neurons are found in the brains of animals and humans. Their number can increase significantly under experimental influences and pathological conditions. There are opinions according to which the shrinking of hyperchromic neurons is associated with a decrease in their functional activity and reflects the processes of inhibition occurring in them.

The low functional activity of hyperchromic shriveled neurons is confirmed by the results of electron microscopic and autoradiography studies, which showed a 2-fold decrease in the rate of excretion of newly synthesized RNA from the nucleus into the cytoplasm of the cell. The process of wrinkling itself is manifested primarily by a decrease in the perikaryons of neurons, they lose their characteristic rounded shape and become angular. Degenerative atrophy of neurons occurs, the biological meaning of which is adaptation to long-term conservation in unfavorable conditions. Hyperchromic neurons are often regarded as hypoxic-altered cells. The appearance of shriveled dark cells in hypoxic and anoxic conditions is a universal manifestation of pathological conditions of neurons, reflecting the severity of damage due to deep energy deficiency caused by damage to mitochondria, changes in the water-electrolyte balance and acid-base state, leading to irreversible consequences for the cell. So, with total cerebral ischemia, neurons with initial signs of hyperchromic after 1 hour of ischemia turn into shriveled hyperchromic neurons, followed by colliquation and coagulation necrosis after 1 day. Morphological changes (wrinkling of neuronal perikaryons) revealed in conditions of total ischemia 1 day after modeling are generally similar to those in subtotal 1-hour ischemia, but more pronounced. Thus, with total ischemia at the 60th minute, normochromic neurons were absent, hyperchromic neurons were practically absent, a large proportion of the cell population consisted of hyperchromic shriveled neurons (fig. 1, 2).

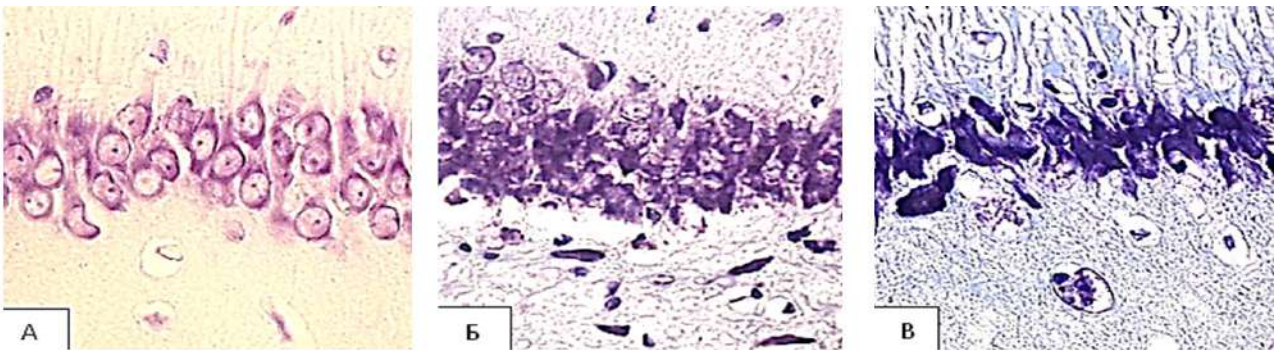

Fig. 1. Neurons of the pyramidal layer of the CA1 field of the rat hippocampus. A – control, B – SCI 1 hour, C – SCI 1 day, Nissl staining. Magnification Ч40. Digital micrograph. SCI – subtotal cerebral ischemia

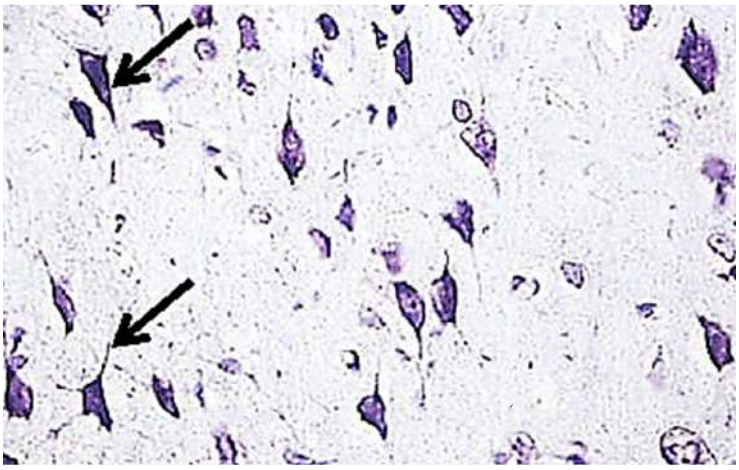

Fig. 2. Hyperchromic shriveled neurons in neocortex, Nissl staining. Magnification Ч40. Digital micrograph

The shriveling of neurons is probably the result of a sharp disruption of its water-salt metabolism and the loss of a significant amount of water. In this case, the cytoplasm and nucleus of the cell decrease in volume, which leads to an increase in the density of the organelles in them, and in particular of the ribosomes (and RNA, respectively) and hyperchromatosis. In addition, there is a fragmentary thickening and thickening of the hyaloplasm of these neurons, which is clearly visible on electronograms. At the electron microscopic level, compaction of organelles is observed in their cytoplasm. There is a displacement of the nucleolus to the periphery of the nucleus and an increase in the concentration of ribonucleoproteins due to their release from the nucleolus. A number of ideas have been put forward that the nature of hyperchromic neurons is associated with dysfunction of the efficient storage of energy by the hyaloplasm, which fills the intracellular space between organelles. These cells are formed as a result of an unprogrammed phase change in the hyaloplasm, are capable of restoring normal functioning, and in case of death, they are phagocytized by microglia. According to the literature, the life cycle of hyperchromic neurons can be divided into two periods. The first period is characterized by a paranecrotic state. In some cases, dark cells come out of this state and turn into normochromic ones. In other cases, the phenomena characterizing the first period progress, dark cells degenerate and are eliminated by subsequent colliquation and coagulation necrosis.

In hyperchromic cells that actively synthesize protein, the activation of the genetic apparatus occurs, comparable to a stress situation at the genome level. Under these conditions, there is a high probability of a failure in the mechanisms of regulation of gene activity. The consequence of such a failure can be "chaotic" expression, leading to cell transformation and programmed cell death – apoptosis.

Thus, shriveling of neurons should be considered as a severe pathological condition, sometimes irreversible and leading to the death of neurons. It is possible that shrunken neurons are formed not from hyperchromic, but directly from normochromic neurons. In any case, one should clearly distinguish between "dark" hyperchromic non-shriveled and "dark" hyperchromic shriveled neurons. At the same time, the functional activity of the former is increased, and the latter is depressed [1].

Disorders of neuronal metabolism

Ischemic hypoxia causes deep and varied disorders of neuronal metabolism. A decrease in the activity of succinate dehydrogenase is noted, indicating the inhibition of aerobic oxidation of succinate in the electron transport chain of mitochondria, as well as the activity of glucose-6-phosphate dehydrogenase – the manifestation of inhibition of the pentose phosphate pathway, NADH dehydrogenase and NADPH dehydrogenase – as a manifestation of the inhibition of mitochondrial and extramitochondrial energy processes. At the same time, an increase in the activity of lactate dehydrogenase occurs in the cytoplasm of neurons, indicating an increase in the activity of the late stages of glycolysis, which are necessary to maintain the vital activity of neurons. An increase in the activity of the marker enzyme of lysosomes, acid phosphatase, is noted as a sign of destruction of organelle membranes and intensification of autophagy processes, which are most pronounced in the neocortex [5, 14, 27].

Molecular markers of ischemic hypoxia

There are a number of molecular markers used to detect ischemic hypoxia. The enzyme neuron-specific enolase (NSE) belongs to the group of enolase enzymes involved in glycolysis. It is a highly specific marker of neuronal death. Neuron-specific enolase characterizes the degree of hypoxic brain damage. Its activity increases significantly during hypoxia, and the high rate of its increase is associated with an unfavorable prognosis of the pathological process. Determinations of NSE in cerebrospinal fluid or serum provide valuable information about the severity of neuronal damage and violations of the overall integrity of the blood-brain barrier [30].

Neuroglobin, a member of the family of globin proteins of the nervous system, is involved in maintaining gas homeostasis of the cell. It is an intracellular hemoprotein that has a high ability to bind oxygen, as a result of which it increases the availability of oxygen to the brain and provides its protection during hypoxia. Neuroglobin acts as a stress sensor, responding to changes in the O_2/NO ratio through conformational changes. Its activity increases significantly at the early stage of hypoxia [20].

Heat shock proteins (hsp) perform the function of a nuclear signal in the activation of the expression of structural genes, are involved in the formation of the structure of proteins and their intracellular transport. Hsp limit damage to the macromolecular structures of the cell; when exposed to stress damaging factors, they contribute to an increase in antioxidant protection. Their content in the cytoplasm of neurons increases at the early stage of hypoxia. The most significant increase in the expression of heat shock proteins, indicating inhibition of protein synthesis during cerebral ischemia, was observed in the neocortex, thalamus and caudate nucleus [2].

HIF-1б (Hypoxia-inducible factor 1-alpha) is a protein considered to be the main regulator of the cellular response to hypoxia. Under hypoxic conditions, the expression of HIF-1б is significantly increased. The HIF-1б protein induces the transcription of more than 60 genes involved in proliferation and regeneration, angiogenesis, erythropoiesis, glucose and iron metabolism, thereby contributing to an increase in oxygen delivery and cell survival during hypoxia [29].

Conclusion

Thus, ischemic hypoxia causes similar structural and metabolic disorders in neurons in different parts of the cerebral cortex, the severity and rate of development of which depends on the phylogenetic age of the formation. To a greater extent, violations are expressed in the neocortex, the neurons of which are most sensitive to a lack of oxygen due to the high level of energy consumption.

Hyperchromic shriveled neurons – cells with an abnormal shape and size can act as a marker of the severity of dystrophic processes. The above-described violations of their ultrastructure (swelling of mitochondria, disorganization of the cisterns of the endoplasmic reticulum and the Golgi complex) also indicate ischemic damage. A number of molecular markers, such as neuron-specific enolase, neuroglobin, heat shock proteins, make it possible to assess the depth and severity of hypoxic damage. Further study of the pathogenesis and consequences of cerebral ischemia will serve as a fundamental basis for improving methods of diagnosis, prevention, treatment and assessment of the effectiveness of the methods used to correct this pathology.

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