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Review Article

The Main Mechanisms of Brain Adaptation to Hypoxia

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Abstract

It shown that hypoxia causes a complex restructuring of the functioning of various body systems, which is aimed to maintain the delivery of the required amount of oxygen to tissues. Adaptation to hypoxia exerts a significant influence on the central nervous system, central hemodynamics, microcirculation in various organs, oxygen metabolism, free radical oxidation of lipids, the main systems detoxification enzymes and immunity. The mechanisms of adaptation to hypoxia in the brain are discussed. The improvement of cerebral circulation appears to be one of the most important protective effects of adaptation to hypoxia.

Keywords: *Brain Adaptation; Hypoxia; Oxygen Metabolism*

Introduction

Hypoxia (from *Latin* hypo - lower and oxygenium - oxygen) - a low oxygen content in the tissues of the body, can be caused by lack of oxygen in the inhaled air, as well as by many diseases. Hypoxia is usually viewed as a pathological process, and there is an opinion among physicians that oxygen is always useful, and its lack is harmful to human health. However, it is known that the state of hypoxia periodically occurs during the natural activity of the body. The reasons for the periodic occurrence of physiological hypoxia can be hard physical work and stay in mountainous areas. It shown that periodic physiological hypoxia develops not only with intense activity of any body system, but also under conditions of relative rest, as evidenced by the constant presence of lactic acid in the blood [2]. Consequently, periodic hypoxia can occur both at rest and during the stress of the functions of organs and systems, which causes constant "training" of compensatory reactions that ensure the elimination of the resulting oxygen starvation. Since oxygen starvation of organs and tissues is either a cause or an important mechanism for the development of pathological conditions, hypoxia training in order to increase the functional reserves of compensatory antihypoxic reactions should be considered as one of the main non-drug methods in the system of modern methods of adaptive medicine. In this case, the technique can be denoted both by the term "hypoxic training" and "hypoxic therapy". The first is used in the case of correction of the state of a healthy person, and the second - in the treatment and rehabilitation of patients [1].

The history of the use of mountain climate for medicinal purposes, the most important therapeutic factor of which is hypobaric hypoxia, goes back millennia. Mountain climatic treatment is mild, physiological and very effective for some diseases, since a whole range of natural healing factors are used that affect the entire body as a whole [2]. Hypobaric hypoxic therapy (HBT) is also carried out in stationary or mobile pressure chambers, in which a decrease in the oxygen content in the inhaled air is created due to a decrease in barometric pressure ("rise" to altitude). Normobaric hypoxic therapy is carried out using hypoxic (with a reduced oxygen content) gas mixtures (oxygen and nitrogen) supplied for breathing (through a pipeline system and an oxygen mask) from cylinders (breathing bags) or from hypoxicators - special devices capable of accurately dosing the oxygen content in inhaled gas mixture [3]. Currently, a hypoxic gas mixture with oxygen content (10 - 12%) and various time intervals (intervals) of its effect are used. Interval normobaric hypoxic therapy (INH) is devoid of a number of disadvantages inherent in hypobaric hypoxic therapy in a pressure chamber (side effects on the body of a rarefied atmosphere, the possibility of barotrauma, excitation of baroreceptors, claustrophobia, etc). According to Plakhatnyuk V.I. and co-authors, the reduced tolerance of normobaric hypoxia was noted 3.7 times less often than hypobaric [4]. When using ING, there is a possibility of strict dosage of the therapeutic factor and adequate direct control of the patient's functional state.

The purpose of this work is to consider the mechanisms of the influence of adaptation to hypoxia on the brain.

Hypoxytherapy mechanisms

In the body, hypoxia causes a complex reorganization of the functioning of various systems, which is aimed at ensuring the delivery of the required amount of oxygen to the tissues, and also causes adaptive changes in tissues to function in conditions of oxygen deficiency. These reactions are based on the mechanisms that ensure a sufficient supply of oxygen to the body when it is deficient in the environment, the supply of oxygen to vital organs under conditions of hypoxemia, the ability of tissues to utilize oxygen at its low voltage, and maintain the formation of ATP by the method of substrate phosphorylation due to glycolysis [2,5,6].

When adapting to hypoxia in the body, the secretion of erythropoietins increases, which stimulate erythropoiesis in the red bone marrow, which leads to an increase in the number of red blood cells and an increase in the concentration of hemoglobin, the ability of hemoglobin to bind oxygen in the lungs and release it to peripheral tissues increases. In addition to hemoglobin A (HbA) typical for an adult organism, embryonic hemoglobin F (HbF) appears, which has a high affinity for oxygen and is able to attach it at a lower oxygen tension in the alveolar air. This contributes to an increase in the capacity of the oxygen transport system (an increase in the oxygen capacity of the blood), which leads to an increase in physical performance or aerobic capacity of the load [7-9]. The content of 2,3-diphosphoglycerate in the erythrocyte increases, which promotes the release of oxygen from the complex with hemoglobin in the tissues. An increase in the oxygen capacity of the blood is complemented by an increase in the concentration of muscle protein in the myocardium and skeletal muscles - myoglobin, which is capable of carrying oxygen in the zone of a lower partial pressure than hemoglobin [10].

In the lungs, the respiratory surface and the number of alveoli increase, the mass of the respiratory muscles increases, and hypertrophy of the neurons of the respiratory center occurs. As a result, the efficiency of the ventilation function of the lungs increases [11-13].

Interval hypoxic training induces the expression of HSP 70 in type II alveolar epithelial cells. Heat shock proteins (HSPs) protect cells and organs against oxidants, nitric oxide, tumor necrosis factor, and endotoxin [14,15].

Adaptation to hypoxia leads to a decrease in hyper- and dyslipidemia. Under experimental conditions, it was shown that in adapted animals receiving a hypercholesterol diet, the level of cholesterol significantly decreased compared to non-adapted animals [16]. It has also been shown that adaptation to periodic hypoxia in patients with myocardial infarction leads to a significant decrease in the level of total cholesterol, triacylglycerides and the atherogenic index [17].

The monooxygenase system of the liver reacts to adaptation to pressure chamber hypoxia by a decrease in the enzymatic activity of cytochrome P-450, amidopyrine-N-dimethylase and aniline-o-hydroxylase. It is known that this system shares a number of functional characteristics with the immune system, and there are reciprocal interactions between them. Thus, inducers of cytochrome P450 exhibit an inhibitory effect on the immune system, and immunity stimulants inhibit monooxygenase activity. The biological meaning of the relationship between these two systems is still unclear. Perhaps, a decrease in P-450 activity is accompanied by an increase in immunity, which was noted during adaptation to hypoxia [18].

When adapting to periodic hypoxia, the activity of the antioxidant system, which is the main system of protection of cell membranes, increases - the activity of lipid peroxidation in cell membranes decreases (the activity of antioxidant enzymes catalase and superoxide dismutase increases, the concentration of malondialdehyde decreases) [19]. This leads to a decrease in the permeability of cell membranes and an improvement in the functioning of the enzyme systems of cells. Also, adaptation to hypoxia increases the resistance of the calcium pump to the action of lipid peroxidation products [20,21]. It was later shown that even a two-week adaptation of rats to periodic hypoxia caused some activation of free radical oxidation and a more pronounced increase in the power of the endogenous antioxidant system. Apparently, these changes are important for the development of the well-known preventive and therapeutic effects of adaptation to periodic hypoxia [22].

The effect of periodic hypoxia on the activity of antioxidant enzymes in the blood of patients with discirculatory encephalopathy was studied. After 10 days of adaptation to hypoxia, the total oxidative activity and the content of substances reacting with thiobarbituric acid decreased, while the activity of superoxide dismutase, catalase and glutathione peroxidase in erythrocytes increased. The results obtained showed the possibility of correcting disturbed oxidative homeostasis by adapting to hypoxia [23].

Adaptation of the organism to environmental factors, including adaptation to hypoxia, is characterized by stress response and activation of catecholamine and corticosterone production [24]. N-methyl-D-aspartate (NMDA) mediated neurotoxic brain damage in rats is enhanced by chronic administration of high doses of corticosterone, while the administration of low doses of corticosterone reduces NMDA-initiated neurodegeneration [25].

During adaptation to hypoxia caused by physical training, a more pronounced increase in nitric oxide (NO) production occurs [26]. In type of adaptation the stimulation of NO synthesis apparently occurs mainly due to an increase in the activity and expression of endothelial nitric oxide synthase (eNOS) [27-29]. This phenomenon may play a role in the well-known preventive and curative effect of adaptation in cardiovascular diseases accompanied by endothelial dysfunction [30]. Adaptation to environmental factors, which stimulates the synthesis of endothelial NO, effectively prevents NO overproduction by inducible nitric oxide synthase (iNOS) and limits it's adverse effects [26].

Two mechanisms may underlie the simultaneous adaptive defense against overproduction and NO deficiency. First, NO overproduction is limited by NO itself by a negative feedback mechanism [31]. Therefore, adaptation-induced preliminary enhancement of NO synthesis may play a role in adaptive prevention of NO overproduction. Second, different types of adaptation are naturally accompanied by the formation of a so-called NO depot in the vessel wall, which is NO-containing complexes [32,33]. Physiological experiments have shown that the formation of a NO depot is apparently an adaptive response aimed at protecting the body from the toxic effect of excess NO. At the same time, the NO depot can serve as an additional non-enzymatic source of free NO, which to a certain extent compensates for its deficiency [33].

Influence of adaptation to hypoxia in the brain

Improving cerebral circulation is one of the important protective effects of adaptation to hypoxia. This effect is based not only on the stimulation of NO synthesis, but also on an increase in vascular density, which is observed during adaptation to hypobaric hypoxia in many organs, including the brain [34,35] and this is most pronounced in the cortex, striatum, and hippocampus [36].

This neovascularization is explained by the activation of the hypoxia-inducible transcription factor (HIF-1). The factor was discovered in the early 90s, it functions as the main regulator of oxygen homeostasis, with the help of which the body, responding to tissue hypoxia, controls the expression of proteins responsible for the mechanism of oxygen delivery to the cell, i.e. regulates the adaptive responses of the cell to changes in tissue oxygenation [37]. Currently, more than 60 direct target genes have been identified for HIF-1. All of them contribute to the improvement of oxygen delivery (erythropoiesis, angiogenesis), metabolic adaptation (glucose transport, increased glycolytic ATP production, ion transport) and cell proliferation. Products of HIF1-regulated target genes act at different functional levels. The end result of this activation is an increase in the flow of O_2 into the cell [38].

In addition to HIF, other transcription factors that are sensitive to hypoxia have recently been discovered, such as metal transcription factor-1 (MTF1), nuclear factor kB (nuclear factor - NF-kB), c-Fos and c-Jun etc. [39].

Structural changes also take place in the central nervous system. The biosynthesis of nucleic acids and protein is activated in neurons and glial cells of the brain, hypertrophy of these neurons and an increase in the activity of enzymes and the number of mitochondria are

observed. This activation of the synthesis of nucleic acids and protein is most pronounced in the cerebral cortex, where the RNA concentration increases by 50%, and protein synthesis doubles. After adaptation to hypoxia, electron microscopy of the cat's somatosensory cortex resulted in an increase in the density of spines of the pyramidal neurons dendrites, complication of the spine apparatus, an increase in the length of active synaptic contacts and the electron density of the matrix areas of the neuronal cytoplasm [20]. These structural changes are manifested by the improvement of the functioning of the central nervous system, primarily conditioned reflex activity: there is an acceleration in the development and an increase in the degree of safety of conditioned reflexes. At the same time, the behavior of animals in conflict situations changes: for example, rats acquire the ability to carry out a vital drinking reflex with the same strength of electrical pain stimulation that previously forced them to move away from the drinking bowl. In adapted rats, resistance to the epileptogenic action of a strong sound stimulus increases and, accordingly, "audiogenic epilepsy" disappears [11].

Analysis of electroencephalograms recorded during breathing with a gas hypoxic mixture with 10% oxygen content (urgent adaptation) revealed moderate generalized changes characterized as slow wave-like inhibition. During long-term adaptation to hypoxia, a stimulating effect of a gas hypoxic mixture with 10% oxygen content on the cerebral cortex is described which is manifested by the activation of the central nervous system [40]. In an experiment with electrodes implanted into the brain of monkeys was shown that the frontal cortex, hippocampus, and hypothalamus are the structures most sensitive to a decrease in oxygen [40]. It should be assumed that the named formations are the zones of application of hypoxic effects in the brain. Considering that the cortex and the limbic system are the highest links of the central nervous system, organizing responses to emotional impact, it is possible to substantiate the positive effect of intermittent normobaric hypoxia on psychoemotional responses of an individual. After a long-term periodic adaptation to a lack of oxygen in extreme conditions, the leveling of differences in the thresholds of aggressiveness in the groups with low and high resistance to hypoxia was revealed. Improved task performance was noted in highly resistant rats. In low-resistance, the most pronounced and long-term changes in the electroencephalogram of the neocortex and ancient brain were observed [41].

Thus, the functional capabilities of the brain increase, which is manifested by an increase in mental performance, an improvement in the processes of information transfer from short-term memory to long-term memory, and an increase in the brain's resistance to the effects of extreme factors (overwork, epileptogens, etc.). In addition, adaptation to hypoxia activates stress-limiting brain systems (GABAergic, serotonergic, endogenous opioid peptide systems), which protects the body from damaging factors of various etiologies [42].

In the low-frequency impulse-hypoxic (LFI) mode of adaptation in the nervous tissue, a number of physiological processes, different in speed and energy intensity, are activated, including the processes of energy production and energy consumption in nerve cells. The energy production of neurons *in vivo* can be judged by the dynamics of oxygen tension (PO_2) and bioelectric potentials are indicators of energy consumption: for neurons, this is impulse electrical activity (IEA), and for cerebral cortex, this is the amplitude (σ) of an electrocorticogram (ECoG). Under the influence of LFI sessions in neurons and nervous tissue of the sensorimotor zone of the cerebral cortex of animals, all functional algorithms (PO_2, IEA, σ) acquired a stable orientation, providing a significant preponderance of energy production over energy consumption. This is supported by the fact that in the nerve cells of adapted animals the level of PO_2 at an "altitude" of 10 km remains 2.13 times higher than in the control, and the level of energy consumption in the cells (according to IEA) decreases 2.05 times. On the whole, energy consumption (in σ) for the nervous tissue decreases by 8.6 times. As a result, the reliability of the oxygen homeostasis of neurons increases, which provides adapted animals with greater survival in conditions of deep hypoxia (10 km "altitude") [43].

When adapting to hypoxia, the synthesis of melatonin is stimulated. This effect is associated with structural changes in the pineal gland, which is the main source of melatonin [44]. It is known that melatonin is highly effective in limiting oxidative damage to the central nervous system, which is associated with its ability to act as an indirect antioxidant. In addition, melatonin stimulates various antioxidant enzymes [45] and is able to protect neurons due to its antiamyloidogenic properties [46].

Under the influence of long-term adaptation to periodic hypoxia, 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. This is

important when restoring blood flow when the risk of reperfusion injury is high. With a decrease in the intensity of oxidative processes, a more efficient work of the respiratory chain was noted - the "paradoxical effect" of adaptation to hypoxia [47].

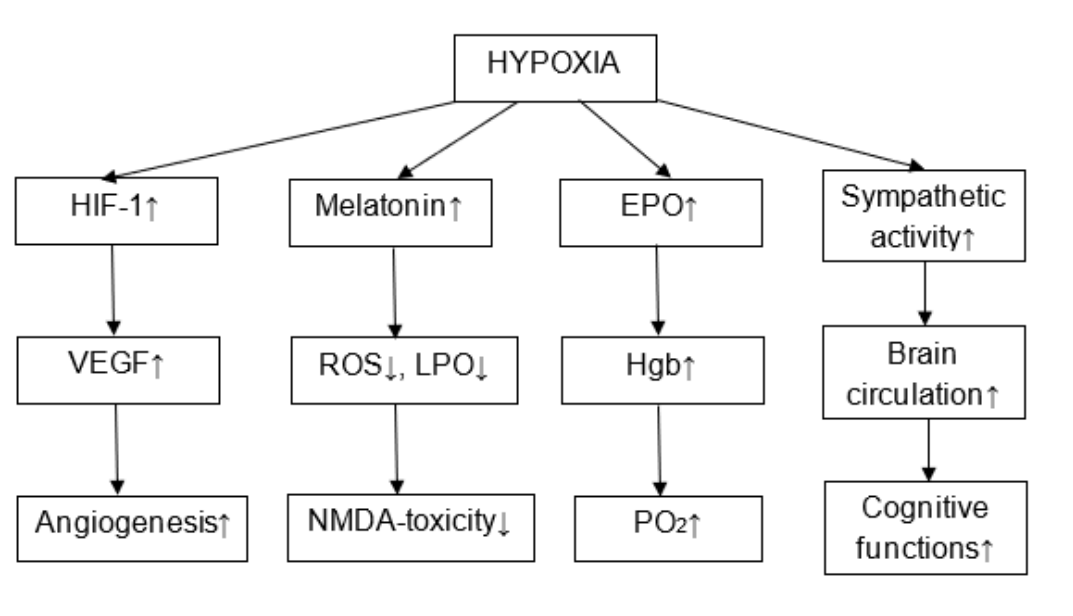
It has been established that the body's response to a single hypoxic training performed in the modes of moderate (10% O_2) hypobaric, normobaric and interval hypoxia develops according to the type of preconditioning. The mechanisms responsible for the formation of urgent adaptation are activated during the hypoxic period. The presence of periodic oxygenation not only delays, but also inhibits this process. However, during the course of hypoxic training, oxygenated intervals weaken the effect of hypoxia and prevent the possibility of an overdose of the irritating factor, i.e. perform a regulatory, normalizing role. Therefore, hypoxic therapy in the mode of interval hypoxia optimizes the conditions necessary for the formation of long-term adaptation [48].

Preconditioning using triple moderate hypobaric hypoxia - hypoxic preconditioning (HP) - increases the tolerance of vulnerable brain neurons to severe hypoxia and other damaging factors. Using immunocytochemistry methods, it was revealed that GP increases immunoreactivity to NF-kB (nuclear factor kappa B) and phosphorylated CREB (c-AMP response element binding protein) in CA1-CA4 fields of the hippocampus and dentate gyrus, and also promotes an increase in the expression of these transcription factors in the hippocampus of preconditioned rats 3 - 24 hours after severe hypobaric hypoxia. The data indicate the involvement of NF-kB and CREB in the mechanisms of formation of brain tolerance, activated by HP [39].

Molecular mechanisms providing neuroprotection during hypoxic exposure include the induction of antioxidants, including mitochondrial manganese-dependent superoxide dismutase (MnSOD). Previously determined that the content of Mn-SOD in hippocampal neurons slightly increases by the 3rd hour after severe hypobaric hypoxia (SHH) [39]. Preconditioning with three sessions of moderate hypobaric hypoxia significantly increased the expression of Mn-SOD in the CA2 and CA3 regions of the hippocampus, but not in CA1 and DG, as compared with non-preconditioned animals. An immunocytochemical study of the intrinsic effect of HP on the expression of Mn-SOD in the rat hippocampus was carried out. It shown that by 24h after three sessions of HP (that is, by the onset of SHH action), immunoreactivity to Mn-SOD was increased in CA1 and DG, but not in CA2 and CA3. Thus, the effect of preconditioning on the expression of Mn-SOD after triglycerides manifests itself in those areas of the hippocampus, in which the HP-effect does not in itself increase the expression of this protein. Consequently, the neuroprotective effect of preconditioning in the early stages after SHH is associated not with the accumulation of Mn-SOD during preconditioning, but with the modification of the reaction itself to severe hypoxia [49].

In an organism adapted to hypoxia, a restructuring of the sympathoadrenal system occurs, which is characterized by hypertrophy of sympathetic neurons, an increase in the synthesis of catecholamines and stores of catecholamines in the adrenal glands, as well as an increase in adrenergic reactivity of the heart [50]. Thus, there is an increase in the reserve capacity of the sympathetic nervous system. It was shown that the course of interval hypoxic training also led to an increase in the power of the mechanisms of autonomic regulation of heart functions at rest due to an increase in the activity of the parasympathetic link of the autonomic nervous system, and also caused optimizing effects on the degree of shifts in the indicators of heart rate variability (HRV) during simulated acute hypoxia. Hypoxic preconditioning promoted an increase in the body's resistance to the conditions of simulated acute hypoxia, which manifested itself in a less pronounced degree of hemoglobin desaturation and a lower increase in heart rate. It was found that the training effects of the course of interval hypoxic training are more pronounced in the group of persons with initially low resistance to the hypoxic factor in comparison with the subjects resistant to acute hypoxia [51].

The previously described mechanisms are shown in the figure.



Figures: *The main mechanisms of the adaptation to hypoxia in the brain, where HIF-1: Hypoxic Inducible Factor-1; VEGF: Vascular Endothelial Growth Factor; ROS: Reactive Oxygen Species; LPO: Lipid Peroxidation; NMDA: N-Methyl-D-Aspartate; EPO: Erythropoietin; Hgb: Hemoglobin; PO2: Oxygen Tension.*

Conclusion

Thus, adaptation to hypoxia has a significant effect on the central nervous system, central hemodynamics, blood microcirculation in various organs, oxygen metabolism, free radical oxidation of lipids, the main enzymes of detoxification systems and immunity. At the same time, compensatory reactions during hypoxic therapy are mainly aimed at:

1. Reducing arterial hypoxemia and maintaining the rate of oxygen supply to the lungs and alveoli at a level close to normoxic, by increasing the minute volume of respiration, increasing the proportion of alveolar ventilation, increasing the diffusion capacity of the lungs, reducing blood shunting in the lungs;

2. Increasing the rate of mass transfer of oxygen by arterial blood from the lungs to tissues by increasing the oxygen capacity of the blood and volumetric blood flow;

3. Providing cells with the necessary amount of oxygen by increasing blood microcirculation in tissues, shortening the distance of oxygen diffusion from the blood of microvessels into cells and increasing oxygen reserves due to an increase in the content of myoglobin in muscles;

4. Increasing the ability to utilize oxygen by increasing the number of mitochondria, their respiratory ensembles, the activity of respiratory enzymes and the antioxidant system.

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