Hypoxia inducible factor (HIF) in ischemic stroke and neurodegenerative disease

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Abstract

Hypoxia is one of the most common pathological conditions which results from ischemic injury, trauma, inflammatory conditions, tumors, etc. The adaptation of the body to hypoxia is a phenomenon that is of great importance both in normal conditions and in pathology. Most of the cellular response' reactions to hypoxia is associated with a family of transcription factors called hypoxia-inducible factors (HIF). They induce the expression of a wide range of genes that help cells adapt to a hypoxic environment. HIF functions are currently being extensively studied. In 2019, William G. Kaelin and Gregg L. Semenza from the USA and Sir Peter J. Ratcliffe from the UK received the Nobel Prize in Physiology or Medicine for the discovery of the basic mechanisms of adaptation to hypoxia and investigation of the role of HIF factor in the regulation of the hormone erythropoietin levels. Based on its pivotal physiological importance, the HIF factor attracts more and more attention as a new potential target for treating a large number of diseases associated with hypoxia. Most of the experimental work dealing with the HIF factor is focused on its role in liver and kidney. However, increasing amount of experimental results clearly demonstrates that the HIF factor-based response represents an universal adaptation mechanism for all kinds of tissues, including the nervous system where HIF is critical for regulating neurogenesis, nerve cell differentiation, and neuronal apoptosis. This mini-review provides actual overview about the complex role of HIF-1 in the adaptation of nerve cells to hypoxia with the focus on its potential role by various neuronal pathologies.

Introduction

The oxygen content in tissues plays a crucial role in maintaining cells' normal functioning and regulating their development. It should be noted that the effect of hypoxia on the body differs depending on the intensity and duration of hypoxic exposure. In adulthood, "physiological" hypoxia

maintains the undifferentiated state of several populations of stem cells and progenitor cells, including neural stem cells, and protects their DNA from oxidative damage (Mohyeldin A, 2010). Prolonged and pronounced hypoxia leads to dysfunction and cells death.

The central nervous system is most sensitive to a lack of oxygen. Although the human brain makes up only a small part of the body weight (about 2%), it is the leading consumer of energy: it accounts for more than 20% of the total oxygen metabolism. Neurons consume 75–80% of this amount of energy (Hyder et al., 2013). The energy is primarily required to maintain synaptic transmission and restore neurons' membrane potentials after depolarization (Harris et al., 2012). Other neuronal functions, such as synaptic vesicle recycling, neurotransmitter synthesis, and axoplasmic transport, are also energy-dependent. They contribute to energy depletion and determine the increased intensity of oxygen metabolism in neurons (Rangaraju et al., 2014; Pathak et al., 2015).

The physiological partial pressure of oxygen varies in different areas of the brain. In the cerebral cortex of rats, it fluctuates in the range of 2.53–5.33 kPa, in the hypothalamus – 1.47–2.13 kPa, and in the hippocampus, it is equal to 2.67 kPa. By pathological conditions, areas with severe hypoxia (with a partial pressure of O2 <0.1 kPa) or anoxic areas appear (Liu et al. 1995, Erecińska, 2001).

It is essential that neurons in the central nervous system can quickly and adequately respond to oxygen concentration changes and hypoxic brain damage (Abe, 2017). Impaired due to hypoxia, oxygen metabolism, and mitochondrial functioning cause destructive structural and functional changes in nerve cells, leading to their death (Zhuravin, 2019; Azevedo, 2020; Kumari, 2020). Ischemic stroke is a widespread disease and is considered the main cause of hypoxic brain stress (Ratan, 2007; Mozaffarian, 2016). Hypoxia can also be one of the components of the pathological complex and be associated with neurodegenerative diseases characterized by a decrease in cognitive functions and memory, for instance, Alzheimer's disease, Parkinson's disease, etc. (Yagishita, 2017; Snyder, 2017; Panchision, 2009).

Transient ischemic hypoxia can cause severe acute brain damage, especially in the hippocampus, extremely sensitive to hypoxia (Gao, 2019; M.L. Gordan, 2012). Apoptosis of hippocampal neurons is one of the main causes of neurological deficits and cognitive impairments since the hippocampus is critical for spatial learning and memory (Simoes Pires, 2014). Damage in this area leads to a pronounced decrease in cognitive functions, which seriously affects patients' quality of life (Lagali, 2010; Yang, 2017). Apoptosis, necrosis, and necroptosis are the main pathways for neuronal death during ischemic injury (Unal-Cevik, 2004; Yang, 2017).

A few minutes after exposure to cerebral ischemia, a necrotic nucleus of irreversibly damaged cells is formed. It is surrounded by an area of less affected cells known as the ischemic penumbra. Cell death in penumbra is mainly apoptotic and develops several hours or days after the onset of ischemic stroke (Wang, 2017). Thus, most treatments for the sequelae of stroke aim to rescue damaged cells in the penumbra (Broughton, 2009; Ratan, 2007). Maintaining the viability and functioning of damaged areas of the brain is carried out mainly by suppressing the processes that lead to their death and induction of neuroregeneration. (Davis, 2020). Promoting neuroregeneration and activating neurogenesis is just as crucial as preventing cell death.

One of the main regulators of the cell's response to hypoxia is the protein hypoxia-inducible factor-1 (HIF-1), which controls the expression of a large number (more than 700) of various target genes mediating both adaptive and pathological processes (Lukyanova, 2015; Sheldon, 2014; Dengler, 2014; Barteczek, 2017; Liu, 2017; Wu, 2019; Semenza, 2004; Salhanick, 2006). The key groups of genes are target genes associated with angiogenesis and energy metabolism, which primarily include the erythropoietin (EPO) gene, vascular endothelial growth factor (VEGF), and genes that are involved in glucose transport or glycolysis, for instance, glucose transporter-1 (GLUT1), pyruvate dehydrogenase kinase 1 (PDK1) and lactate dehydrogenase A (LDHA) (Leu et al., 2019).

HIF-1 is a diheterodimer and consists of constitutively expressed α and β subunits. However, if the β-subunit is constitutively present in the cell, then the α-subunit undergoes under normoxic

conditions rapid ubiquitin-dependent proteasome degradation under the action of oxygen-dependent HIF prolyl hydroxylase (PHD) (Semenza, 2004, 2009). Under hypoxic conditions, PHD is inactivated. It leads to the stabilization of HIF-1α and its further translocation into the nucleus, where a heterodimeric complex with HIF-1β is formed. This complex interacts with DNA and activates the expression of many genes, the products of which contribute to an increase in oxygen supply to tissues by increasing erythropoiesis and angiogenesis (Figure 1). Thus, activation of the HIF complex initiates neuroprotection and, as a result, restoration of the functioning of cells damaged by hypoxia (Ivan, 2001; Salceda, 1997; Cho, 2015; Semenza, 2017; Sheldon, 2009; Bergeron, 2000). When HIF-1α is inactivated (for example, by a mutation in the corresponding gene), more pronounced impairments to learning ability and a decrease in neurogenesis are observed in the postischemic period (Carrica, 2019). Besides, inactivation of HIF-1α increases brain damage and decreases the survival rate of animals when simulating ischemia (Baranova, 2007; Milosevic, 2007; Sheldon, 2009).

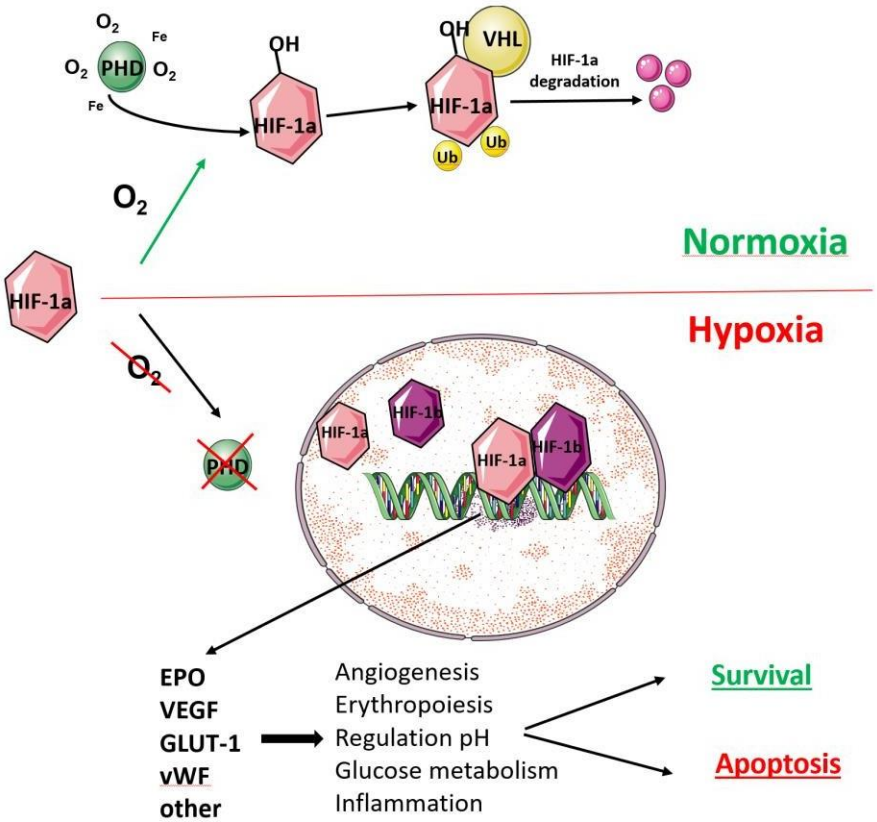

Figure 1. Scheme of HIF-mediated regulation of cell adaptive reactions. Scheme of HIF-mediated regulation of cell adaptive reactions. EPO – Erythropoietin; GLUT-1 - facultative glucose transporter 1; HIF- hypoxia-inducible factor; PHD - HIF prolyl hydroxylase; Ub – ubiquitin; VGEF - vascular endothelial growth factor; VHL - von hippel–lindau protein; vWF - von Willebrand factor.

The HIF-1 signaling pathway is a major molecular cascade for transmitting signals from many factors associated with hypoxic-ischemic brain injury. HIF-1 appears to be the main universal switch in the activity of molecules controlling cell survival, glucose metabolism and transport, and metabolic adaptation. It is interesting to note that HIF-1α has a complex effect on the brain, depending on the time of hypoxic damage development. It has been shown that the accumulation of HIF-1α immediately after ischemia promotes cell death at the earliest stage (<24 h, death effect) (Barteczek, 2017; Cheng, 2014; Yang, 2017). In contrast, HIF-1α limits infarct size at a later stage of ischemic injury (> 4 days,

survival effect) (Baranova, 2007; Sheldon, 2014; Hsiu-LingLi, 2019). Thus, the role of HIF-1 in nerve cells survival is multifactorial and controversial.

Moreover, HIF appears to be involved in other ways of hypoxic response regulation. For example, this factor induces microRNAs sensitive to hypoxia; they play an essential role in modulating the cellular response to hypoxic stress (Chen et al., 2013; Zhang et al., 2020). MiRNAs are a class of small non-coding RNAs that regulate mRNAs' stability and translation by binding to the 3'UTR of mRNA, resulting in decreased protein levels. It has been shown that HIF-1α can regulate miRNAs at the transcriptional level (Yang et al., 2018). Moreover, conversely, HIF expression is regulated by miRNA. However, most studies of HIF-linked miRNAs have focused on cancer cell lines; the role of miRNAs in other types of cells is often ignored (Serocki et al., 2018). Currently, about 40 siRNAs that modulate HIF expression have been identified (Serocki et al., 2018).

It is also important to note that HIF-1α is extensively involved in regulating the activity of the PI3K / Akt pathway, one of the downstream targets of which the transcription factor NF-κB is (Kim et al., 2017**;** Lyu et al., 2018; Bao et al., 2018; Walmsley et al., 2005; Lee et al., 2016a; Liu et al., 2019; Haque et al., 2011; Chai et al., 2013; Zhang et al., 2015). This pathway is involved in maintaining cell viability and regulation of apoptosis.

The neuroprotective role of HIF-1 in ischemic injury

Various methods for regulating the expression and activity of the HIF-1 complex can be a way to prevent hypoxic brain damage development. At the moment, several approaches are used to modulate the activity of the HIF-1 complex. First, a widely used method for HIF-1 induction is the use of enzyme blockers involved in the degradation of the HIF-1α subunit under normoxic conditions or the knockout of their genes. PHD blockers are the most commonly used (Siddiq, 2005; Li, 2016; Barteczek, 2017; Jeon, 2019; Ramamoorthy, 2018). Secondly, proteins and various agents that control the expression of the HIF-1α subunit and its stabilization have been developed (Neuregulin-1 (NRG1) (Yoo, 2019; Davis, 2018, 2020; Wang, 2012). Lastly, physiological induction of HIF-1α accumulation by hypoxic preconditioning prior to acute hypoxia is also possible (Wu, 2020; Gu, 2008; Li, 2018). It has been reported that hypoxic preconditioning increases resistance to ischemic brain damage and reduces neuronal apoptosis by enhancing HIF-1α expression (Snigdha, 2012).

It was found that with an increase in the content of HIF-1 α upon deletion of prolyl-4-hydroxylase 2 (PHD2), the HIF suppressor, the expression of EPO and VEGF in the cell increases. An increase in neurogenesis in the hippocampus and an improvement of cognitive functions in mice suffering from chronic hypoperfusion of the brain are also noted. At the same time, the local density of microvessels, the morphology of dendritic spines, and the expression of genes associated with synaptic plasticity in the hippocampus did not change (Gruneberg, 2016; Li, 2016).

The use of PHD blockers, most of which are iron chelators, also leads to inhibition of cell death by ferroptosis, which may mediate their neuroprotective properties (Speer, 2013).

It was found that the activation of the HIF-1α signaling pathway is closely related to the inhibition of neuronal apoptosis (Gao, 2019). However, the effect of the HIF-α complex stabilization on apoptosis is ambiguous, as evidenced by a large amount of conflicting data. HIF-1α can likely both induce and inhibit apoptosis. Overexpression of HIF-1α leads to an increase in the expression of many protective genes, which makes cells resistant to apoptosis caused by hypoxia or lack of nutrients (Akakura, 2001; Yang, 2017). HIFα subunits are involved in regulating the activity of many members of the Bcl-2 family with both pro-apoptotic and anti-apoptotic properties (Fang, 2020). Anti-apoptotic changes include increased levels of Bcl-2 (Sasabe, 2005) and Mcl-1 (Liu, 2006, Palladino, 2012, Sharma, 2011), induction of Bcl-xL (Chen, 2009, Menrad, 2010) (via binding HIF-1α with an element of the response to hypoxia in Bcl-xL) and a decrease in the levels of pro-apoptotic factors Bid, Bax,

and Bak (Sasabe, 2005). HIF-1α has also been associated with the regulation of mitochondrial function through hexokinases. It was reported that hexokinase II catalyzes the first stage of glycolysis and shifts the apoptotic balance by binding to the voltage-dependent anion channel (VDAC) on the mitochondrial membrane (Pastorino, 2008). Like many other glycolytic enzymes, hexokinase II can be induced by HIF-1α, and recent research has shown that hexokinase II is critical for the Warburg effect in glioblastoma multiforme. This direct interaction, most likely independent of Bax and Bak (Lambert, 2010, Wolf, 2011), could combine the preferential use of aerobic glycolysis (Warburg effect) with apoptosis inhibition.

However, HIF-1α is able to trigger p53-induced apoptosis. At least three different types of interactions between HIF-1α and p53 have been proposed. First, direct protein-protein interaction has been proposed as the main mechanism for hypoxia-induced p53 stabilization. Two different studies provided in vitro data suggesting direct binding of the ODD (oxygen-dependent degradation) domain of HIF-1α to p53. Moreover, direct interactions between HIF-1α and Mdm2 to modulate p53 function and the association of VHL and p53 to stabilize p53 in vitro and in vivo have been reported (Roe, 2006). This aspect will be discussed in more detail later in this article.

One of the important pathways of the neuroprotective action of HIF-1α is the increased expression of erythropoietin (EPO), which plays an essential role in the processes of adaptation to hypoxia (Li, 2020; Li, 2014; Zhang, 2009). It is known that EPO production is activated by hypoxia in the brain, uterus, and kidneys of mice (Chikuma, 2000). EPO administration protected embryonic and postnatal hippocampal neurons from death caused by hypoxia, stimulated oligodendrogenesis, and reduced white matter damage in simulating hypoxic brain damage (Iwai, 2010). Besides, EPO attenuated the inflammatory response by decreasing the production of cyclooxygenase 2 and inducible NO synthase, suppressing microglial activation and inhibiting autophagy activation in neuromuscular dysfunction caused by burn injury (Wu, 2018). It has been shown that an increase in the expression of HIF-1α in neurons and astrocytes leads to an increase in the expression of EPO, which, in turn, led to an acceleration in the recovery of neurological functions due to a decrease in neuronal apoptosis (Li, 2020, Rey, 2019).

In addition to ischemic stroke, traumatic brain injury (TBI) can lead to ischemic-hypoxic brain damage. In vivo studies have shown that cerebral hypoxia-ischemia caused by traumatic brain injury (TBI) plays a decisive role in the occurrence of various severe secondary brain injuries (Xu, 2012; Shu, 2016). After TBI, oxygen delivery to nerve cells decreases, which leads to impaired glucose metabolism (Yamaki, 2018). This is one of the main causes of neuronal apoptosis and neurological disorders after TBI (DeVience, 2017). The glucose transporter (GLUT) is the most important protein for glucose transport (Wood, 2003) and plays an essential role in energy production in the brain after injury (Zhou, 2017). As a result of the increased expression of HIF-1α during hypoxia, the levels of GLUT1 and GLUT3 grow, which allows to increase the supply of glucose to hypoxic neurons for glycolysis (Sadlecki, 2014). Improving energy supply helps reduce neuronal death.

It has been shown that compounds affecting the HIF-1α signaling pathway, for example, Neurotrophin, Empagliflozin, Dexmedetomidine (Fang, 2017, Abdel-latif, 2020, Luo, 2017), can protect nerve cells from death in ischemia. Likewise, activation of the HIF-1α / p53 signaling pathway may play a role in treating neonatal hypoxic encephalopathy. This is the theoretical basis for effective treatment with dexmedetomidine (DEX) in hypoxic encephalopathy of the newborn (Gao, 2020).

Another important aspect of the neuroprotective effect in hypoxic damage is its involvement in neurogenesis. Inhibition of neurogenesis can induce memory impairments (Pereira-Caixeta, 2018; Hollands, 2017). The enhancement of neurogenesis can be used as an approach to compensate for cognitive loss associated with age or various diseases (Kempermann, 2008; Berdugo-Vega, 2020). It has been demonstrated that HIF-1α is one of the regulators of hippocampal neurons' neurogenesis in postnatal organisms (Carrica, 2019). Therefore, HIF-1α is a potential therapeutic target for maintaining

cognitive functions and correcting behavioral disorders in various brain pathologies, i.a. by modulation of neurogenesis (Braun, 2014).

Genetic inactivation of HIF-1α in nestin+ hippocampal neural precursor cells in mice and their offspring causes a pronounced, almost twofold, decrease in neurogenesis. This leads to a deterioration in the spatial and contextual recognition of objects and the ability to learn. Thus, HIF-1α expression is critical for maintaining neurogenesis in the adult brain and maintaining hippocampal functions (Carrica, 2019, Dillen, 2020)

It is interesting to note that HIF-1α is not degraded in stem cells, including neural stem cells of the subventricular zone (SVZ) of the hippocampus, even under normoxic conditions, unlike other types of cells (Palomaki, 2013; Kim, 2019). It has been demonstrated that the self-renewal of stem cells is regulated by the HIF-1α complex of transcription factors, acting together with epigenetic regulators CBX7. Hypoxia seems to regulate CBX7 expression through HIF-1α activation. Upregulation of CBX7 after ischemic brain injury may play an essential role in enhancing neuronal progenitors' proliferation in the postischemic period (Chiu, 2019).

Adverse effects of HIF-1α in ischemia

Since most HIF target genes mediate both adaptive and pathological processes, the role of HIF-1α in neuronal survival is controversial (Sheldon, 2009; Barteczek, 2017).

It has been shown that activation of HIF-1 in the early acute phase of the hypoxic response triggers a cascade of adverse cerebral events associated with suppressing the pentose phosphate pathway (Vetrovoy, 2019). The pentose phosphate pathway of glucose oxidation limits the development of oxidative stress caused by oxygen-glucose deprivation since it affects the redox homeostasis and the antioxidant system of the cell (Fernandez, 2012; Sun, 2017; Vetrovoy, 2019).

Besides, one of the genes under the control of HIF is the gene for cotransporters Na-K-Cl 1 (NKCC1) (Yang, 2019), the expression of which increases sharply during hypoxia. Their activation aggravates edema and brain damage (Chao, 2020).

There is experimental evidence that limiting the HIF-1α expression in the early stages of hypoxic damage can contribute to an increase in neuronal viability in modeling hypoxia both in vitro and in vivo. For example, a positive effect of suppressing the hypoxia-induced accumulation of HIF-1α with the use of caffeine in clinically relevant doses has been demonstrated (Li, 2019).

Barteczek (2017) described that in mice with double knockout of Hif1a / Hif2a, the expression of the proapoptotic genes Bnip3, Bnip3L and Pmaip1 is reduced. It led to a decrease in cell death and reduced cerebral edema 24 hours after occlusion of the middle cerebral artery. However, this effect was not observed after 72 hours of reperfusion. Neurological status and sensorimotor functions in animals with Hif1a / Hif2a deficiency had higher indices on the first day after modeling ischemia/reperfusion, but after 72 hours, they significantly decreased compared to wild-type animals. The deterioration in the animals' condition was accompanied by an increase in apoptosis and a decrease in angiogenesis. A similar positive effect on pharmacological inhibition of HIF-1 by the 2ME2 blocker (Sigma-Aldrich (M6383)) immediately after surgery has been demonstrated (Cheng, 2014). An improvement in animals' performance (Улучшение показателей у животных) was observed 24 hours after ischemia/reperfusion. A decrease in the levels of cleaved caspase-3, transcription factor NF-κB phospho-p65, phosphorylated kinase JNK1, 2/3, and total kinase JNK1, 2/3 was revealed (Cheng, 2014).

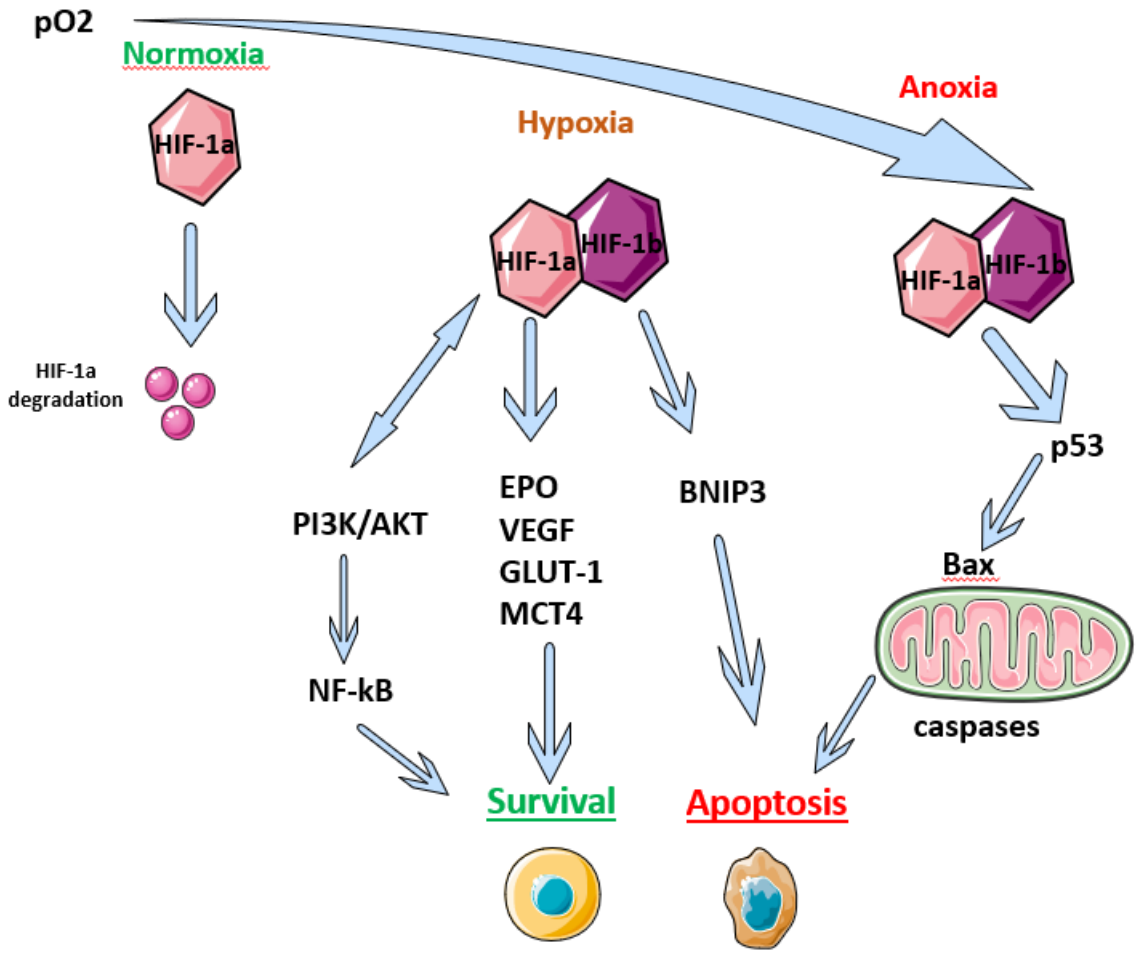

Figure 2. Decreasing oxygen concentration in tissues elicits alterations in metabolism through a number of HIF-induced mechanisms. AKT1 - the serine-threonine protein kinase AKT1; Bax - apoptosis regulator protein, also known as bcl-2-like protein 4; BNIP3 - a member of the apoptotic Bcl-2 protein family; EPO – Erythropoietin; GLUT-1 - facultative glucose transporter 1; HIF- hypoxia-inducible factor; MCT4 - monocarboxylate transporter 4; p53 - pro-apoptotic transcription factor; PI3K- phosphoinositide 3-kinase; VEGF - vascular endothelial growth factor.

Thus, when nerve cells are exposed to chronic or severe acute hypoxia, the adaptive protective mechanism induced by HIF-1 is obviously insufficient, which leads to cell death. Besides, HIF-1 is involved in the initiation of apoptosis. It has been shown that one of the genes under the control of HIF-1α is the gene encoding the Nip3 protein, a pro-apoptotic member of the Bcl-2 family (Sowter, 2001; Bruick, 2000). Moreover, under hypoxia, stabilization of the pro-apoptotic protein p53 is observed, which co-occurs with the accumulation of HIF-1α and depends on its presence (An, 1998; Krick, 2005). Direct interaction between p53 and HIF-1α leads to stabilization of p53 and inhibition of HIF-1-dependent transcription of many genes that can prevent hypoxic damage (Madan, 2019; Wang, 2019; Wang, 2018).

Thus, a large group of experimental data indicates an adverse effect of the HIF pathway inhibition in nerve cells in the most acute phase after ischemic stroke.

It is important to note that the role of HIF in the induction of apoptosis also depends on the severity of hypoxia: in mild hypoxia, its effect is rather protective due to the induction of the expression

of various antiapoptotic proteins. On the other hand, severe hypoxia (anoxia) leads to cell death, at least partly caused by HIF-1α-mediated p53 stabilization (Levine, 1997; Suzuki, 2001).

So, HIF-1 activators can be used in neuroprotection but with extreme caution.

HIF-1α in neurodegenerative diseases

In recent years, experimental data indicating a significant role of HIF-1α in neurodegenerative diseases' pathogenesis have emerged.

Alzheimer's disease

Alzheimer's disease (AD) is a severe neurodegenerative disease characterized by a complex etiology, several forms of the disease, and different manifestation times. This pathology is one of the most common neurodegenerative diseases. Alzheimer's disease incidence is 15% among people aged 65 and over and about 50% among people over 85 years old (Bonda, 2011). AD is characterized by two main histological and biochemical features: accumulation of amyloid beta-peptide (Aβ) in the brain and the presence of neurofibrillary tangles consisting of hyperphosphorylated tau protein. Amyloid beta-peptide comes in various lengths and exists in several forms, including globular, fibrillar, and oligomeric ones (Vinters, 2015).

At present, the paradigm of the correlation between cerebral hypoxia and AD is getting more and more experimental evidence. For example, cardiovascular risk factors are strongly correlated with sporadic AD (LOsAD) (Leszek et al., 2020). Other significant risk factors for LOsAD include traumatic brain injury, especially chronic traumatic encephalopathy (Van Den Heuvel C, et al. 2007; Stein & Crary, 2020). There is a decrease in blood flow in the brain and dysfunction of the neurovascular unit in AD, which probably causes impaired oxygenation (Ajmal Ahmad, 2020, Xing Yu 2020). Recent research suggests that aerobic exercise can reduce AD risk by improving the brain's oxygen supply (De la Rosa, 2020).

Pharmacological activation of HIF-1 can have a neuroprotective effect in AD and can be used in therapy (Ashok, 2017; Guo, 2015; Guo, 2017; Merelli, 2018). Increased HIF-1 activity and/or expression of HIF-1 target genes involved in glycolysis or regulation of capillary blood supply are a component of early adaptation to oxidative stress and can slow down the decline in cognitive functions and the progression to more severe stages of AD (Iyalomhe, 2017). Transduction of primary hippocampal cultures by the viral vector rAAV-HIF-1α significantly reduced the level of apoptosis in cultures induced by amyloid beta-peptide (Chai, 2014). The clinical use of HIF-1 inducers has also demonstrated the neuroprotective effect of HIF-1 in AD (Ashok, 2017). Deferoxamine (DFO), a widely used inducer of HIF-1, has been used in clinical trials in AD patients and slowed down a cognitive decline (Zhang, 2011).

However, it has been revealed that HIF-1 also plays an essential role in modulating amyloidogenic processing of the amyloid-beta precursor protein, and in people with ischemia, the risk of AD is increased (Zhang, 2007; Ogunshola & Antoniou, 2009; Lee, 2016; Kim, 2017). Thus, the role of HIF stabilization in the development of AD is rather controversial and requires further research.

Parkinson's disease

Parkinson's disease is another widespread neurodegenerative age-related disorder associated with motor impairment (De Magalhães & Costa, 2009; Rodriguez, 2015). Parkinson's disease affects 0.3% of the world's population and 1-3% of people over 65 years (Shalash, 2018; Tysnes & Storstein, 2017). The causes of PD are not completely clear. The main feature of this disease is the progressive loss of dopaminergic neurons. In the initial stages of the disease, it occurs in the substantia nigra, bulb and dorsal nucleus of the vagus nerve, on the terminal stages in the pons, medulla, midbrain, mesocortical regions and neocortex. Another typical feature of the disease is the accumulation of α-

synuclein's Lewy bodies (LB) in the neuron's soma (Shahmoradian, 2019; Kalia & Lang, 2015; Singleton & Hardy, 2016; Braak, 2004; Stefanis, 2011).

Besides, there is strong evidence that mitochondrial dysfunction and oxidative stress contribute significantly to PD's pathogenesis (de Lau & Breteler, 2006; Hauser & Hastings, 2013; Ryan, 2015; Zhang, 2018; Burbulla, 2017). There is a decrease in the number and damage to the structure of mitochondria, as well as a decrease in the activity of mitochondrial respiratory chain complex I, which is possibly associated with the α-synuclein's action (Santos, 2014; Bir, 2014; Di Maio, 2016; Stefanis, 2011).

At present pharmacological dopamine replacement is the main therapeutic approach in PD. However, it provides only symptomatic treatment without a neuroprotective effect. Therefore, an active search for new promising therapeutic strategies is currently underway (Zádori, 2012; Jankovic, 2020; Mao, 2020).

The HIF-1 complex induces the activation of the expression of a whole complex of genes (Strowitzki et al., 2019; Semenza, 2014; Schofield and Ratcliffe, 2004), including the EPO and VEGF genes, the increased expression of which has a neuroprotective effect in PD models *in vitro* and *in vivo* (Xue et al., 2009; Falk et al., 2009; Sheikh et al., 2017). In the study by Feng, 2014, it was shown that the neuropeptide orexin-A has a neuroprotective effect in modeling PD in vitro by inducing HIF-1α and its downstream targets of HIF-1α, including vascular endothelial growth factor and erythropoietin. Systemic administration of EPO also modulates long-term synaptic plasticity (Almaguer-Melian et al., 2016), has antioxidant effects when injected into the striatum (but not into the substantia nigra) and reduces inflammatory responses (Thompson et al., 2020).

Therefore, HIF-mediated regulation of erythropoietin and other genes is also considered a possible approach to Parkinson's disease therapy.

Induction of HIF-1α can protect neurons from one of the damaging effects of PD - oxidative stress. It can be initiated in various ways based on the inhibition of proteins that mediate the degradation of HIF-1α via the ubiquitin-dependent proteasome pathway.

For example, it is possible to inhibit the expression of the von Hippel-Lindau protein (vHL) and E3 ubiquitin ligase using orexin (Feng et al., 2014; Liu et al., 2018; Liu et al., 2020) or inhibition of HIF prolyl hydroxylases using low molecular weight inhibitors and interfering RNA (Mehrabani et al., 2020; Johansen et al., 2010; Li et al., 2018b; Wu et al., 2010; Aimé et al., 2020). The use of a low molecular weight inhibitor of HIF prolyl hydroxylase made it possible to enhance tyrosine hydroxylase's expression and activity and thereby enhance the synthesis and release of dopamine. The studies were carried out on cell lines simulating PD *in vitro*, for example, PC12 (Johansen et al., 2010), SH-SY5Y (Li et al., 2018b; Wu et al., 2010; Aimé et al., 2020; Mehrabani et al., 2020) and on primary cultures of nerve cells from mice with PD or treated with the neurotoxin 6-OHDA for PD modeling (Zhang et al., 2020; Johansen et al., 2010). It is noted that inhibition of HIF prolyl hydroxylase makes it possible to normalize mitochondrial functioning. It has been demonstrated that stabilization of the HIF-1 complex in PD modeling normalizes the mitochondrial membrane potential, the rate of mitochondrial oxygen consumption and reduces the production of reactive oxygen species in PD modeling in vitro (Zhang et al., 2018). An interesting fact is that inhibition of apoptosis, stabilization and accumulation of HIF-1α are accompanied by an increase in autophagy (Wu et al., 2010). In animal models, it has been demonstrated that low molecular weight PHD inhibitors reduce the loss of tyrosine hydroxylase-positive neurons of the substantia nigra and attenuate behavioral disturbances in mice.

Among PHD inhibitors, compounds that do not bind iron seem to be more promising for use in the treatment of chronic neurodegenerative diseases since chronic administration of chelators can lead to restless legs syndrome (RLS) (Earley et al., 2014) or anemia (White, 2005).

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease or motor neuron disease, is a severe neurodegenerative age-related disorder characterized by the death of the upper and lower motor neurons of the spinal cord and motor cortex (Brown and Al-Chalabi, 2017; van Es et al., 2017). About 0.03% of the world's population is affected by ALS, and, usually, death occurs 3-4 years after the onset of the disease (Oskarsson et al., 2018; Longinetti and Fang, 2019; Wittie et al., 2013; Huisman et al., 2011; Logroscino et al., 2009; Hardiman et al., 2017). ALS causes muscle weakness and atrophy, which affects the muscles involved in breathing and can cause chronic respiratory failure (Brown and Al-Chalabi, 2017; Lechtzin et al., 2018; Niedermeyer et al., 2019).

In the pathogenesis of ALS, pronounced vascular changes and disturbances in blood flow accompanied by a decrease in the expression of EPO and VEGF develop (Miyazaki et al., 2011; Pronto-Laborinho et al., 2014), which causes tissue hypoxia. A decrease in oxygen concentration in tissues leads to excessive production of ROS and, in the future, to cell death (Tafani et al., 2016). Hypoxia and impaired adaptive responses are considered one of the probable factors of motor neuron death in ALS (Vanacore et al., 2010; Kim et al., 2013; Yamashita et al., 2020). Increased blood flow in hypoxic areas of the spinal cord may play an essential role in protecting against neurodegeneration in an animal model of ALS (Zheng et al., 2004; Tada et al., 2019).

In ALS, an increase in HIF-1α expression even before the onset of clinical symptoms, followed by a decrease, is observed (Nomura et al., 2019). It was found that dysregulation of both HIF-1α expression and the downstream pathway in response to hypoxia causes degeneration of motor neurons in ALS (Moreau et al., 2011; Sato et al., 2012; Nagara et al., 2013).

Reducing hypoxic damage by enhancing HIF-1α significantly prolongs survival in ALS mice, has a neuroprotective and anti-inflammatory effect and reduces motor neuron degradation (Nomura et al., 2019). It can be used for developing new therapeutic strategies for the treatment of ALS patients.

At the same time, in the study (Tada et al., 2019), the use of a prostacyclin analogue with ONO-1301-MS increases the survival rate and motor functions of animals with the ALS model by reducing the expression of HIF-1α, erythropoietin and vascular endothelial growth factor in the spinal cord. Further in-depth study of the role of a hypoxia-induced factor in ALS pathogenesis is required.

Huntington's disease

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disease characterized by chorea, dystonia, impaired coordination of movements and decreased cognitive functions (Walker, 2007; McColgan and Tabrizi, 2017; Kieburtz et al., 2018). The prevalence of the disease ranges from 0.0001% to 0.15% in different parts of the world. In general, HD can be found in 0.006% of the world's population McColgan and Tabrizi, 2017; Ohlmeier et al., 2019; Cheng et al., 2020).

The mutation responsible for HD is a higher number of CAG repeats in the huntingtin protein gene, which leads to an abnormally long expansion of a polyglutamine (polyQ) in the protein ((Rubinsztein et al., 1996; Chattopadhyay et al., 2003; Ha and Fung, 2002). This changes the protein and determines its toxic properties, causing neurodegeneration (MacDonald, 1993; Jimenez-Sanchez et al., 2016; Carroll et al., 2015). The disruption of mitochondrial proteins' production, oxidative phosphorylation and fragmentation of mitochondria are among the consequences of the destructive effect of mutant huntingtin protein (Yano et al., 2014; Browne, 2008; Riguet et al., 2020; Zheng et al., 2018)

Various ways to enhance mitochondrial function are currently considered as promising strategies for counteracting neurodegeneration (Yang et al., 2020; Burtscher et al., 2020). To slow down HD's development, influencing the molecular cascades involved in cell adaptation to hypoxia appears to be effective. However, there are still too few studies. For instance, the diminution of symptoms and the slowing down of the disease's progression in mice model of HD was demonstrated when using low molecular weight HIF PHD inhibitors in mice with an HD model. At the same time,

an increase in the viability of cortical neurons correlated with an increase in the expression of the VEGF gene, but not with the PGC-1α gene expression (Niatsetskaya et al., 2010).

Multiple sclerosis

Multiple sclerosis (MS) is a chronic autoimmune inflammatory neurological disease of the central nervous system that occurs most often in middle age (Goldenberg, 2012; Dobson and Giovannoni, 2018; Lin et al., 2018; Gilmour et al., 2018). The main cause of MS remains unclear. Today it is believed that a complex of genetic predisposition and the influence of a trigger factor (UV radiation, vitamin D, viral infections, smoking, obesity and other environmental factors) make the most significant contribution to the development of MS. (Ascherio, 2013; Handel et al., 2010; Mohammed, 2020; Belbasis et al., 2019; Nishanth et al., 2020; Ghareghani et al., 2018; Dobson and Giovannoni, 2018).

The development of inflammation, destruction of the myelin sheath, and axons' degradation are typical for multiple sclerosis. They manifest themselves in the form of sensory, motor and cognitive disorders, visual and speech disorders, increased fatigue and pain (Lin et al., 2018; Compston and Coles, 2008; Garg and Smith, 2015; Kamm et al., 2014).

There is currently no effective therapy for MS. There are three main strategies for the treatment, which are also used in combinations to provide complex therapy: treatment of relapse with anti-inflammatory drugs, symptomatic treatment and the use of drugs that change the course of the disease (disease-modifying therapies, DMTs) (Hart and Bainbridge, 2016; Dobson and Giovannoni, 2018; Auricchio et al., 2017; Gholamzad et al., 2018; Goldschmidt and McGinley, 2021; DeLuca et al., 2020; Hauser and Cree, 2020)

Among the factors predisposing to MS are decreased cerebral blood flow, impaired microcirculation, and local formation of toxic metabolites that inhibit mitochondrial activity. All these factors together lead to the development of a hypoxic state (Lassmann, 2003; Yang and Dunn, 2018; Aboul-Enein and Lassmann, 2005). Hypoxia is a universal pathogenetic component for all forms of multiple sclerosis in the early stages. It is assumed that hypoxia can act as a trigger in the pathogenesis of multiple sclerosis (Halder and Milner, 2020; Kappus et al., 2015; Yang and Dunn, 2018; Juurlink, 2013).

The significance of hypoxia in MS is that it can modulate the inflammatory processes that accompany the development of MS. In turn, inflammation can provoke the development of hypoxia, forming a vicious circle (Halder and Milner, 2020; Yang and Dunn, 2018; Martinez Sosa and Smith, 2017). The search for ways to break this vicious circle involves affecting molecular cascades activated under the influence of hypoxia, including the HIF signaling pathway.

Inflammatory processes are associated with increased oxygen consumption, which leads to local hypoxia and subsequently to local activation of HIF-1. The data on the effects of HIF-1 in multiple sclerosis are rather contradictory. Some studies show that stabilizing HIF-1 can slow down MS progression (Yao et al., 2008a; Yao et al., 2008b; Sun et al., 2010; Deng et al., 2016; Guan et al., 2017). On the other hand, it was revealed that HIF-1 might be involved in the activation of T cells in multiple sclerosis and contribute to a more severe course of the disease (Deng et al., 2016; De Riccardis et al., 2015; Juurlink, 2013).

Summing up, it should be noted that although a significant number of studies show that stabilization of HIF-1α protects neurons in various diseases associated with hypoxia and neurodegeneration, there is also evidence of a positive effect of a decrease in its expression. Further studies are needed to understand the boundary criteria for using modulators of the HIF signaling pathway.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

EM, MS and EP wrote the manuscript with input from all authors. EP ensured the financing of the project. EM and MV supervised the project, conceptualized the original idea and was in charge of overall direction.
All authors read and approved the final manuscript

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