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REVIEW

Cerebral Mechanisms of Hypoxic/Ischemic Postconditioning

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Abstract—This review analyzes recent data on mechanisms of cerebral hypoxia and the protective methods of hypoxic and ischemic postconditioning, as well as their interrelationship with the key mechanisms responsible for neuroprotection and neuroplasticity. Upregulation of expression of antiapoptotic factors and neurotrophins and modulation of activity of several protein kinases and transcription factors such as hypoxia-inducible factor-1 (HIF-1) are considered as the most important aspects in the neuroprotective potential of postconditioning. The presented information indicates substantial transformative promise of the noninvasive techniques of hypoxic postconditioning as well as significant similarity between the adaptive pathways activated by various postconditioning methods, which are far from being fully understood.

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Hypoxia is one of the most damaging factors during adverse external and internal influences. It is well known that acute forms of hypoxia suppress neuroplasticity, cause disruptions in cognition and memory, as well as exert a disruptive effect on the neurons of the most susceptible brain structures such as the hippocampus. On the other hand, moderate forms of hypoxia exhibit the opposite effect, and this phenomenon has been used for the development of preventive measures for increasing resistance of the brain to hypoxia (intermittent hypoxic training, hypoxic and ischemic preconditioning) or rehabilitation after damaging action (early, delayed, and distant ischemic postconditioning (IPostC), normobaric and hypobaric hypoxic postconditioning (NBHPostC and HBHPostC, respectively). Currently available information on the cerebral mechanisms of severe brain hypoxia and the protective effects of various types of ischemic (IPostC) and hypoxic (HPostC) postconditioning will be briefly presented, as well as arguments indicating that the noninvasive NBHPostC and HBHPostC approaches should be considered as promising for medical practice.

Abbreviations: BBB, blood–brain barrier; CNS, central nervous system; HBHPostC, hypobaric hypoxic postconditioning; HIF-1, hypoxia-inducible factor 1; HPostC, hypoxic (non-ischemic) postconditioning; IPostC, ischemic postconditioning; LPO, lipid peroxidation; NBHPostC, normobaric hypoxic postconditioning; NMDA-receptor, N-methyl-D-aspartate-binding receptor; PostC, all types of postconditioning; SH, severe (damaging) hypobaric hypoxia.

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HYPOXIA AND MECHANISMS OF ITS ADVERSE EFFECT ON NEUROPLASTICITY

Hypoxia is the state of oxygen deprivation of either the entire organism or its separate organs and tissues. An organism can be found in the state of hypoxia as a result of the effects of external factors, such as for example, being at high altitude, in outer space, or in an inadequately ventilated facility. Hypoxia can also develop as a result of internal unfavorable condition such as clogging/ischemia of blood vessels or anemia. Hypoxia is an important component of pathogenesis of many diseases.

The following types of hypoxia are recognized [1]:

1. Hypoxic hypoxia (hypoxemia). The main symptom – low partial pressure of oxygen in arterial blood and, as a consequence, low oxygen content in the entire organism.

2. Anemic hypoxia (hematic) – hypoxia developing on the deficiency of hemoglobin and/or erythrocytes and normal oxygen pressure in arterial blood.

3. Stagnant hypoxia (circulatory), which develops when enough hemoglobin and normal oxygen pressure are maintained in blood, but the amount of blood reaching tissues does not correspond to the oxygen demand due to, for example, vessel clogging or rupture.

4. Histotoxic hypoxia (hypoxidosis) – develops as a result of disruption of functioning of respiratory chain enzymes and, hence, the oxygen supplied to the tissues cannot be used in oxidative processes.

All types of hypoxia have one common feature – deficiency of oxygen supply causing the development of irreversible changes in vital organs. Ischemic heart disease and stroke are the most widespread diseases associated with hypoxic state, and these occupy the third place in the list of leading causes of death among all diseases after myocardial infarction and oncological diseases. Ischemia is a form of the circulatory hypoxia in which blood supply to the certain tissue or organ is partially or completely blocked. The essential difference in the response of an organism to non-ischemic and ischemic hypoxia lies in the fact that in the first case the blood flow is maintained or significantly increased as well as supply of tissues with substrates and removal or products of oxidative metabolism. The decline of high-energy compounds, acidosis, and other metabolic disruptions occurring during non-ischemic hypoxia intensify not so drastically as in the case of ischemia. Disruption of motor, sensory, and visual reflexes is observed in patients with stroke caused by brain hypoxia/ischemia as well as aphasia and apathia. Neurophysiological disorders can emerge following ischemia (during the reoxygenation period) such as intellectual decline, apraxia, spatial orientation deficit, and memory loss [2].

Hypoxia/ischemia of the brain can be caused not only by stroke, but can also develop due to the other adverse effects such as cardiac arrest, brain embolism, or acute hypotension, especially during surgery. Furthermore, the state of brain hypoxia can emerge because of external adverse factors such as hypobaric hypoxia (plane decompression at high altitude).

Independent of the cause of cerebral hypoxia, the "ischemic cascade" chain of pathobiochemical changes resulting in damage to nerve tissue and brain neuron death via either necrosis or apoptosis, permanent disruption of neuronal plasticity such as, for example, suppression of activity of the adaptive transcription factors and as a consequence, disruption in the expression of protective proteins always develops [3, 4]. The initial step in the induction of a hypoxic/ischemic cascade is decrease in oxygen supply to the brain, which inevitably leads to deficit of macroergic compounds. The decease in aerobic oxidation rate in mitochondria results in a decrease in ATP amount and increase in ADP and AMP content. The enzyme phosphofructokinase is activated at low ATP/(ADP + AMP) ratio, which allows sharp increase in the rate of anaerobic glycolysis reactions that have low energy efficiency and occur with accumulation of lactate [3]. In the early stages, adaptation to hypoxia and stabilization of energy exchange is still possible, because lactate is formed due to NADH-dependent pyruvate reduction, and removal of the excess of NADH facilitates maintenance of glycolysis processivity. Moreover, it has been shown that lactate plays an important role in providing protection from glutamate excitotoxicity via modulation of activity of ionotropic glutamate receptors selectively binding N-methyl-D-aspartate (NMDA-receptors) [5]. However, such stabilization is usually short-lived and is accompanied by rather fast depletion of glycogen stores [3, 6].

Due to the excess of mitochondrial NADH related to the absence of terminal oxidizer capable of transferring electrons for generation of proton gradient, inhibition of the activity of citric acid cycle enzymes occurs together with redirection of alpha-ketoglutarate to the synthesis of glutamate – the major excitatory mediator of the central nervous system (CNS). The increase in the amount of lactate produced as a result of glycolysis initiates intracellular acidosis. The progressing acidification denatures some proteins. In this stage of hypoxia real deficit of ATP is formed, as the aerobic mechanism does not work due to oxygen deficit, and anaerobic – due to acidosis [3]. The ATP deficit is inevitably reflected on the most energy-consuming enzyme in neurons – Na^+/K^+-ATPase – resulting in decrease in its activity, which, in turn is manifested by the loss of the ability to maintain potassium and sodium gradients across neuronal cell membranes. The most important direct consequence of the decrease in Na^+/K^+-pump activity is penetration of excess sodium into cells, which causes hyperhydration and cerebral edema. The excessive influx of sodium into neurons also leads to depolarization of membranes, influx of Ca^{2+}, and Ca^{2+}-dependent release of glutamate from presynapse with the development of glutamate excitotoxicity in the postsynapse.

Glutamate is the main excitatory mediator of the CNS; it participates in realization of cognitive functions, sustains the level of wakefulness together with acetylcholine, but at high concentrations is toxic to neurons. The excitotoxic effect of glutamate is due not only to sharp release of glutamate, but also due to the disruption of mechanisms of its reverse capture [7]. If reperfusion is conducted in early stages of ischemia, the glutamate concentration reverses to normal values. Glutamate realizes its effect via the group of ionotropic membrane receptors: NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-receptors), kainate receptors, as well as via metabotropic receptors (mGluR). Excitation of the glutamate NMDA-receptors on the background of depolarization of cell membranes developing due to the ATP deficit causes enhanced influx of extracellular Ca^{2+}, and activation of mGluR cause release of intracellular Ca^{2+} from endoplasmic reticulum (ER) [8]. Ca^{2+} at moderate concentrations plays a role as the key intracellular modulator of synaptic plasticity, in particular through change in the number of receptors on the membranes, activation of kinases controlling growth of axons, and formation of new synapses; however, its excessive accumulation in cytosol modifies the activity of a number of enzymes (proteinases, phospholipases, NO-synthases, and others), which eventually mediate damage to membranes, nuclei, and other cellular organelles [9]. This stage of the "ischemic" cascade is accompanied by the generation of reactive oxygen species. The brain is the

organ most sensitive and susceptible to the induction of free radical processes especially on the background of ischemia. This is related to the high content of polyunsaturated fatty acids in brain tissues and with low amounts of vitamin A, extremely low activity of glutathione peroxidase, practically complete absence of catalase, high content of bivalent iron ions, and low level of transferrin and ceruloplasmin [10]. This stage is already irreversible and cannot be corrected by the restoration of oxygen supply.

Next, the "delayed" consequences of hypoxia emerge such as local inflammation reactions, microvascular disorders, deterioration of the blood–brain barrier (BBB), and others. The signs of degradation of the BBB are present from the first minutes of acute focal ischemia, although they are most manifested after several hours. Inflammation reactions are characterized by migration of neutrophils from blood vessels to tissue, microglia activation, and secretion of potentially cytotoxic compounds such as antiinflammatory cytokines interleukin 1 beta (IL-1β) and tumor necrosis factor (TNF). Introduction of antiinflammatory cytokines or compounds decreasing the synthesis of antiinflammatory cytokines significantly decreases the degree of neuron damage following ischemia [11]. Hence, inflammatory reactions are involved in the pathogenesis of post-hypoxic states and facilitate neuronal death.

Induction of a program of delayed apoptotic cell death is a characteristic consequence of acute forms of brain hypoxia. Apoptotic changes can be observed in the CA1-field of the hippocampus and neocortex 3-4 days after transient global cerebral ischemia [12]. Application of protein synthesis inhibitors or growth factors counteracting apoptosis and facilitating normalization of the adequate signal transduction system in brain decreases ischemic damage [13].

Hence, the molecular-biological disorders caused by brain hypoxia/ischemia affect organism very unfavorably. Although the introduction of antioxidants or preparations stimulating the expression of growth factors that stabilize ion gradients can to a certain degree mitigate the consequences of hypoxia, it is still insufficient to ensure complex neuroprotection from hypoxia and ischemia during acute stroke, because they affect only one particular stage of the pathological cascade [14].

HYPOXIC/ISCHEMIC POSTCONDITIONING

Hypoxic/ischemic postconditioning (PostC) is a promising procedure for structural–functional brain rehabilitation following the damaging action of factors of hypoxic nature. The protective effect of PostC on heart was first demonstrated in 2003. It was shown by a group of American authors that conducting three intermittent 30-s sessions of coronary occlusion with 30-s intervals, when the coronary blood flow was restored, in the reperfusion period following 60-min coronary occlusion in dogs helped to decrease the degree of myocardial injury. The phenomenon was termed ischemic PostC (IPostC) [15]. In a wide sense, PostC is a procedure of exposure to damaging factors of moderate intensity following an acute damaging action with the objective to induce endogenous mechanisms facilitating correction of damages. In their pioneer study, Zhao et al. compared the protective effect of post- and pre-conditioning. The size of the infarction zone was analyzed 3 h after reperfusion. The area of injury decreased by 44% when IPostC was used in comparison with 60-min control ischemia, which was comparable with the protective effect of pre-conditioning.

The IPostC effect that corrected negative consequences of myocardial ischemia was later confirmed by many research groups in experiments with various animals *in vivo* [9, 16-19], as well as *in vitro* in cell cultures [20]. Clinical testing of IPostC in patients after myocardial infarction also demonstrated positive results [21]. The cardioprotective effect of IPostC is currently actively investigated, data on the efficiency of PostC methods in different organs are being accumulated, and intensive studies the molecular-cellular mechanisms underlying the protective action realized with this method are being conducted [15, 22-25].

Several years after the discovery of the protective effect of IPostC on myocardium, this phenomenon was demonstrated for brain. The first study on brain PostC was published in 2006 by a group of American neurosurgeons lead by H. Zhao. Stroke was modeled in rats by permanent occlusion of the middle cerebral artery (MCA) and transient bilateral occlusion of the common carotid artery, and IPostC was performed 2 min after reperfusion using three cycles of 10-s occlusion and 30-s reperfusion of the common carotid artery. The size of the infarction area was evaluated 2 days after the MCA ligation. IPostC ensured 80% decrease in the necrosis area in comparison with the control acute ischemia and facilitated decrease in apoptosis intensity [26]. The results of this study have been reproduced by many scientific groups worldwide that used various regimes of acute ischemia and IPostC [27-30]. The effect of PostC was also demonstrated in *in vitro* experiments using hippocampal slice culture [31] and primary neuronal culture [32].

NEUROPROTECTIVE MECHANISMS ACTIVATED BY ISCHEMIC POSTCONDITIONING

The mechanisms of neuroprotective action of IPostC are under active investigation. It was shown that IPostC suppressed the generation of free radicals and initiation of apoptosis during the reperfusion period, and it decreased the level of malondialdehyde (MDA) and of oxidative protein modifications with simultaneous increase in the activity of superoxide dismutase and catalase in brain tis-

sues [26, 27, 30, 33, 34]. This suggests high antioxidant effect of IPostC.

By analogy with heart, it was shown that IPostC of brain mediated an increase in the amount of phosphorylated protein kinase Cε (PKCε) with simultaneous decrease in the amount of phosphorylated protein kinase Cδ (PKCδ), which according to the present notion facilitated cell death [35]. The c-Jun N-terminal kinase (JNK), which activates c-jun and p53 transcription factors, plays an important role in neuronal death and in pathogenesis of neurodegenerative disorders [36]. The researchers from California established that IPostC caused a decrease in the amount of phosphorylated JNK in brain [35].

Protein kinase Akt plays a special role in the suppression of apoptosis-induced signals, thus ensuring normal functioning of cells and intercellular interactions [37, 38]. It was found in experiments with hippocampal slices that the selective inhibition of the Akt activator alleviated the neuroprotective effect of IPostC [31]. The American physiologists also showed in *in vivo* experiments that brain IPostC resulted in the phosphorylation of Akt and, as a consequence, increase in activity of this enzyme [35]. Moreover, a decrease in the size of the infarction area was not observed under conditions of PI3-kinase blockade; however, there was a decrease in the expression of ER chaperones, and induction of the ER-dependent apoptosis involving caspase 12 was observed [39]. In addition, the role of Akt in realization of the IPostC effect via activation of mTOR kinase was demonstrated. Interestingly, anesthetics mimicking the PostC phenomenon (propofol and isoflurane) also activate Akt and PI3-kinase [40, 41].

ERK phosphorylated by MEK is another kinase ensuring survival of cells under adverse conditions [42, 43]. In 2009, Jiang et al. [44] established that IPostC of the rabbit spinal cord (*in vivo* model) resulted in phosphorylation of ERK, and the neuroprotective effect did manifest itself under conditions of MEK blocking. The involvement of ERK in the mechanisms of the brain tolerance to hypoxic conditions was acknowledged during investigation of the older phenomenon of hypoxic preconditioning [45] of rat brain in the model of hypobaric hypoxia. However, the data of Jiang et al. contradict the results American and Chinese specialists [35, 46], who observed a decrease in the amount of phosphorylated ERK following ischemic and normobaric hypoxic PostC; moreover, the latter demonstrated the role of the MEK/ERK signaling pathway inhibition in compensation of the consequences of transient global cerebral ischemia [46]. The cause of this discrepancy remains unclear. The role of each separate kinase and peculiarities of their interactions during the PostC procedure is still poorly explored as well as the final effects of IPostC.

The enzymes of antioxidant cell protection [26, 27, 30], chaperones [34, 39], as well as factors controlling mitochondria-mediated induction of apoptosis [34, 47] are suggested as key effectors in IPostC. One of the best-investigated proteins suppressing this apoptotic pathway is the Bcl-2 (B-cell lymphoma 2) protein. Bcl-2 expression in brain is determined by the efficiency of signal transduction between neurons, and it reflects the balanced operation of the signaling pathways involved in ensuring neuroplasticity [48]. Xing et al. found that IPostC facilitated an increase in Bcl-2 level, decrease in proapoptotic Bax protein, and prevented the increase in cytoplasmic cytochrome *c* level in the neuron [34]. The same group of authors reported an antiinflammatory effect of IPostC that was manifested by a decrease in myeloperoxidase activity, decrease in the amount of malondialdehyde (marker for lipid peroxidation, LPO), as well as by suppression of the synthesis of proinflammatory cytokines TNFα, IL-1β, and of intercellular adhesion molecules (ICAM) – markers for inflammation [49]. The signaling pathway causing attenuation of autophagy is considered as a no less interesting IPostC-mediated stimulation; however, the amount of data on the long-term effects of such rearrangements of the cellular molecular machinery on further neuron functioning is still insufficient to make any firm conclusions [50].

The work of Zhang et al. demonstrating the contribution of IPostC to redistribution of glutamate in rat brain due to enhanced activity of glutamine synthase and upregulated expression of neuronal glutamate transporters (GLT1) leading to decrease in excitotoxicity and, respectively, decrease in post-ischemic injuries, is worth notice [51, 52].

Recently the possibility of inclusion of processes of neuronal cell proliferation as a pathway to compensate post-stroke neuronal death attracted considerable attention of scientists investigating IPostC. Experimental corroboration of this hypothesis was demonstrated by Esposito et al. [53].

For the most part, the literature accumulated so far are related to models of the so-called rapid IPostC, when reperfusion interruption is conducted in early stages (seconds and minutes) after ischemia; however, in addition to early IPostC, "delayed" [27, 29, 32, 54, 55] and distant [56, 57] IPostC of brain are also recognized. Furthermore, combination of different variants of IPostC and their application together with the previously described phenomenon of ischemic preconditioning have been also used, which has been reviewed in detail in several publications [57-61]. Successful attempts to model the effect of IPostC by so-called pharmacological PostC using anesthetic inhalation were also reported [41, 62, 63].

NONINVASIVE METHODS OF POSTCONDITIONING

Despite the well-documented neuroprotective efficiency of IPostC, the transformative potential of this approach to brain rehabilitation remains questionable

due to several serious drawbacks. In particular, the way of conducting IPostC by intermittent occlusion of the carotid and cerebral arteries is an invasive method requiring surgical intervention, which poses significant risks and limitations, especially for patients who survived a severe episode for which exactly the application of PostC is required. Moreover, according to the abovementioned literature data, IPostC must be conducted within a rather narrow therapeutic window (from several minutes to 1-2 h after the ischemic stroke), which also presents limitations for practical application. That is why the search for noninvasive approaches for PostC and elucidation of the mechanisms of its action hold significant promise.

A novel, noninvasive method of PostC using moderate hypobaric hypoxia (hypobaric hypoxic postconditioning, HBHPostC) was developed recently in the laboratory of regulation of neuron function at the Pavlov Institute of Physiology, Russian Academy of Sciences, which employed a procedure of exposing the organism to low atmospheric pressure causing decrease in oxygen supply (method for hypoxic postconditioning, Patent of the Russian Federation No. 2437164, 20.12.2011) [4, 64-69]. Simultaneously, our Chinese colleagues published the results of a series of studies confirming the efficiency of normobaric hypoxic postconditioning (NBHPostC) for correction of the consequences of transient global cerebral ischemia [46, 70, 71]. The efficiency of NBHPostC for compensation of the consequences of 10-min transient global brain ischemia was demonstrated. The NBHPostC involved 2-h exposure to an atmosphere comprising a mixture of 8% oxygen and 92% nitrogen in a chamber one day after the ischemia imposed by occlusion of the two vertebral and two carotid arteries.

HYPOBARIC HYPOXIC POSTCONDITIONING

The efficiency of the HBHPostC method for correction of the consequences of severe hypoxia was demonstrated in experiments with rats. Severe hypobaric hypoxia (SH) was created by 3-h exposure to the pressure of 180 mm Hg (which is equivalent to 5% of O_2 and corresponds to the altitude of 11 km above sea level) in a flow-through-type barochamber. This model is well studied. It is known that approximately 50% of rats do not survive under the conditions of SH, and the remaining manifest signs of brain swelling, deterioration of the BBB, massive cell death in the hippocampus and neocortex, abnormalities in behavior and cognition, and memory disorders. The postconditioning procedure in this model involved three 2-h sessions of moderate hypobaric hypoxia (360 mm Hg, which corresponds to 10% of normobaric oxygen and is equivalent to the altitude of 5 km above sea level) with 24-h intermissions starting 24 h after SH.

As earlier, the animals that survived SH exhibited clearly pronounced behavioral abnormalities including mobility retardation, increased anxiety, disruption of stereotypic activities, and other signs of depressive-like conditions. The basal level of corticosterone in the blood plasma of these animals was 6-fold lower than in the control group, while the stress-reactivity of the hypophysial–adrenocortical system to minor (non-pathogenic) stress increased 5-fold. Application of HBHPostC according to the abovementioned scheme alleviated these disorders [66].

Histological analysis of brain slices stained using the Nissl procedure showed that the loss of ~30% of pyramidal neurons occurred in susceptible brain areas such as the hippocampal CA1-field by the 7th day after SH, but HBHPostC almost completely prevented this neuronal death [66]. As shown earlier, massive induction of reactive oxygen species (ROS) and intensification of LPO occurred in the early stages of re-oxygenation after SH in the brain of rats [72, 73], which could be the reason for the neuronal death mentioned above. Based on data on antioxidant action of IPostC [27, 30, 33, 34], we suggest that the HBHPostC-mediated prevention of cell death is related to normalization of the functioning of intracellular signaling pathways supporting antioxidant protection. The combination of these and other facts led us to conclude that HBHPostC exhibited high neuroprotective effect.

MECHANISMS OF NEUROPROTECTIVE EFFECTS OF HYPOXIC POSTCONDITIONING

Unlike in the case of ischemic postconditioning, the mechanisms of neuroprotective action of hypoxic postconditioning (HPostC) are still poorly understood. Two parallel lines of enquiry must be noted that are based on application of different models – normobaric PostC (NBHPostC) and hypobaric PostC (HBHPostC). It was shown that HBHPostC stimulated the expression of antiapoptotic protein Bcl-2 and neurotrophin BDNF in the rat hippocampus [68]. Similar data were obtained in the model of early IPostC [34]. The stimulation of signaling pathways regulating the expression of neurotrophins and antiapoptotic protein is characteristic for many forms of neuroplasticity, and it likely plays a key role in the protective function of PostC preventing cellular death, normalizing LPO as well as behavioral characteristics of rats [68]. Moreover, the key transcription regulator inducing adaptation to conditions of oxygen deficiency (hypoxia inducible factor-1, HIF-1) and the target of its transcriptional activity – protective cytokine erythropoietin (Epo), which as demonstrated is an important regulator of the synapto- and neurogenesis – clearly provide a significant contribution to these processes. It was found that SH suppressed the expression of the regulatory alpha-subunit of HIF-1 (HIF-1α) and, as a result, led to a decrease in the Epo level, which was in agreement with

literature data on HIF-1 regulation pathways [74] and peculiarities of the activity of protein kinases during reoxygenation periods in the ischemic models [31, 35, 39, 42, 43]. At the same time, HBHPostC facilitates an increase in the amount of HIF-1α and Epo, which supposedly also contributes to the neuroprotective effect of HBHPostC [67].

The group of Chinese researchers under the leadership of En Xu was very successful in investigation of modulation of activity of protein kinases controlling the functioning of HIF-1 under conditions of pathological and adaptive hypoxia using NBHPostC to compensate for the consequences of 10-min transient global brain ischemia. The NBHPostC in this case involved 2-h exposure to a mixture of 8% oxygen and 92% nitrogen one day after an ischemia episode caused by the occlusion of the two vertebral and two carotid arteries.

In the first experiments, the authors showed that NBHPostC resulted in an increase in phosphorylation of the Akt kinase and neuroprotective transcription factor FoxO, which correlated with a decrease in infarct size and prevention of cell death. Similarly to the case of IPostC [35, 39], the use of the PI3K inhibitor alleviates the neuroprotective effect and is accompanied by a decrease in Akt and FoxO phosphorylation, as well as by intensification of cell death. At the same time, NBHPostC mediates a decrease in phosphorylation of the MEK and ERK kinases that are activated in the model of transient global cerebral ischemia, and the MEK inhibitor facilitates a decrease in neuronal loss following the acute ischemia [46].

In the next stage, the same group of authors demonstrated the role of neuronal (but not glial) kinase p38 in the neuroprotective effect of NBHPostC via phosphorylation of MSK kinase, which activated the c-Rel subunit of a transcription factor of the NF-κB family [70]. In addition to the direct protective action known in the CNS, NF-κB plays a role of coactivator of the α-subunit of the hypoxia-inducible factor (HIF-1α), which makes the data on the involvement of this hypoxia adaptation factor into providing neuroprotection during the NBHPostC very noteworthy. Indeed, NBHPostC increases the expression of HIF-1α, as well as the expression of the products of its gene targets such as vascular endothelial growth factor (VEGF), thus mediating the prevention of cell death and decrease in the level of active caspase-3 in the hippocampus. The inhibitors of both the p38 kinase and the Akt kinase cause complete blocking of this signaling pathway in the process, and, on the contrary, the inhibitor of MEK/ERK-signaling stimulates the HIF-1α-dependent neuroprotective pathway in response to global cerebral ischemia in the absence of NBHPostC [71].

In conclusion, accumulated data indicate significant similarity between the neuroprotective pathways of ischemic and hypoxic (either hypobaric or normobaric) postconditioning, as well as their significant overlapping with mechanisms of brain neuroplasticity. However, these issues require further investigation, in particular to understand the role of neuron–glial interactions in providing plasticity to the brain exposed to hypoxia.

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