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Hypoxic Conditioning as a Stimulus for the Formation of Hypoxic Tolerance in the Brain

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This review addresses the problem of moderate hypoxic exposure as a natural, non-drug stimulus which activates the mechanisms forming hypoxic tolerance in the brain. The history and current level of research into this phenomenon are highlighted, and the conditions in which hypoxic conditioning has neuroprotective efficacy as preventive (preconditioning) and corrective (postconditioning) effects are considered. Physiological and molecular-cellular mechanisms of pre- and post-conditioning are discussed. Particular attention is paid to our own research on cerebral conditioning using mild hypobaric hypoxia.

Keywords: hypoxia, ischemia, hypoxic tolerance, preconditioning, postconditioning, hypobaric hypoxia, brain.

Abbreviations: PreC – preconditioning; PostC – postconditioning; AMPK – 5'-AMP-activated protein kinase; ROS – reactive oxygen species; HIF-1α – hypoxia-induced factor 1α; RI – remote ischemia; PHB – prohibitin; NMDA – N-methyl-D-aspartate; NMDAR – N-methyl-D-aspartate receptors; AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DHPG – (*S*)-3,5-dihydroxy-phenylglycine; OGD – oxygen-glucose deprivation; BDNF – brain-derived trophic factor; CREB – cAMP-responsive element binding protein; BBB – blood–brain barrier; MHH – moderate hypobaric hypoxia; SHH – severe hypobaric hypoxia; PTSD – post-traumatic stress disorder; HPAS – hypothalamic-pituitary-adrenal system.

Introduction. Hypoxia is a potentially pathogenic state of the body leading to cardiovascular and neurological disorders which consistently occupy first place in prevalence among the factors causing disability and mortality. Regardless of the reasons for the occurrence of hypoxic conditions in the body, cerebral neurons have extreme vulnerability to their harmful effects. Major tasks in clinical physiology include identification of the mechanisms of damage to the central nervous system occurring during or after hypoxia/ischemia and the search for new ways to increase the hypoxic tolerance of the brain.

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The conventional approach to countering hypoxic brain damage consists of developing and employing medications (nootropics, neuroprotectors, antihypoxants, neurotrophins, etc.). However, it is important to recognize that the molecular mechanisms of action of many existing drugs are still insufficiently understood, the efficacy of their actions is not always high, and side effects can initiate additional pathological processes.

Another approach is provided by use of non-drug stimulation of endogenous, evolutionarily acquired, and genetically fixed intracellular defense mechanisms. Since the end of the last century, the efficacy of such stimulation and its molecular mechanisms have been intensively studied in many scientific centers. Most studies address the task of deciphering the phenomenon of moderate sublethal hypoxic or ischemic effects as a "natural" trigger of the mechanisms of cerebral tolerance to the pathogenic consequences of severe episodes of ischemia. The experimental studies and reviews cited here address the mechanisms and optimal parameters of adaptive hypoxic or ischemic stimuli (nature, dose, time window, multiplicity, etc.). Variants of both their preventive application (preconditioning) and corrective (postconditioning) are considered, the latter preventing the further development of already ongoing pathogenetic processes.

Cerebral Tolerance to Hypoxia/Ischemia. At the beginning of the century, the work of Ulrich Dirnagl and colleagues formulated an important hypothesis – that vir-

tually any potentially harmful, stressful action on the body, if it does not reach the threshold of damage in its intensity, can activate endogenous defense mechanisms in the organ and individual tissues and reduce the pathogenicity of subsequent, stronger harmful effects [46]. This hypothesis was soon supplemented by the assertion that adaptation to such "threatening attacks" is apparent not only at the organ or tissue levels, but also at the cellular, subcellular, and possibly gene levels [54].

The concept of the potential tolerance of excitable tissues to harmful effects, the mechanisms of which can be "switched on" by stressful stimuli of moderate strength, was formed on the basis of pioneering studies in the late 20th century, which demonstrated the phenomenon of ischemic tolerance initiated by an ischemic stimulus, first in relation to the heart [82] and, soon after, the brain [50, 65, 67, 81]. Our in vivo and in vitro studies revealed the phenomenon of cerebral tolerance to harmful long-term anoxia induced by a preventive short-term anoxic stimulus [20].

The ability to express hypoxic or ischemic tolerance as a result of moderate (sublethal) effects of the same nature has now been found in various tissues in a variety of vertebrate species, including humans. This ability is based on a set of adaptive "antihypoxic" genes formed by evolution, which in some species have constitutive activity associated with seasonality or habitat change [86], while in others they are expressed under the stressful conditions of metabolic disorders. It should be emphasized that the impacts of "awakening" hypoxic tolerance of the brain are particularly effective when presented in the form of more or less long series, alternating with periods of normoxia or hyperoxia. Many variants of this kind of "intermittent" stimulation of endogenous neuroprotective mechanisms have been widely developed in modern medicine within the framework of the technology of *intermittent hypoxia training* [97].

Most experimental models (mainly in rodents) initially generate tolerance using anticipatory stimuli. This led to introduction of the term *preconditioning* (PreC). Highly detailed in vivo and ex vivo experimental models have been developed, demonstrating the induction of hypoxic/ischemic tolerance of the brain as a whole or its individual parts by short-term global or focal ischemia, anoxia, normo- and hypobaric hypoxia, and intermittent hypoxia/reoxygenation. As the clinical use of PreC is not appropriate in cases of sudden ("unplanned") ischemic attack or brain injury, experimental protocols have been developed in which hypoxic or ischemic tolerance stimuli are used after a severe ischemic incident in order to reduce its pathological consequences. These models use the term *postconditioning* (PostC). In clinical practice, hypoxic/ischemic tolerance of the heart or brain can also be achieved either in a planned manner as PreC, for example, before surgical intervention accompanied by temporary ischemia, or as PostC on the background of the developing adverse consequences of such an intervention [45].

Hypoxic or ischemic PreC increases the resistance of nerve cells not only to subsequent severe hypoxia, but also to harmful effects of different nature, particularly oxidative stress [72], the actions of excitotoxins [47], and pathogenic psychoemotional stress [16]. Furthermore, our studies showed that single sublethal episodes of anoxia [8] and repeated moderate hypobaric hypoxia [3] have geroprotective effects, stimulating weakened cognitive functions in elderly monkeys.

These and many other data allow us to regard ischemic or hypoxic PreC as a universal stimulus for adapting nervous tissue to adverse factors of various types. In addition, the fact that cerebral tolerance can be induced, as noted above, by factors other than hypoxic PreC, forms views regarding the molecular basis of this so-called cross-tolerance of nervous tissue [102].

On the other hand, a number of in vivo and in vitro studies have shown that a variety of (not only hypoxic) effects producing metabolic stress can have a neuroprotective modality. Cerebral tolerance to severe ischemia and other physical and chemical pathogenic factors can be initiated, in particular, by lipopolysaccharides [114], hyperoxia [117], hypothermia [122], hyperthermia [37], epidural electrical stimulation [62], inhalation anesthetics [68], application of weak doses of kainic acid, glutamate, or NMDA [109, 73], etc.

Neuroprotective Effects of Hypoxic or Ischemic Preconditioning. Hypoxic PreC can induce the neuroprotective effect by triggering a number of stepwise or parallel protective mechanisms in different tissues and cell types. These include increased vascular regulation, suppression of glutamate-mediated excitotoxicity, activation of anti-apoptotic and antioxidant signaling pathways, stimulation of cell proliferation, and many others [48].

Studies reported in the 1990s by Japanese authors demonstrated the first use of a combination of transient (2 min) and longer-lasting harmful (5 min) ischemia in Mongolian gerbils. The latter caused delayed neuronal death in hippocampal field CA1, this being the most vulnerable area of the brain. However, when preceded by a brief PreC ischemia, a distinct protective effect was observed – the number of surviving neurons increased significantly. A single episode of ischemic PreC only partially reduced structural damage to cells in the hippocampus, neocortex, and striatum caused by severe ischemia, while two episodes of PreC provided neurons with a much higher level of protection [67, 81]. Ischemic PreC effects were then found in a number of experimental models in vivo and in vitro and in all vulnerable areas of the brain. For example, ischemia for 3 min reduced the extent of infarct damage due to subsequent 60-min focal ischemia of the rat cerebral cortex [88]; 6-min preventive ischemia significantly reduced the number of mouse forebrain cells dying after 20 min of severe ischemia [119]. Our experiments on cats in vivo [21, 31] and rat piriform cortex slices in vitro [22] showed that a rapid neuroprotective effect of anoxic PreC required a cer-

tain duration of exposure (1.5–2 min) and a particular time between the PreC stimulus and the severe harmful anoxia (60–90 min). Neuroprotection did not develop when these time periods were reduced.

There has been a recent increase in interest in a convenient and effective model of PreC using in vivo remote ischemia (RI), for example, by transient periodic application of a tourniquet to a patient's arm [103]. Many clinical variants of RI have been developed, with different durations and frequencies of ischemia of remote organs. There is also a distinction between immediate and delayed preconditioning RI, i.e., 1–2 hours or 1–2 days before cerebral ischemia respectively. Finally, RI can be created in the form of postconditioning (immediate or delayed) or even *during* severe cerebral ischemia, in this case as periconditioning [123].

The amount of evidence for the neuroprotective potential of moderate doses of hypoxia (ischemia) is constantly growing and leads to the conclusion that at least two conditions are required for the formation of hypoxic or ischemic cerebral tolerance using hypoxic or ischemic PreC: an optimal intensity of the PreC stimulus and a particular time window within which it is effective. It was initially believed that the PreC stimulus in model experiments should be sufficiently strong, reaching a "sublethal" intensity. However, this approach seems risky in medicine and translational studies were aimed at the possibility of achieving the optimal intensity of hypoxic PreC not with a single "subletheal" dose of hypoxia, but with a series of moderate hypoxic episodes. Use of this method of intermittent – or interval – hypoxia, as already noted above, revealed additional conditions for the development of the neuroprotective efficacy of PreC, namely, the duration and intensity of each hypoxic PreC session, their number, the frequency of repetition, etc.

This led to the development of effective approaches to stimulating hypoxic tolerance in humans by repeated moderate hypoxia. One protocol consisted of normobaric interval hypoxia, based on the studies of Kolchinskaya et al., as well as the Russian classic studies reported by Chizhov and Strelkov [33], who developed the world's first hypoxicators for breathing with hypoxic gas mixtures (the *Mountain Air* system) or by rebreathing (Strelkov's hypoxicator, *Vershina*). In the early 2000s, guidelines for doctors were written and a series of hypoxicators for medical use was developed [15, 32].

Sequence of Phenomena in the Formation of Brain Tolerance due to Ischemic or Hypoxic Preconditioning. Despite more than 20 years of research on the mechanisms of formation of hypoxic/ischemic tolerance of the brain using hypoxic or ischemic conditioning, there is still a lack of clarity regarding its earliest triggering mechanisms. The subcellular and molecular systems that directly respond to a decrease in oxygen tension, i.e., "hypoxic sensors," must clearly be in first place in the chain of events initiated by hypoxic conditioning and leading to the development of hypoxic (ischemic) tolerance of the brain as a whole or its individual neuronal populations. These systems activate subsequent links in the chain, which include early (triggering) and late stages of the formation of cerebral tolerance to more severe hypoxic/ischemic episodes which might occur.

Hypoxic sensors and trigger processes of hypoxic PreC. *Mitochondria*. The primary sensor of any form of hypoxia at the subcellular level is mitochondria [41]. During the first tens of seconds of systemic hypoxia or ischemia, the limited oxygen supply to the mitochondrial oxidative phosphorylation system leads to a reduction in ATP production, which reduces the energy supplies to a number of endergonic processes which control cellular homeostasis and activate the corresponding compensatory reactions.

When the balance is shifted from ATP to AMP, the sensitivity of 5'-adenosine monophosphate-activated protein kinase (AMPK) to phosphorylation increases, AMPK being the main metabolic sensor within cells. In particular, activated AMPK stimulates phosphofructokinase, increasing glycolytic ATP production; it activates the transcription factor FOXO3, which can stimulate the expression of antioxidant genes, and it indirectly activates energy-producing autophagy. These and many other effects of AMPK suggest that this kinase is an important trigger in PreC-mediated neuroprotection [59].

A moderate increase in the production of reactive oxygen species (ROS) is seen as a significant element of the mitochondrial response to hypoxia [90]. This process has several implications. In vitro experiments have established that ATP-dependent potassium channels in the inner mitochondrial membrane are activated in PreC on the background of moderate accumulation of ROS and that the use of appropriate blockers suppresses the neuroprotective efficacy of PreC [52]. Opening of these channels presumably accelerates electron transport in the respiratory chain, thus increasing ATP production [74, 76]. In addition, increases in ROS levels have been shown to suppress prolyl hydroxylase activity, which stabilizes hypoxia-induced factor 1-alpha (HIF-1α) [42] and ensures the expression of neuroprotective products, particularly erythropoietin [75].

Relatively recent studies have identified and investigated NO-dependent mechanisms initiating cerebral hypoxic tolerance. Previous studies have shown that NO produced by inducible NO synthase, despite its known detrimental effect in the late stages of ischemic brain damage, can, under moderate hypoxic exposure, promote the development of tolerance to ischemia by protecting mitochondrial functions, though the mechanism of this effect remained unknown [40]. Studies using an in vivo model with PreC by 2 min of cerebral ischemia in the Mongolian gerbil showed that tolerance to subsequent 10-min ischemia develops in conditions of the expression of endothelial NO synthase mediated by the PI3K/Akt signaling pathway [55]. Later research found that prohibitin (PHB), a protein of the chaperone family, has a neuroprotective role; this substance is located on the inner mitochondrial membrane and exhibits an activity criti-

cal for maintaining oxidative phosphorylation in conditions of cellular stress [35]. The recent hypothesis that there is a mechanical link between NO and PHB in neuroprotection has received support. Experiments using hypoxic PreC in neuron cultures showed that moderate NO accumulation activates PHB via S-nitrosylation, which creates a neuroprotective effect against ischemic brain damage [89].

The hypoxic signal is perceived not only by neuronal mitochondria, but also by mitochondria in astrocytes. There are more astrocytes than neurons in the brain, and they are regarded as specialized sensors of hypoxia. Even in conditions of a physiological decrease in pO_2, astrocytes release vasoactive substances which control local cerebral microcirculation [38]. In vivo and in vitro experiments have convincingly demonstrated the mechanism of the rapid response of astroglia to the slightest decreases in pO_2 in the cerebral parenchyma [79]. This mechanism is triggered by depolarization of astrocyte mitochondria and increased production of free radicals, which leads to the activation of phospholipase C and IP3-mediated release of Ca^{2+} from intracellular depots. One of the many consequences of moderate accumulation of intracellular Ca^{2+} is activation of vesicular release of ATP into the extracellular medium and blood. In this situation, the systemic reaction is apparent as stimulation of external respiration. It has been suggested that this independent mechanism of increased external respiration is more sensitive to hypoxia than the mechanisms of activation of chemoreceptor cells in the carotid bodies [36]. Recent work found that moderate ATP release from cerebral neurons in ischemic PreC in vitro was accompanied by activation of astrocytic, but not microglial, purinergic P2X7 receptors. The molecular mechanism of their selective sensitization to low extracellular ATP levels in conditions of PreC was identified [57]. Activation of these receptors initiates signaling pathways leading to a stable up-regulation of HIF-1, accompanied by known gene-dependent proadaptive processes [58].

Prolyl hydroxylase. Simultaneously with the triggering of mitochondrial reactions during hypoxia, cytosolic process are also triggered; here, enzymes of the prolyl hydroxylase family can be regarded as the primary sensor, as their activity decreases with decreases in pO_2. In normoxia, the regulatory α subunit of HIF-1α undergoes constant degradation via prolyl hydroxylation and a subsequent cascade of biochemical reactions [101]. Prolyl hydroxylase is inactivated in conditions of oxygen deficiency, leading to stabilization of HIF-1α, its heterodimerization with the HIF-1β subunit, and activation of HIF-1 transcription factor [56]. This mechanism is part of the early stage of the hypoxic response, but its powerful neuroprotective effect is apparent at the later stages of the formation of hypoxic tolerance (see below).

Glutamatergic transmission. Experiments on living slices of the mouse somatosensory cortex using the patch clamp technique demonstrated convincingly that local depolarization of the postsynaptic membrane and a sharp increase in the calcium concentration directly below it occur within seconds of the onset of hypoxic incubation. An increase in the EPSP frequency and depletion of presynaptic glutamate pools are also seen. Interestingly, these events develop long before the drop in total membrane potential on neurons. The authors took the view that the earliest response of cortical neurons to acute hypoxia consists of the opening of calcium channels of ionotropic glutamate receptors [91], which is likely to trigger further rapid intracellular events in the early phase of PreC.

Ionotropic glutamate receptors, primarily N-methyl-D-aspartate (NMDA)-excited receptors, have traditionally received extensive attention in studies of both pro-adaptive and pathogenic glutamate-mediated mechanisms of neuronal hypoxic reactions. In vitro experiments with application of different doses of glutamate or NMDA have shown that low agonist concentrations stimulate predominantly those types of NMDA receptors (NMDAR) whose tetraheteromeric structure includes one or two NR2A subunits in place of NR2B [71, 77]. The C-terminal region of the NR2A subunit supports activation of the key signaling pathway PI3K/Akt, which mobilizes a number of intracellular survival mechanisms through CREB-mediated gene expression. High glutamate doses produce arousal of NMDA receptors including two NR2B subunits, thus triggering classical excitotoxicity mechanisms, initiating a chain of events leading to neuron death [77, 105, 118]. Our previous studies using rat cerebral cortex slices showed that application of the agonists of different glutamate receptors – L-glutamate, NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and (S)-3,5-dihydroxyphenyl glycine (DHPG) – causes significant increases in intracellular Ca^{2+}, though the use of PreC in these animals, with three episodes of moderate hypobaric hypoxia, significantly reduced the calcium response to the same doses of agonists and completely eliminated the glutamate-dependent calcium overload caused by application of anoxia to the slices [100]. Recent studies in hippocampal slices showed that excitotoxic doses of AMPAR and NMDAR agonists mimicking calcium overload in an oxygen-glucose deprivation (OGD) model lost their pathogenic effect when NMDAR or metabotropic glutamate receptors mGluRI were preemptively stimulated by low concentrations of their agonists [109]. Moreover, application of these previously known in vitro chemical PreC methods to neurons has been demonstrated to suppress AMPA-mediated excitotoxicity by various mechanisms. While stimulation of NMDAR causes internalization of AMPAR, activation of mGluRI suppresses glutamate transmission via activation of the endocannabinoid system [53].

Studies of the involvement of NMDAR in neuroprotective processes found that moderate activation of these receptors leads to a rapid release of brain-derived neurotrophic factor (BDNF), activation of its receptor TrkB, and triggering of the corresponding signaling [60]. Both NMDAR and TrkB receptors activate expression of the nuclear transcription fac-

tor kappaB (NF-κB) in neurons, which, with further development of hypoxic tolerance mechanisms, protects hippocampal neurons from apoptosis. NMDAR-mediated increases in intracellular calcium levels activate the transcription factor cAMP-responsive element binding protein (CREB), glycogen synthase kinase 3β (GSK3β), phosphatidylinositol-3-kinase (PI3K), and protein kinase B (Akt). Interestingly, these kinases, which are involved in neuroprotective signaling pathways for the further development of neuronal hypoxic tolerance, can only be stimulated by low doses of NMDA [76] or, probably, by moderate hypoxic stimulation in PreC. We ran an immunocytochemical analysis of brain sections from rats surviving 1–3 sessions of hypobaric PreC. The results showed that each series of hypobaric PreC increased the level of Akt phosphorylation, while severe hypobaric hypoxia did not produce any such effect [2].

Along with neuronal mechanisms, the role of the capillary/glial/neuronal system in the induction of cerebral hypoxic tolerance is discussed. A few studies have noted the possibility that the cerebral endothelium is a site of primary perception of the conditioning hypoxic stimulus. These consider possible mechanisms of protection of the blood–brain barrier (BBB), limiting the intake of potential neurotoxic compounds from the blood and exacerbating ischemic brain damage. Evidence is also provided on the release of signaling factors by the endothelium, these compounds mediating neuroprotective functions [85, 120].

Since the beginning of the current century, there has been discussion of the idea that the process forming the neuroprotective effects of both hypoxic and ischemic PreC includes two successive stages (phases): an early stage with induction of short-term tolerance and a late stage with expression of stable tolerance [for reviews see 23, 66, 84, 104, 106, 107]. The early phase includes the rapid mechanisms described above, which are triggered by sensory and trigger systems within tens of seconds and exert neuroprotective effects within tens of minutes or several hours after PreC treatments. These include mechanisms activating protein kinases and proteases, along with post-translational modifications of ion channel proteins, receptors, and redox-sensitive proteins. This phase is largely due to modification of neuronal intracellular signal transduction processes [2, 16, 24], activation of succinate-mediated signaling pathways [78], and changes in the activity of pro- and antioxidant systems [49, 87, 90]. The late phase is characterized by the production of de novo synthesized proteins which activate many protective functions, both in neurons themselves and in the surrounding brain tissues, as well as in the whole organism. See below for further detail.

As noted above, many biochemical, physical, pharmacological, and other non-hypoxic effects of PreC actions increasing the brain's tolerance to hypoxia have now been identified. Although this topic is not within the remit of this review, brief coverage seems appropriate if we suppose that the final components of the neuroprotective mechanisms induced by moderate harmful actions of any nature and common in type [54]. PreC stimuli naturally require different sensors at the tissue, cellular, and subcellular levels, as well as specific trigger elements for the formation of tolerance. Below are some examples.

Lipopolysaccharides, by binding to plasma membrane TLR receptors, have been shown to activate signaling pathways for the expression of anti-inflammatory genes, thus reducing the proinflammatory effect of severe ischemia [114].

Hyperthermia initiates the production of heat shock stress protein HSP70 in the bodies and synaptic endings of cerebral neurons [37]. In conditions of ischemia/reperfusion, these chaperones correct the denaturation of many signaling proteins and block the production and spread of proapoptotic factors, and they also stimulate the transcription of anti-inflammatory genes [64].

The triggering target of the respiratory anesthetic isoflurane is likely to be ATP-dependent mitochondrial potassium channels [68], whose opening prevents ischemic calcium overload of mitochondria and the subsequent chain of known destructive consequences leading to apoptosis.

The anti-ischemic PreC effect is exerted by stimulation of NMDAR with low doses of agonists [73, 109]. A procognitive effect of stimulation of α2A adrenoreceptors has also been demonstrated in rats surviving severe hypobaric hypoxia [63].

The neuroprotective potential of opioid receptor agonists, which are widespread in the neocortex and hippocampus, has been demonstrated in in vivo and in vitro models of ischemia. In particular, morphine has been shown to activate PKC-mediated anti-apoptotic signaling [128]. Stimulation of δ-opioid receptors by enkephalin leads to activation of AMPK, a neuroprotective signaling pathway that enhances autophagy [69].

An important effect of neuroprotective PreC stimulation is that of countering the increase in BBB permeability occurring in severe forms of hypoxia or ischemia/reperfusion [84]. Among the effects able to reduce BBB permeability are certain modes of hypercapnic ventilation (permissive hypercapnia) used in medicine for traumatic brain injury [121]. Neurosurgical statistics on hemorrhagic stroke show that patients with obstructive sleep apnea have significantly greater resistance to the adverse consequences of subarachnoid hemorrhage than patients without sleep apnea. This phenomenon is explained by the neuroprotective PreC action of hypercapnia and acidosis [61]. Russian in vitro and in vivo studies have demonstrated the beneficial PreC effect of permissive hypercapnia (especially in combination with intermittent normobaric hypoxia) on the systems controlling BBB functions, acting by increasing the expression of A1-adenosine receptors and mitochondrial K^+ (ATP) channels in astrocytes [110, 111].

Despite the different natures of these non-hypoxic PreC stimuli, the mechanisms by which they form delayed persistent hypoxic brain tolerance are, in all likelihood, similar; they include a limited number of intracellular survival

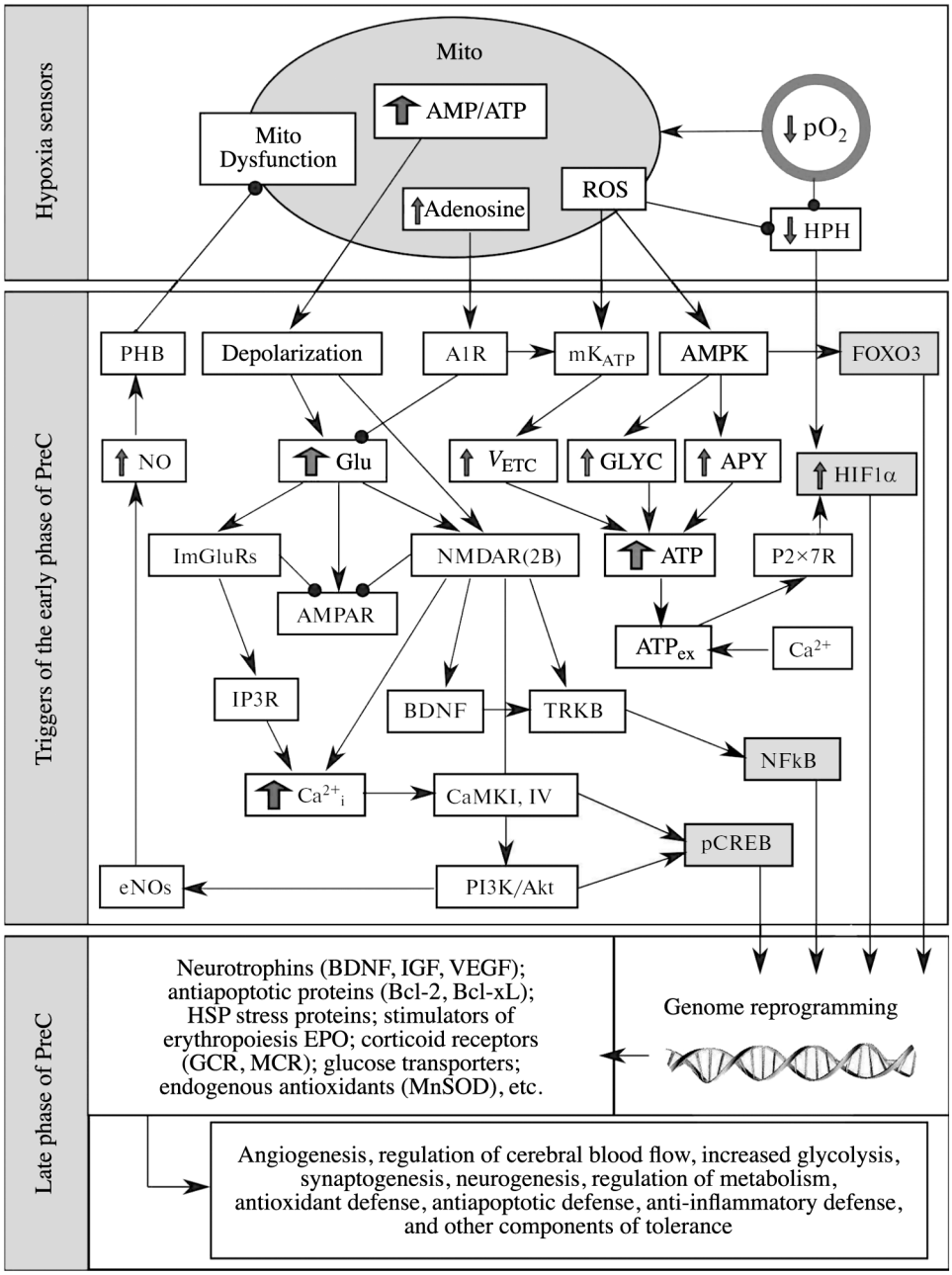

Fig. 1. Perception of conditioning stimuli consisting of moderate hypoxia by brain cells. The scheme shows the main hypoxia sensors, the molecular triggers inducing the mechanisms of the early phase of brain tolerance, and some signaling pathways for the expression of the genome-dependent late phase of the formation of cerebral hypoxic tolerance. Lines with arrows show activatory connections and lines with circles show inhibitory connections. MX – mitochondria; AMP/ATP – adenosine phosphates ratio; ROS – reactive oxygen species; HPH – HIF prolyl hydroxylase; PHB – prohibitin; A1R – adrenoreceptor 1; mK_{ATP} – mitochondrial ATP-potassium channels; AMPK – 5'-adenosine monophosphate-activated protein kinase; FOXO3 – transcription factor Forkhead box O3; NO – nitric oxide; Glu – glutamate; V_{ETC} – speed of the mitochondrial electron transport chain; GLYC – glycolysis; APY – autophagy; HIF1α – transcription factor 1-α induced by hypoxia; mGluRI – group I metabotropic Glu receptor; AMPAR – AMPA glutamate receptor; NMDAR(2B) – NMDA glutamate receptor with a predominance of the NR2B subunit; P2X7R–P2X(7) – ATP purinoreceptor; IP3R – inositol-3-phosphate receptor; BDNF – brain-derived neurotrophic factor; TRKB – tyrosine kinase receptor B of trophic factors (BDNF); ATP_{ex} – extracellular ATP; NFkB – nuclear transcription factor kappa B; CaMKII,IV – Ca^{2+}/calmodulin dependent protein kinases II and IV; eNOS – endothelial NO synthase; PI3K/Akt – signaling pathway mediated by phosphoinositide-3-kinase and protein kinase B; pCREB – phosphorylated cAMP response element binding protein, a transcription factor.

signaling systems. The main processes of formation of hypoxic (ischemic) tolerance of the brain initiated by hypoxic conditioning as described above can be graphically summarized with some simplification (Fig. 1). Here, the emphasis is on the perception and early phase of the cell's response to a conditioning hypoxic stimulus. The processes of the subsequent genome-dependent formation of tolerance are reflected more briefly (Fig. 1).

Expression of persistent tolerance induced by hypoxic PreC. In the late phase, for at least a day, persistent genome-dependent tolerance mechanisms are triggered, providing intracellular plastic rearrangements mediating antihypoxic structural and functional rearrangements of the vital activity of cerebral neurons. The main role in the development of these proadaptive mechanisms is played by transcription factors which, after translocation from the cytosol to the nucleus, regulate target gene promoter and enhancer activity [112]. The key components of the activation of late-acting genes, whose products are involved in the mechanisms of neuronal plasticity and cell survival, include inducible (c-Fos, NGFI-A, HIF-1) and activatory (pCREB, NF-κB) transcription factors. The targets of these are the genes for a number of proadaptive proteins, such as neurotrophins (BDNF, NT3, IGF, VEGF, etc.), anti-apoptotic proteins of the bcl-2 family (Bcl-2, Bcl-xL), erythropoietin, glucocorticoid and mineralocorticoid receptors, glutamate receptors, and stress proteins HSP70 and HSP90, which regulate the folding, refolding, stabilization, activation, and degradation of many proteins in condition of stress, including hypoxic stress [76, 80, 113].

It is interesting that HSP70 and HSP90 display activity linked with HIF-1 at the early stages of hypoxia. Experiments on preconditioning in rats using series of episodes of hypobaric hypoxia of varying severity and duration showed that only a moderate level of severity (equivalent to 5000 m above sea level) and a limited number of daily repetitions (3–8) induced the HIF1α/HSP90-dependent mechanisms of hypoxic tolerance. Smaller and larger PreC doses were less effective [10].

The targets of the main regulator of reactions to hypoxia, HIF-1 transcription factor, consist of several thousand genes whose products are involved in forming adaptive rearrangements in conditions of hypoxia [70]. Studies in our laboratory have shown that an increase in the resistance of brain neurons to severe forms of hypoxia induced by hypoxic PreC is accompanied by immediate activation of factor HIF-1, this being followed by expression of its target genes [19]. The extent of the increase in the expression of the HIF-1α regulatory subunit correlates with the neuroprotective efficacy of PreC [27]. Accumulated data indicate that the HIF-dependent mechanisms of formation of cerebral hypoxic tolerance induced by hypobaric PreC include the expression of EPO and BDNF [99], as well as the main enzyme involved in the pentose phosphate pathway of glucose metabolism, glucose phosphate-6 dehydrogenase [115]. It should be noted that activation of the pentose phosphate pathway in hypoxic conditions is one of the important proadaptive reactions that ensure the functioning of enzymatic antioxidant systems.

In addition, the neuroprotective role of HIF-1 clearly cannot be seen as unconditional. There have recently been reports of adverse effects occurring on activation of HIF-1. In particular, our studies have shown that in vivo blockade of HIF-1 induction by the inhibitor topotecan in conditions of severe hypoxia promotes better survival of hippocampal neurons [116]. A probable mechanism of this effect, associated with HIF-1-induced suppression of the activity of the transcription factor Nrf-2, which regulates the expression of the antioxidant glutathione, has been described [25]. In addition, persistent induction of HIF-1α has been shown to occur in models of pathogenic psychoemotional stress and to accompany the formation of depressive-like states [1]. Thus, the issue of the dual role of this factor in conditions of hypoxic or ischemic PreC requires balanced study.

Discussion the PreC-mediated mechanisms of induction and expression of tolerance of brain neurons to harmful effects requires their probable differences in conditions of application of hypoxic or ischemic PreC stimuli to be taken into account. These mechanisms must clearly have their own specific features. In the case of ischemia, in addition to O_2 deficiency, there is a complex ischemia-related factor that includes not only aglycemia, but also restriction of transport of metabolites within tissues and humoral signaling factors.

Experimental Hypobaric Hypoxia as an Action Producing PreC. In seeking the optimal PreC regimen that provides a fully-fledged neuroprotective effect, a convenient hypobaric hypoxia model was selected in our laboratory. This is a physiologically quite appropriate model, easily controlled, dosed, suitable for studying both harmful and protective preconditioning effects, without surgical intervention and without toxic components.

Presentation of hypobaric hypoxia as an adaptogenic factor that increases the resistance of pilots' bodies to injuries of various etiologies has been used in Russia since the 1930s by Vladimirov and by Sirotinin et al. [7, 28]. Kreps et al. [11] performed experimental studies of elevated resistance to severe hypoxia after animals were kept at a reduced partial pressure of oxygen. Studies of high-mountain acclimation showed that this increased resistance to epileptogenic agents [14] and suppressed the development of bronchial asthma and schizophrenia [29]. These studies are mainly based on the phenomenon of hypoxic acclimation, i.e., adaptation of the body to prolonged moderate hypoxia. Protective mechanisms at the systems level are gradual and are mobilized in stages. Erythropoiesis and angiogenesis are stimulated, glucose utilization is increased, the oxygen transport system is rebuilt, etc. [30]. It should be emphasized that the mechanisms of acclimation are different from the immediate mechanisms of hypoxic tolerance induced by hypoxic/ischemic PreC as described above.

We developed an experimental model of acute hypobaric exposure in the early 2000s. This model is based on presentation to the animal of a limited number of transient episodes of acute sublethal hypoxia in a pressure chamber. Various different hypobaric regimens are used. Severe harmful hypobaric hypoxia (180 mmHg, 3 h) is used as the test exposure, while single or multiple (3–6) episodes of

moderate hypobaric hypoxia (360 mmHg, 2 h, at 24 h intervals) are used as PreC for research into the mechanisms of induced tolerance.

Influence of severe hypobaric hypoxia (SHH) on the brain and the corrective effect of moderate hypobaric hypoxia (MHH). Our researchers found that SHH causes the death of more than 50% of rats, while surviving animals showed significant structural damage to neurons in the areas of the brain most vulnerable to hypoxia (the hippocampus and neocortex), mainly of the apoptotic type. Animals surviving reoxygenation after SHH were found to develop profound impairments to behavior, learning, and memory [4, 26, 34, 93]. The mechanism of the harmful effects of SHH on the brain is very complex and not fully deciphered. In particular, as noted above, HIF-1 signaling has recently been found to have a role in this process. Three episodes of MHH presented 24 hours before exposure to SHH significantly increased both brain tolerance and the resistance of the body as a whole to SHH. Death in response to SHH in preconditioned rats was reduced to 15%, though single-episode MHH had almost no protective effect on survival or structural and functional impairment in rats.

Hormonal mechanisms of MHH-PreC. The adaptive capabilities of the body depend directly on the mode of functioning of the hypothalamic-pituitary-adrenal system (HPAS) and the balanced activity of all its elements. Selye attributed the key role to appropriate activation of the HPAS and its timely inactivation by inhibition by negative feedback [98]. Impairment of HPAS function and its regulation by feedback mechanisms causes the development of maladaptive conditions leading to severe functional disorders of the body, to the point of death [44].

In our research, the dynamics of the functional activity of the HPAS in rats was studied in terms of plasma levels of the main glucocorticoid hormone, corticosterone (the analog of cortisol in humans). Three-episode MHH produced marked activation of the HPAS, with a three-fold increase in the peak corticosterone level (3 h), while single-episode MHH, which was insufficient to generate neuroprotection, induced only a slight increase in the hormone level. Along with an increase in the basal glucocorticoid level, hypoxic PreC significantly modified HPAS reactivity to immobilization stress. Rats with three-episode preconditioning, as compared with controls, showed a sharp increase in HPAS stress reactivity, which was particularly marked in the early stages after the action of the stressor. By 24 h, the corticosterone level returned to baseline, which indicates the normal triggering of regulatory mechanisms by negative feedback. The biphasic dynamic of HPAS was deranged in rats subjected to SHH. The blood corticosterone level in these animals gradually increased to 24 hours post-exposure, indicating impairment to the mechanisms of immediate activation and glucocorticoid inhibition of the HPAS. Three-episode PreC had a marked protective effect, normalizing the phasic nature of the HPAS reaction (activation–inhibition) [17].

The protective effects of PreC by hypobaric hypoxia on the brain are not restricted to the harmful effects of severe hypoxia. In particular, we have demonstrated that such PreC has a restraining effect on the development of anxious-depressive states induced by stress. A significant role in this appears to be played by triggering of the mechanisms of the so-called cross-adaptation as defined by Meerson [13], due to modifications of the hormonal regulation of adaptive processes aimed at effective mobilization of hormone-dependent defense mechanisms. It is important from both the theoretical and practical points of view that the neuroprotective effect of PreC occurs regardless of the modality of the harmful factor presented. It was known from previous work that cerebral cross-tolerance occurs in relation to hypoxia, ischemia, and toxins, i.e., factors whose harmful mechanisms, including oxidative stress, are largely related. Our own studies provided the first demonstration of the efficacy of the protective action of hypobaric cerebral PreC in relation to fundamentally different harmful factors, i.e., psychoemotional and traumatic stress, whose pathogenic effect is based on disorders of systems-based and nonspecific adaptation mechanisms [94, 95]. These studies used an index of resistance in rats conditioned with three sessions of MHH to severe forms of stress (psychoemotional and traumatic) in experimental models based on learned helplessness (a model of depression-like pathology) and stress-restress (a model of post-traumatic stress disorder, PTSD) respectively. The PreC procedure, along with a marked antidepressant effect on behavior, restored normal HPAS stress reactivity. Presentation of short-term immobilization stress (restress) to animals that had previously experienced severe traumatic stress led to the formation of a stable anxiety state in the "stress–restress" model of PTSD. Use of MHH as PreC prevented the development of the anxiety state serving as the analog of PTSD.

Neuroprotective Ischemic/Hypoxic Postconditioning. Postconditioning (PostC) is the presentation of adverse factors of moderate intensity *after* severe harmful effects. The phenomenon of PostC was described relatively recently (in 2003) in an ischemic model in the heart. Presentation of brief episodes of ischemia in the early stages of reperfusion was found to produce significant reductions in the size of the damage zone after infarction and to improve the survival of cardiomyocytes [125]. The protective effect of ischemic PostC on the brain was first described in 2006 in a rat model of focal ischemia [126]. Ischemic PostC with transient episodes of cerebral ischemia alternating with periods of reperfusion was found to lead to a significant decrease in the size of cerebral lesions, the extent of neuroprotection depending on the specific PostC regime, i.e., the frequency and duration of ischemia-reperfusion cycles and the time of onset of PostC, which could be in the early or the delayed period [92]. Despite the fact that the efficacy of ischemic PostC neuroprotection in the brain has been confirmed, this method, according to many researchers and clinicians, has no real clinical prospects due to a

number of drawbacks (surgery, narrow therapeutic window, high likelihood of side effects, etc.). There is therefore a need to seek other PostC methods. We have proposed a new non-drug PostC method using hypobaric hypoxia. In pilot experiments, SHH and the "stress–restress" paradigm were used as harmful factors. PostC was carried out with three sessions of MHH one day after SHH or terminal stress in the PTSD model. PostC consisting of three episodes of MHH was found to produce significant reductions in the volume of posthypoxic structural damage to sensitive brain formations (hippocampal fields CA1–CA4 and the neocortex), to ameliorate SHH-induced behavioral impairments in the open field test and elevated plus maze, and to restore normal activity and the stress reactivity of the HPAS [96]. Hypoxic PostC was found to have a powerful anxiolytic effect in animals undergoing both SHH and psychoemotional traumatic stress in a model of PTSD [18].

The effectiveness of this approach has also been confirmed in studies by other leading laboratories which have investigated the neuroprotective efficacy of our PostC MHH method in their models. In particular, PostC has been shown to produce significant reductions in the volume of ischemic brain damage after hypoxia–ischemia in the early stages of ontogeny [51].

Mechanisms of ischemic and hypoxic PostC. Due to the fact that intensive studies in recent years have convincingly demonstrated the therapeutic potential of various PostC methods, elucidation of the cardioprotective and neuroprotective mechanisms induced by these methods is currently one of the most pressing problems in physiology and medicine. Of all the pathways of PostC, those most studied are the molecular and cellular mechanisms of ischemic PostC of the myocardium, where the leading role is presumptively played by activation of anti-apoptotic processes [108], the expression of HIF-1α and its targets, the EPO gene, etc. [127]. Both in the heart and the brain, ischemic PostC suppresses free radical generation and the initiation of apoptosis [124] and activates intracellular signaling cascades involved in the regulation of cell death/survival (protein kinase C, PI3K/Akt, MAPK), etc. (for review see [12]). These points apply mainly to models of early (or rapid) PostC, when reperfusion is interrupted in the early period (seconds and minutes) after ischemia. From a practical point of view, this method of PostC is not promising in actual clinical practice. Regarding the mechanisms of so-called delayed PostC, which is carried out hours or days after severe ischemia, only fragmentary data are currently available. Suppression of the synthesis and translocation of the pro-apoptotic Bax protein [83, 129], as well as a transient increase in the activity of the antioxidants superoxide dismutase and catalase [43] in rat hippocampal neurons 5 h after ischemic PostC, have been shown. Administration of the protein synthesis blocker cycloheximide almost completely prevented the neuroprotective effect of delayed ischemic PostC in rat hippocampal field CA1 [39], which demonstrates the need for de novo protein synthesis for the neuroprotective effects of PostC to be realized.

In contrast to ischemic PostC, the protective mechanisms of hypoxic PostC, especially in the brain, have received virtually no study. Our pioneering research found that the expression of Bcl-2, BDNF, the α subunit of factor HIF-1, and its transcriptional target erythropoietin in hippocampal and neocortical neurons in rats are activated to varying degrees on presentation of hypobaric hypoxia in the PostC regime. Comparative analysis of expression profiles showed that among the factors studied, HIF-1 clearly played the most important role in the mechanisms of this PostC [6, 7, 115]. The role of HIF-1α and its targets was also confirmed in another model of hypoxic PostC [130]. Along with induction of HIF-1α, activation of antioxidant systems was also demonstrated in our MHH model [51]. Realization of the anxiolytic effect of PostC in the model of poststress pathology was accompanied by stimulation of the production of the neurotrophin BDNF in the hippocampus and neocortex, while no significant changes in the expression of HIF-1α or EPO were detected [9].

On the basis of current data, it can be suggested that the mechanisms of the neuroprotective action of hypoxic PreC and PostC are largely similar, though this point requires further study, as does identification of universal and specific mechanisms for preventing the harmful effects of factors of different natures (hypoxia, psychoemotional stress).

Conclusions. Analysis of the literature indicates that intensive studies are being pursued around the world, using different experimental models to address the influence of the hypoxic factor on the induction of both pathological and adaptive states of the brain. This challenge is relevant and has great practical importance. There is interest in results obtained in the last decade, including our own, using moderate hypobaric hypoxia as pre- and post-conditioning to prevent structural and functional cerebral disorders caused by harmful effects (severe forms of hypoxia and stress), as well as for rehabilitation after these influences. In the near future, it will be possible to develop practical and oriented approaches for medicine and healthcare based on them.

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