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Dual Role of HIF-1α in Ischemic Stroke and Neurodegenerative Disorders

Akansha Jain[a], Rahul K. Maurya[a]*, Alok S. Tripathi[b], Mohammad Yasir[a], Lucy Mohapatra [a]

[a]Amity Institute of Pharmacy Lucknow Campus, Amity University Uttar Pradesh, Sector 125, Noida-201313 India
[b]Era College of Pharmacy, Era University, Lucknow-226003 India

ABSTRACT :

Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's, and Huntington's diseases are major socioeconomic burdens. Environmental and molecular variables may cause neurodegeneration (ND), which causes progressive brain dysfunction and motor or intellectual disability. Hypoxia reduces organ/tissue oxygen exposure. Reduced oxygen supply occurs during ND pathogenesis and aging. Despite their well-established association, the molecular events or mechanisms linking hypoxia to ND may be due to the effects of the transcription factor, HIF-1α, either positively or negatively. The pathophysiology of most NDs involves HIF-1α overexpression. HIF-1α's dual role as a "killer factor" or "protective factor" relies on the local cellular environment. This study examines the dual function of HIF-1α in both ischemic stroke and neurodegeneration, as well as the specific mechanisms by which HIF-1α is implicated in the response to these conditions.

Keywords: Neurodegenerative disorders, HIF-1α, Ischemic Stroke, Alzheimer's disease, ROS

1. Introduction :

The oxygen content in tissues is essential for the proper functioning of cells and the regulation of their development. Hypoxia, or a decrease in oxygen availability, can have varying consequences on the body based on factors such as the specific tissue, the intensity of exposure, and the duration of exposure. Extended and significant lack of oxygen leads to cellular impairment and mortality1. Conversely, hypoxia can stimulate molecular pathways in some stem cell systems, such as brain stem cells, to preserve their differentiation status and safeguard their DNA against oxidative harm2,3. Neurons in the central nervous system (CNS) are very susceptible to hypoxia, which can cause detrimental alterations in oxygen metabolism and mitochondrial activities4–6. These changes can ultimately lead to the death of neurons, resulting in damaging structural and functional consequences7,8.
Comprehending the significance of HIF-1α in ischemic stroke and neurodegenerative illnesses is essential because of its neuroprotective and harmful impacts on various cell types within the CNS9–12. In neonatal hypoxic-ischemic brain damage, HIF-1α can be neuroprotective or neurotoxic13. HIF-1α promotes erythropoietin (EPO) transcription, which activates neuroprotective pathways. Hypoxic-ischemic brain areas have neovascularization due to HIF-1α promotion of VEGF production. HIF-1α also increases EPO expression under mild hypoxia, which inhibits apoptosis13–16. During extreme hypoxia, HIF-1α increases p53 stability and participates in the apoptotic process, causing neurotoxicity17,18. HIF-1α affects cell necrosis by interacting with calcium and calpain. HIF-1α increases blood-brain barrier permeability, worsening brain edema. These qualities make HIF-1α neuroprotective and neurotoxic after hypoxia-ischemia.

HIF-1α is seen as a promising target for treating ischemic stroke, with ongoing development of new techniques and drugs that aim to regulate it for neuroprotection. Nevertheless, the wide range of downstream targets of HIF-1α in many cell types is a complex challenge, necessitating additional research to prevent contradictory outcomes. After a stroke, HIF-1α plays a critical role and may be therapeutically useful. HIF-1α, a pivotal controller of cellular reactions to low oxygen levels, serves a double function in ischemic stroke and neurodegenerative ailments. During a stroke, it facilitates the activity of neural stem and progenitor cells, stimulating the body's reparative reactions and improving behavioural recovery19. Neurodegenerative illnesses cause changes in the activity of HIF-1α and the expression of genes it controls, indicating a possible function in protecting the nervous system20. HIF-1α's participation in the adjustment of neurons and glia cells to low oxygen levels highlights its dual function, which may have significant consequences for different neurological disorders21. Furthermore, HIF-1α plays a crucial role in the adaptive metabolic response during cerebral ischemia, contributing to processes such as metabolism, proliferation, and angiogenesis.
HIF-1α is crucial in brain ischemia as it facilitates adaptive metabolic responses to low oxygen levels and is involved in activities such as metabolism, cell growth, and blood vessel formation22,23. Ischemic stroke is seen as a therapeutic target, with the potential to have both neuroprotective and harmful effects depending on the specific kind of cell. HIF-1α is controlled by oxygen levels and plays a role in multiple signalling pathways associated with neurological disorders, such as ischemic stroke. HIF-1 activation can enhance the transcription of genes associated with adaptation and survival24–28. HIF-1 is composed of α and β subunits and functions as a basic-helix-loop-helix-PAS heterodimer. HIF-1β forms a complex with other basic-helix-loop-helix-PAS proteins and is present in high amounts in cells. Therefore, the levels of the HIF-1 protein mostly control the transcriptional

activity of HIF-1. HIF-1α and Notch-1 signaling collaborate to induce neuronal cell death in ischemic stroke29. After ischemia-reperfusion, this triggers a sequence of events in the brain that lead to apoptosis, inflammation, and neurodegeneration. Evidence has demonstrated that inhibiting γ-secretase and HIF-1α can provide protection against ischemia stress and reduce neuronal death30. The combined use of both inhibitors yields superior results compared to their individual use. Various studies demonstrate that HIF-1α can elicit diverse responses following an ischemic stroke. There is data indicating that HIF-1 may protect neurons from cerebral ischemia. However, other research suggests that blocking HIF-1 with YC-1 can lead to higher mortality rates and larger areas of tissue damage in a rat model of ischemic stroke31–33.

Additionally, HIF-1 inhibition by YC-1 can ameliorate ischemia-induced blood-brain barrier disruption but does not affect brain edema20,21. The differential effects of HIF-1 in different brain cells highlight the complexity of its role in cerebral ischemia20,21. These effects could be attributed to the fact that HIF-1α has numerous downstream targets that function in various cell types within the neurovascular unit (NVU). HIF-1α is present in neurons, astrocytes, endothelial cells, and microglia, and has distinct effects on each cell type11. Inducing HIF-1α can initiate the process of transcribing genes that facilitate cellular adaptation and survival in low-oxygen conditions. However, due to its impact on many cell types and surroundings, it poses a challenge to specifically target it as a therapeutic intervention in cases of acute ischemic stroke.

1.1. Mechanisms by which HIF-1α is activated in response to ischemic stroke

HIF-1 regulates a responsive system in low oxygen conditions and is influenced by the level of oxygen. Hypoxia-inducible factor activation is a key part of how cells adapt to low oxygen levels, controlling how cells respond to hypoxia and helping cells stay alive by encouraging the production of endogenous metabolites and proteins that control metabolic pathways. HIF-1α remains stable through the assistance of co-activators and combines with HIF-1β to create a heterodimer[34,35]. Subsequently, this heterodimer activates genes that are involved in numerous physiological and pathological processes. Ischemic stroke causes inadequate blood flow to the brain, leading to the loss of nerve cells. Under conditions of low oxygen levels, the process of proline hydroxylation is inhibited, leading to the rapid accumulation of HIF-1α. This protein then binds with the β subunit and is transported to the nucleus, where it acts as a transcriptional activator for more than 100 genes[36–38]. A significant number of these genes participate in glycolytic pathways and result in a transition of energy generation from oxidative phosphorylation to glycolysis. HIF-1 promotes glycolysis by boosting the production of glycolysis enzymes, enhancing glucose transporters, and inhibiting mitochondrial energy metabolism[25,39–41]. HIF-1 facilitate the activation of pyruvate dehydrogenase kinase (PdK), which phosphorylates and inhibits pyruvate dehydrogenase (PDH). This is the step that limits the rate at which pyruvate is converted to acetyl CoA, which is used to fuel the mitochondrial TCA cycle[41–43]. Additionally, HIF-1 prevents the formation of Fe/S clusters that are necessary for oxidative phosphorylation. Additionally, it simultaneously obstructs the communication between the nucleus and mitochondria, hence preventing the expression of subunits encoded by the mitochondria in oxidative phosphorylation complexes. Upon activation of HIF-1, the transcription of genes associated with adaptation and survival can be enhanced. HIF-1 is composed of α and β subunits and functions as a basic-helix-loop-helix-PAS heterodimer. HIF-1β forms a complex with other basic-helix-loop-helix-PAS proteins and is present in high amounts in cells[6,44]. As a result, the transcriptional activity of HIF-1 is mostly controlled by the levels of HIF-1α protein.

The signalling pathways including Parkin/PINK1, DJ-1, PINK1, and Parkin knockouts are known to interact with HIF in the context of neurodegeneration[45,46]. Hypoxia and the hypoxia-inducible factor 1-alpha (HIF-1α) also modulate the expression of genes associated with Parkinson's disease. HIF-1α can directly alter the expression of PD-related genes such as LRRK2 and ATP13A2[9]. Insufficient oxygen levels can also lead to the accumulation of α-synuclein. Genes linked to Parkinson's disease can engage with hypoxia and HIF-1α signalling to control protein degradation, management of reactive oxygen species (ROS), and functioning of mitochondria[4,43,47–49]. Prolyl hydroxylase inhibitors have the ability to maintain stable levels of HIF-1α and exhibit potential as a therapeutic approach for neurodegenerative disorders like Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS)[50,51]. These inhibitors have the ability to enhance the synthesis of dopamine, reduce neuronal degeneration, enhance mitochondrial function, and decrease the creation of reactive oxygen species in cell models of Parkinson's disease. Oxidative stress can modulate the expression and functionality of HIF-1α by interacting with signalling molecules like NF-κB and TGF-β[52–55]. Neurotransmitters may influence the level of HIF-1α in neurons by influencing the functioning of complex I, facilitating alternate ATP production via glycolysis, or influencing energy production and the generation of ROS in the mitochondria. Inhibition of HIF-PHDs can stabilize HIF-1α and activate neuroprotective pathways in neurons. Modulating the levels of neurotransmitters can influence the expression of HIF-1α. CaM kinase, ARD1, and the generation of reactive oxygen species in mitochondria are responsible for this process[56,57]. Intermittent hypoxia triggers the activation of HIF-1 transcriptional activity and the expression of TH mRNA[58]. This process is inhibited by KN93, which is a calcium/calmodulin-dependent protein kinase inhibitor. CaM kinase II, which is constitutively active in non-hypoxic cells, also enhances HIF-1 transcriptional activity and TH mRNA levels. HIF-1 is essential for the survival of embryos and has a crucial function in the process of vascularization by controlling the activity of angiogenic growth factors such as VEGF[15,22,32,58] (Table-1).

Table 1 – Mechanisms by which HIF-1α is activated in response to ischemic stroke.

Mechanism	Description	Reference
Oxygen Sensing	Hypoxia due to ischemia leads to decreased oxygen levels, which stabilizes HIF-1α by preventing its degradation.	59
ROS Production	Ischemia-reperfusion injury generates reactive oxygen species (ROS) that can stabilize HIF-1α by inhibiting prolyl hydroxylases (PHDs).	
Metabolic Stress	Reduced ATP levels and increased glycolysis activate HIF-1α to adapt to the metabolic changes.	48,60
Calcium Signalling	Ischemia-induced calcium influx can activate signalling pathways that stabilize HIF-1α.	61–63
Inflammatory Cytokines	Release of cytokines like TNF-α and IL-1β during ischemia can activate HIF-1α through	

	NF-κB and other pathways.	
Growth Factors	VEGF and other growth factors released in response to ischemic injury can enhance HIF-1α activity.	64
pH Changes	Acidosis resulting from anaerobic metabolism during ischemia can stabilize HIF-1α by affecting PHDs.	39,65,66
PI3K/Akt Pathway	Activation of the PI3K/Akt pathway in response to ischemic injury promotes HIF-1α stabilization and activity.	67–69
Hypoxia-Responsive Elements (HREs)	HIF-1α binds to HREs in target genes, upregulating genes that aid in hypoxic adaptation.	70–72

Table2- Mechanisms by which HIF-1α is activated in response to neurodegeneration.

Mechanism	Description	Reference
Chronic Hypoxia	Sustained low oxygen levels in neurodegenerative conditions stabilize HIF-1α by preventing its degradation.	73
Mitochondrial Dysfunction	Impaired mitochondrial function leads to reduced cellular oxygen consumption, indirectly stabilizing HIF-1α.	49,74,75
Oxidative Stress	Accumulation of reactive oxygen species (ROS) in neurodegenerative disorders can inhibit prolyl hydroxylases (PHDs), stabilizing HIF-1α.	43,47,50
Protein Aggregation	Aggregates of misfolded proteins, a hallmark of neurodegenerative diseases, can induce ER stress and stabilize HIF-1α.	76,77
Inflammatory Cytokines	Chronic inflammation releases cytokines like TNF-α and IL-1β, which can activate HIF-1α through NF-κB and other pathways.	78–81
Metabolic Changes	Altered glucose metabolism and increased glycolytic activity stabilize HIF-1α under hypoxic conditions.	40,82
Calcium Dysregulation	Disturbances in calcium homeostasis can activate signalling pathways that enhance HIF-1α stability and activity.	61,63,83
Growth Factors	Neurotrophic factors and other growth factors released in response to neuronal damage can promote HIF-1α activity.	41,64,84,85
Autophagy	Impaired autophagy in neurodegenerative disorders can stabilize HIF-1α by reducing its degradation.	86–88
Hypoxia-Responsive Elements (HREs)	HIF-1α binds to HREs in target genes, upregulating genes involved in neuroprotection and adaptation to chronic stress.	89–91

1.2. Role of HIF-1α on neuronal cell survival and death

HIF-1α plays a role in regulating cellular apoptosis in developing rat brains under hypoxia and hypoxic-ischemic conditions. The expression of HIF-1α is upregulated after hypoxia or HI, with stronger staining in hypoxia compared to HI. The death of cells was worse in rats that were given HI than in rats that were given hypoxia. This suggests that HIF-1α may play a protective role in controlling apoptosis in neonatal hypoxia-ischemia brain injury. In the context of hypoxia-induced apoptosis, the activation of HIF-1 can initiates the process of cell death by upregulating the expression of pro-apoptotic proteins such as BNIP3, and by maintaining the stability of p53[17,18,87,92,93]. However, in the condition of hypoxia, the expression of antiapoptotic proteins such as IAP-2 can be stimulated, while the expression of proapoptotic proteins like Bax can be reduced, indicating a delicate equilibrium between factors that promote or inhibit apoptosis[94,95]. Research has proven that the absence of HIF-1α activity in neurons makes them more vulnerable to hypoxia-induced neuronal death, whereas the absence of HIF-1α activity in astrocytes can shield neurons from hypoxia-induced cell death. Even under conditions of severe and protracted hypoxia, HIF-1α continues to fulfill its protective function in neurons.

The expression of HIF-1α in specific neural cells is believed to be regulated by mTOR signaling, BMP2, and short-term exposure to high levels of oxygen[96–98]. Akt/mTOR pathway activation and BMP2 had a similar effect in stabilizing HIF-1α in cells generated from GBM[28,97,99]. Under hypoxic conditions, BMP2 reduces the levels of HIF-1α via modulating intracellular succinate levels and regulating the activity of PHD2 protein through inhibition of FKBP. Stabilizing HIF-1α suppresses the activation of Akt/mTOR in GBM cells caused by high levels of oxygen[28,97]. In certain forms of cancer, a reduction in SDH activity can lead to the stabilization of HIF-1α, even in the presence of normal oxygen levels[100]. Evidence proves that the PI3K/Akt signaling pathway regulates the production of HIF-1α in neurons under conditions of oxygen or blood flow deprivation. Research has shown that levels of p-Akt rise in response to hypoxia, occurring before the expression of HIF-1α. Application of wortmannin, a substance that inhibits the PI3K/Akt pathway, can greatly decrease the levels of HIF-1α and VEGF expression in cultured cortical neurons following oxygen and glucose deprivation (OGD)[73]. Downstream targets in ischemic stroke play a crucial role in neuroinflammation, oxidative stress, and cell death. Drugs that target signaling pathways like complement activation, inflammasome activation, and microglial phagocytosis can help people who have had an ischemic stroke.

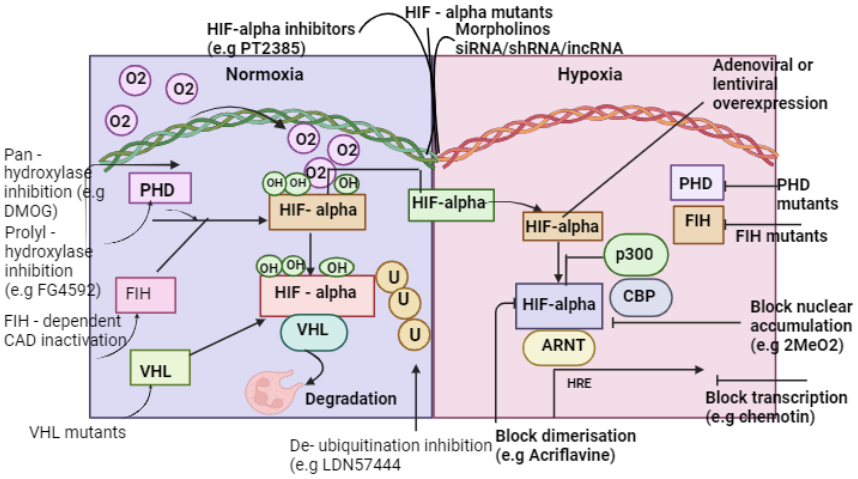

Fig.1- Molecular mechanism of HIF-1α induced neurodegeneration.

2. HIF-1α in ischemic stroke and neurodegenerative disorders: similarities and differences

HIF-1α plays a critical role in adjusting metabolic responses to low oxygen levels, such as metabolism, cell growth, and the formation of new blood vessels, in cerebral ischemia. The individuals with acute ischemic stroke and large vascular disease (LVD) had elevated levels of HIF-1α compared to individuals with small vascular disease (SVD)[101,102]. The levels of HIF-1α were significantly associated with both the initial and discharge NIHSS scores, indicating that HIF-1α could serve as a predictive marker for stroke outcomes[103]. HIF-1 controls the synthesis of chemokines in astrocytes under conditions of low oxygen. This affects the process of neuroinflammation that occurs after an ischemic stroke. This exacerbates neuroinflammation associated with stroke. During the progression of ischemic injury, astrocytes secrete proinflammatory cytokines such as IL-1β, IL-6, and TNF-α in an HIF-1-dependent manner. Microglia activation during an ischemic stroke leads to tissue damage and neuroinflammation. HIF-1 governs the process of neuroinflammation and the activity of glial cells[23,100,104]. The relationship between HIF-1α expression levels and the severity of neuroinflammation is suggested by the findings that HIF-1α+/- cells responded to hypoxia at a higher magnitude than HIF-1α+/+ cells, and MCP-5 expression correlated with the levels of HIF-1α in cells[105]. HIF-1α expression correlates with inflammatory indicators. Under simulated hypoxic circumstances, the activation of HIF-1α is achieved by inhibiting hydroxylases. Stabilizing HIF-1α in various animals reduces inflammatory markers such as IL-1β, IL-6, IL-12, and TNF-α[81,106].

Comorbidities can worsen the connection between HIF-1α expression and inflammatory indicators, resulting in heightened inflammation and the advancement of disease. In conditions such as osteoarthritis, the presence of comorbidities can worsen the outcomes of the disease by intensifying the inflammatory response, which is dependent on the HIF-1α protein. Proinflammatory cytokines increase the levels of HIF-1 in prostate hyperplasia, leading to the enlargement of the prostate[107]. Studies suggest that the presence of other medical conditions associated with inflammation can trigger the activation of HIF-1α and worsen the progression of the disease. There is a correlation between HIF-1α levels and disease severity in neurodegenerative disorders. Stabilization of HIF-1α might have a neuroprotective effect on Alzheimer's disease (AD) and other neurodegenerative disorders, potentially slowing down disease progression[12]. In AD patients, lower levels of HIF-1α are linked to higher levels of tau protein phosphorylation and neurofilament formation. Pharmacological activation of HIF-1 has shown promise in therapy for neurodegenerative disorders[20,21,108]. Elevating HIF-1 activity is regarded as a potential approach to address ischemic brain injury due to its ability to promote angiogenesis in injured brain tissue.

Similarities between Ischemic Stroke and Neurodegenerative Disorders

Hypoxia Response- The activation of HIF-1α in both ischemic stroke and neurodegenerative diseases in response to hypoxia triggers comparable initial defensive mechanisms that promote cell survival and adaptability[103].

Angiogenesis and Metabolism- HIF-1α promotes angiogenesis and metabolic changes to improve cellular adaptability in low oxygen levels under both situations[109,110].

Inflammation Modulation- The modulation of inflammatory responses by HIF-1α is essential in both situations, but the effect may differ depending on the setting and duration of the hypoxia insult[73,80,111].

Differences between Ischemic Stroke and Neurodegenerative Disorders

Acute vs. Chronic Hypoxia- In the case of ischemic stroke, hypoxia is often abrupt and severe, while in the case of neurodegenerative illnesses, hypoxia is typically persistent and mild to moderate in severity. As a result, the activation of HIF-1α and its subsequent effects undergo distinct temporal dynamics during this progression[6,19,20,29].

Pathophysiological Context- In ischemic stroke, the main damage occurs when there is a sudden interruption of blood flow to the brain. On the other hand, neurodegenerative illnesses are characterized by a slow deterioration of neurons over time, which can be caused by factors such as the accumulation of proteins, oxidative stress, and problems with the functioning of mitochondria[4,59,112].

Cellular Outcomes- The consequences of HIF-1α activation can vary depending on the context. In the case of stroke, the aim is to ensure rapid survival of cells and repair of tissue. On the other hand, in neurodegenerative illnesses, it aims to provide long-term protection for neurons and maintain cellular balance[81].

Inflammatory Responses- If inflammation generated by HIF-1α is not rapidly addressed, it can result in later damage in ischemic stroke. Conversely, in neurodegenerative illnesses, the ongoing inflammation controlled by HIF-1α might lead to gradual harm to the neurons[79,80,107].

3. Conclusion

HIF-1α facilitates adaptability and survival mechanisms in ischemic stroke and neurodegenerative diseases by regulating cellular responses to hypoxia. The intricacy of HIF-1α's participation in these situations is highlighted by the variations in the nature and duration of hypoxia, pathophysiological background, and cellular consequences, despite major parallels in its functions. Gaining a comprehensive understanding of these subtle distinctions can aid in developing specific therapeutic approaches that utilize HIF-1α's defensive capabilities while minimizing its possible harmful consequences. HIF-1α activation has been linked to the release of phagocyte extracellular traps and pro-inflammatory targets. Moreover, studies have shown that supporting the stability of HIF-1α leads to a decrease in inflammatory mediators and an increase in cell survival under ischemic conditions. It is worth exploring the potential application of hypoxia training to activate HIF-1α-induced cytoprotective signaling and reduce the severity of illness.

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