Review

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Activation of the HIF1α Pathway in Neurologic Disease: A Targetable Master Regulator to Reduce Neuropathology

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Abstract

Hypoxia is a prevalent characteristic of neurological diseases, including ischemic injury, neurodegeneration and infectious disease complications. Concurrently, hypoxia shapes both protective and pathological responses within the central nervous system (CNS). Central to this process is hypoxia-inducible factor 1α (HIF1α), a transcription factor that regulates cellular adaptation to reduced oxygen availability through coordinated glycolytic, inflammatory and cell survival pathways. Under hypoxic conditions, HIF1α transcriptional activity influences microglial activation, mitochondrial quality control, and cytokine production, thereby modulating neuroinflammation and neuroprotection. Preclinical evidence points toward hypoxia preconditioning being neuroprotective through HIF1α-dependent mechanisms in a context-dependent matter. This review synthesizes the current understanding of the role of HIF1α across neurological disease contexts, highlighting the intersection of hypoxia, neuroinflammation and neuronal survival. Ultimately, defining the cell-specific and context-dependent involvement of HIF1α will be critical for targeted therapeutic approaches to alleviate neuronal death and slow disease progression.

Keywords: hypoxia; HIF1α; CNS; neuroinflammation; hypoxia preconditioning; intermittent hypoxia; BBB disruption; neurological diseases; infectious diseases

Introduction

Neurological complications from infections, age-related diseases, and genetic disorders are a major cause of death worldwide. A key player in neurodegenerative diseases such as Alzheimer's, ALS, Cerebral Malaria (CM) and stroke are morbidities from neuronal death as a result of neuroinflammation, blood brain barrier (BBB) disruption and hypoxia [1–5]. While there are distinct downstream neuropathologies associated with these discrete diseases, the oxygen sensing pathway remains a core pathway associated with neurologic deficits [6–13]. Specifically, Hypoxia-Inducible Factor (HIF) signaling is an early event following CNS insults [14]. There are multiple Hypoxia-Inducible factors (HIFs), which are key proteins required for adaptations to low oxygen (hypoxic) environment, driving cell growth, metabolism and survival [15].

Inadequate oxygenation of tissue leads to the loss of homeostasis characterized by oxidative stress induced by reactive oxygen species (ROS) release, mitochondrial DNA release, and cell death [13,16,17]. Oxidative stress and inflammatory signaling pathways are intricately interconnected and result in a multi-level faceted response to stress [5,17–19]. Hypoxia allows for cell-specific

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transcriptional activity to adapt to the changes in the environment through regulation of HIFα proteins [20,21]. Transcriptional activity of HIF1α at the onset of hypoxia modulates immune mediation, as well as central nervous system (CNS) cell activity such as microglia, astrocytes, brain endothelial cells, pericytes and neurons [20,22,23]. These cells make up the neurovascular unit (NVU), which is a multicellular complex that functions to maintain brain homeostasis by regulating cerebral blood flow, maintaining the blood brain barrier (BBB), and controls nutrient supply through neurovascular coupling [24–27]. Recent studies have reported varying modulation of HIF1α transcriptional activity in the NVU and its contribution to neuroprotection [28–30] (Figure 2). Collectively, demonstrating that HIF1α expression modulates immune mediation in disease progression and regulates glial activation in BBB disruption and ischemia [31–33]. Therefore, this review aims to highlight the intricate modality of HIF1α transcriptional activity in neurovascular disease and distinguish the discrete roles of the HIF1a pathway in mitigating damage in the CNS.

1. HIF1α Transcriptional Activity Is Mediated by a Tight Network of Signaling Interactions

HIF signaling initiates a cascade of mechanisms that participates in an intricate feedback loop that heavily modulates the translation of HIF1α protein, its availability, transcriptional activity and its target genes. The levels of HIF1α regulation are protein synthesis, protein stability, and transactivation. In oxygen-rich organs such as the brain, heart, and lungs, oxygen homeostasis is crucial for normal function. Oxygen-sensing serves to initiate signaling cascades to ensure the clearance of damage cells and tissue [34,35]. Initiated in hypoxic regions, HIF signaling plays a major role in regulating inflammatory response and damage clearance. HIF1α transcriptional activity regulated by oxygen availability, regulates the expression of VEGF, TNFα, PDGFα, EPO, iNOS and genes associated with iron metabolism and glycolytic adaptations [15].

Under acute hypoxia, HIF1α protein accumulates in the cytoplasm, translocates to the nucleus, and heterodimerizes with HIFβ. The formation of this heterodimer binds to the hypoxia response element (HRE) of target genes, driving adaptations to damage and inflammation in the body [36,37]. This process involves distinct HIFα isoforms, HIF1α, HIF2α and HIF3α, which heterodimerize with HIF1β. HIF1α has been shown to play a major role as an early regulator of glycolytic genes, erythropoiesis and angiogenesis, whereas HIF2α has been shown to play a role in chronic adaptations in tissue-specific response, mainly in tumor microenvironments [38–41]. Alternatively, HIF3α functions as a negative regulator to HIF1/2α [42–46] by competitively binding to the HIF-1β subunit.

1.1. PHD Mediated Degradation by VHL Controls the Availability of HIF1α Protein

The prolyl hydroxylase domain (PHD) is an oxygen sensor which recruits von Hipple Lindau protein (pVHL) mediated degradation of HIFα [47]. Functionally, PHD proteins belong to a family of the 2-oxyglutarate-depedent dioxygenases, including PHD 1,2, and 3. Under normal oxygen levels (normoxia), through an iron-dependent mechanism, PHD reacts with molecular oxygen to hydroxylate the active (proline) residues of HIFα. Once hydroxylated, HIFα is recognized by pVHL which initiates 26S proteasomal degradation by the oxygen- dependent (VHL) E3 ubiquitin ligase complex [48]. Under hypoxia, limited molecular oxygen prevents PHD-mediated hydroxylation of the proline residues, thereby inhibiting HIFα degradation. As a result, HIFα protein accumulates in the cytoplasm and translocates to the nucleus for its transcriptional activity.

HIF signaling is a part of an intricate network of signaling cascades to promote response to infection, which led to extensive research on druggable targets of this pathway [49]. While research has shown that HIF1α, HIF2α and HIF3α degradation is modulated by PHD-mediated proteasomal degradation, there is limited research that shows signaling events modulating HIF2α and HIF3α [50,51]. Therefore, the signaling pathways discussed below will focus on HIF1α protein regulation.

1.2. Kinase Signaling Pathways Drives HIF1α Activity Through Phosphorylation Events

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The translation of HIF1α protein is tightly regulated by kinase signaling pathways. The activation of phosphatidyl inositol-4,5-biphosphate-3-kinase (PI3K) regulates protein synthesis through protein kinase B (Akt) and mammalian target of rapamycin (mTOR), where mTOR phosphorylation of eukaryotic translation initiation factor 4E (eIF-4E) binding protein (4E-BP1) regulates the initiation of cap-dependent mRNA translation to promote efficiency of HIF1α protein synthesis [51–54]. Additionally, growth factors on the cell surface stimulate the RAS/RAF/MEK/ERK (MAPK) kinase cascade, where activated ERK phosphorylates 4EBP1 and S6K and MAP interacting kinase (MNK) can directly phosphorylate eIF-4E [49,54]. These signaling events work to regulate HIF1α protein synthesis.

1.3. Transactivation Pathways Promote HIF1α Transcriptional Activity in the Nucleus

Once translated, HIF1α accumulates in the cytoplasm where mechanisms in place regulate the translocation of the protein in the nucleus to initiate transcriptional activity and protein stability. These are the transactivation pathways and degradation pathways, which are interconnected with the signaling pathways. For instance, PM1 or ERK1/2 can directly phosphorylate HIF1α to inhibit PHDs binding to the protein, stabilizing and increasing activity [15,51]. Phosphorylation events play a key role in creating an additional level of post-translational modifications to regulate HIF1α activity, where MAPK/ MNK pathway can regulate HIF1α independently of hypoxia (Figure 1). Ultimately, phosphorylation events occur at the translation level, post-translational level, and transactivation level of HIF1α. For instance, ERK phosphorylates the co-activator CBP/p300, stimulating HIF1α transcriptional complex formation and activation [55].

Other mechanisms involved in transactivation are heat shock protein 90 (Hsp90) and the FIH-1 pathway. Following the translation of the protein, Hsp90 can bind directly with HIF1α [56]. This induces conformational change to optimize coupling with HIF1β, forming the heterodimer necessary for transcription of its target genes. These distinct levels of HIF1α regulation illustrate the intricacies of HIF1α activity and the network of signaling pathways in place to respond to damage. These levels of HIF1α regulation are druggable targets for therapy.

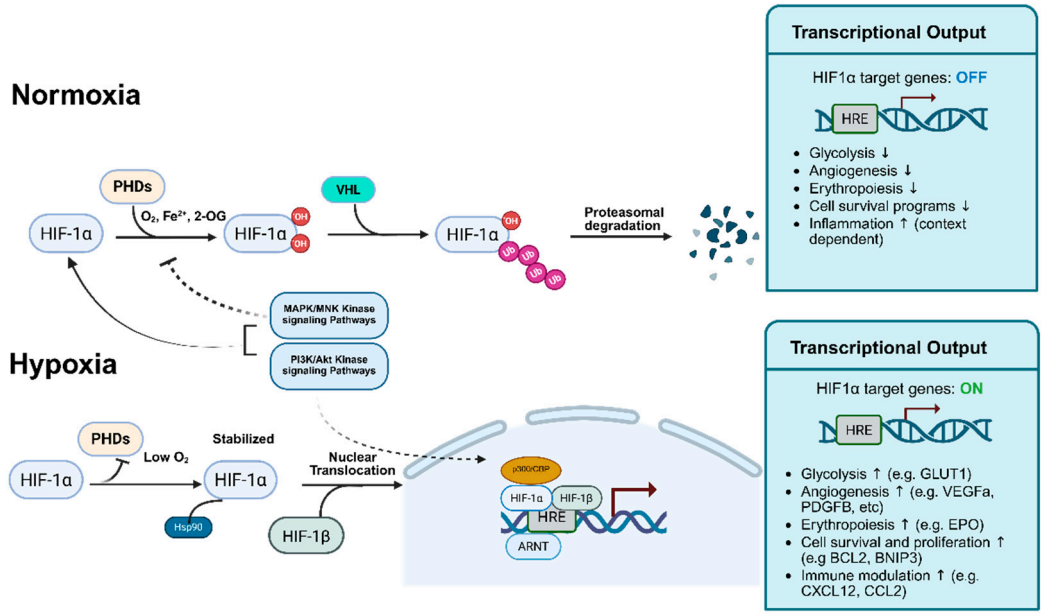

Figure 1. Post-translational modifications of HIF1α regulate its transcriptional activity. Under normoxia, HIF1α protein stabilization is modulated by prolyl hydroxylase domain (PHD) protein mediated proteasomal degradation, which suppresses its transcriptional activity. Under hypoxia, limited oxygen availability prevents

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PHD from binding to HIF1α, allowing for it to translocate to the nucleus and upregulate transcription of target genes. MAPK/MNK pathways and PI3K/Akt pathways regulate protein synthesis independent of hypoxia.

2. Hypoxia Preconditioning Yields Neuroprotective Effects in Cerebral Edema

Many studies exploring the effect of hypoxia and HIF1α manipulation stem from altitude sickness research. High altitude hypoxic injury, known as high altitude cerebral edema, is a life-threatening illness that develops when people are not properly acclimated to low oxygen levels in mountainous areas. Historically, to hasten acclimatization to high altitudes, people were exposed to low oxygen levels for short periods of time, known as intermittent hypoxia, or hypoxia preconditioning. Hypoxia preconditioning in ischemia and brain injury in murine models has been demonstrated to promote neuroprotection [35,57–61].

2.1. HIF1α Regulation of Microglial Activity Is Neuroprotective

Microglia have emerged as a major cellular component that mediates the effects of hypoxia. Microglial activation can release inflammatory cytokines, nitric oxide (NO), reactive oxygen species and tumor necrosis factor-α (TNFα), which are essential for normal nerve functions, but overexpression of these factors can result in damaging neuronal death [58,62–64]. Hypoxia preconditioning effectively reduces microglial hyperactivation following cerebral edema [65,66]. One study treated mice with hypoxia following middle cerebral artery occlusion brain injury, functioning to induce hypoxia following ischemia. Treatment with hypoxia significantly increased levels of HIF1α expression in microglia, and significantly lower iNOS expression compared to the normoxic group. This indicated that short-term hypoxia can effectively promote anti-inflammatory effects and protect neurons at early stages of cerebral ischemia [67,68]. This is further supported by in vitro studies in cultured activated microglia treated with 2-methoxyestradoil (2-ME), a HIF1α inhibitor. Treating both the normoxic and hypoxia treated group with 2-ME resulted in no difference in iNOS expression, concluding that HIF1α plays a vital role in iNOS expression in microglia. These findings indicate that HIF1α transcriptional activity in microglia drive the neuroprotection in hypoxia-induced cerebral ischemia [65].

2.2. Hypoxia Preconditioning Prevents Microglial Hyperactivation and Has Anti-Inflammatory Effects

Due to the extensive involvement of HIF1α transcriptional activity across diverse biological processes, there has been preclinical studies supporting the use of Roxadustat treatment for arthritis inflammation, myocardial infarction, ischemia, and AD. Employing the murine lipopolysaccharide (LPS) neuroinflammation model, it was determined that Roxadustat has access to the brain and preemptive treatment enhances hippocampal HIF-1 signaling pathways. Compared to intermittent hypoxia studies in mice, this finding revealed Roxadustat pre-treatment stimulates HIF1α, suppressing microglial hyperactivation. This was shown through transcriptional analysis of microglia following Roxadustat treatment. Additional transcriptional analysis of BV2 cells pretreated with Roxadustat determined that BNIP3, a target of HIF1α, is upregulated in this in vitro analysis. BNIP3 is BCL2/adenovirus E1b 19 kDa protein-interacting protein 3, regulated by HIF1α under hypoxic conditions acts a key mediator of mitophagy and programmed cell death. It has therefore been proposed that the HIF1α/ BNIP3 axis in hyperactivation of microglia occurs during neuroinflammation. To test this, in vivo shRNA knockdown of BNIP3 was performed and resulted in reduction of microglial hyperactivation with Roxadustat pre-treatment. Additionally, BNIP3-deficiency further exacerbated the expression of pro-inflammatory cytokines IL-6 and IL-1β mRNA levels [69–71]. These findings indicate that HIF1α transcriptional regulation of BNIP3 contributes to microglial activation and the anti-inflammatory effects of hypoxia preconditioning.

2.3. HIF Activation Induces Central Carbon Reprogramming in the CNS

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Hypoxia induces glycolytic changes and metabolic adaptations in following injury or infection through HIF1α transcriptional regulation. The human brain has a high energy demand which requires large amounts of glucose and O2 for ATP production, making it extremely susceptible to hypoxia and ischemia. Employing the murine middle cerebral artery stroke model, it was determined that neuron-specific PHD2 inactivation reduces brain injury and functional impairment through HIF-dependent mechanisms. This study generated a neuron-specific conditional knockout strategy expressing Cre recombinase under the calcium/calmodulin-dependent protein kinase II alpha (Camk2a) promoter crossed with PHD2 loxP mice to generate a neuron-specific PHD2 knock down. These neuronal Phd2-deficient mice exhibited significant upregulation of mitochondrial biogenesis, similar to observations in intermittent hypoxia mouse studies [72]. This confirmed prior observations where reversal of the altered expression of genes with Hif1α and Hif2α genetic ablation. Using western blot analysis and semi-targeted GC/MS transcriptional analysis, it was determined that a HIF-dependent central carbon metabolic reprogramming switch to aerobic glycolysis was responsible for improved neuronal ischemic tolerance [72]. Consistent with this observation, transcriptional analysis of preventative Roxadustat treatment to PHD-deficient mice identified statistically significant overlap in differential metabolites, confirming that both genetic and pharmacological activation of HIF transcription activity and signaling leads to changes in central carbon metabolism in the CNS [72]. Ischemic studies have therefore demonstrated that hypoxia preconditioning is a promising therapeutic for chronic stroke.

2.4. Hypoxia Preconditioning Improves Patient Outcome in Clinical Trials

This is further supported by recent clinical studies testing hypoxia preconditioning as a novel therapeutic intervention to facilitate recovery of function in stroke patients [60]. A clinical study concluded that acute intermittent hypoxia can be tolerable for chronic stroke patients through improving strength without adverse side effects [73]. While this is a promising intervention, further investigation is necessary to ensure treatment viability and maximize therapeutic outcomes in human patients [74–77]. An alternative approach to induce the effects of hypoxia is through PHD inhibition. FG-4592, also known as Roxadustat, is a (HIF-PHD) dioxygenase inhibitor that has been FDA approved for anemia in cystic kidney disease (CKD) patients [78,79]. Roxadustat functions through inhibiting HIF-PHD interaction, which in turn simulates hypoxic conditions. The treatment resulted in improved red blood cell production and increased iron metabolism in CKD patients [80–82] and rescues neurogenesis and synaptic plasticity in experimental animal models [83]. While these studies are conducted in stroke and CKD, it is important to understand the overarching implications in neurological disease pathologies. Especially given that chronic stroke is among neurological disorders characterized by neurodegeneration following vascular disease.

3. The HIF1a Pathway as a Therapeutic Target to Prevent Neurodegeneration

Beyond ischemic models, there is emerging evidence that report varying contributions of HIF1α transcriptional activity to neuropathology in neurologic disease. For instance, in vitro and in vivo preclinical studies pinpoint HIF1α transcriptional activity as a driver for Aβ pathology in Alzheimer's Disease [59,84–86] Some reports even indicate that HIF1α in fact plays no role in Aβ pathology [87]. Recent studies, report that HIF1α protect against Aβ plaque induced toxicity and reduce tau phosphorylation, promoting neuroprotection [14,88–91]. Like ischemia models, a few AD studies, indicate the anti-inflammatory and neuroprotective role of HIF1α through downregulation of GLUT-1 and GLUT-3 and other metabolic adaptations [92–94].

Additional preclinical studies have determined that effective drug treatment of experimental AD models is increasing levels of HIF1α which reduces Aβ aggregation and p-tau. The iron chelator, M30 (2-octahydroisoquinolin-2(1H)-ylethanamide) was reported to have a neuroprotective effect and improve spatial memory in mice [95–98]. Another iron chelator deferoxamine (DFO) can upregulate HIF1α and its target genes through the p38 MAPK signaling pathway [99–102]. Altogether, the neuroprotective effects of HIF1α activation across different neurological disease models, demonstrate

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the central role of HIF1α in antiinflammation and preventing neurodegeneration. Therefore, targeting HIF1α has become an attractive option in neurological diseases.

4. Hypoxia-Induced Neuroinflammation in Infectious Diseases

4.1. HIF1α Stimulation May Improve Immunity Against Viral Infection

In response to viral infection, HIF signaling and the inflammatory response is recruited to clear and kill damaged cells and tissue [103–105]. Studies have shown that HIF1α expression in myeloid cells is essential for promoting glycolysis, energy production, phagocytosis, cytotoxicity, and migration to hypoxic regions in SARS-CoV-2 infection [106]. HIF1α transcriptional activity in infiltrating myeloid cells can increase expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα) and interleukin-1 (IL-1β) to promote pathogen clearance and drive effector differentiation, IFN-γ, perforin expression. Additionally, HIF1α activity modulates co-stimulatory receptors to promote cytolytic function and reduce T cell exhaustion in viral infection [107,108]. A COVID-19 clinical study reported that cytotoxic lymphocytes are functionally exhausted, where SARS-CoV-2 infection may reduce antiviral immunity at an early stage [109].

Various studies in preclinical models show that HIF stabilizers improve viral infection outcome. For example, a hamster model of SARS-COV-2 infection demonstrated Roxadustat treatment reduced viral load and epithelial damage [110]. Comparatively, HIF stabilizers, Daprodustat and Roxadustat, reduced viral load and inflammation in the lungs in murine syncytial virus infection [61] and reduced lung inflammation and improved outcomes in murine influenza A [111], respectively. Translated into clinical study, Vadadustat treatment, another FDA-approved oral HIF-PHD inhibitor for CKD, resulted in improved patient outcomes and reduced systemic inflammation from SARS-CoV-2 infection in acute and chronic lung injury [112]. Collectively, HIF1α transcriptional activity enhances pathogen clearance and allows for a metabolic switch to effectively allow immune response to combat chronic infection.

4.2. HIF1α-Targeted Therapy as a Strategy to Reduce Morbidity Associated with Cerebral Malaria

To recapitulate BBB disruption and neuropathologies seen in human CM, the Experimental Cerebral Malaria (ECM) model is employed, where BBB disruption occurs following Plasmodium berghei ANKA (PbA) infection in mice [4,113–115]. In ECM, HIF1α levels correlate with increased VEGF protein levels as parasite load increases [116]. Where it has been shown that hypoxia in the brain, blood, spleen, heart and various organs also increase with parasite load, which can be a result of red blood cells death and neuroinflammation [116]. Additionally, studies show malaria infection induces VEGF upregulation to promote angiogenesis and improve oxygen supply to tissues experiencing infection-induced hypoxia [18,117,118]. Bridging these findings, there is a strong role of the HIF-VEGF pathway in the pathologies observed in CM. While CM is a complex neurological disease that is still widely not understood, HIF1α still plays a vital role in the pathologies associated with morbidity [119,120]. Interestingly, a clinical study reported that elevated levels of VEGF are associated with a decreased risk of readmission or death in children with severe malaria anemia [121], and a preclinical trial explores EPO therapy to combat cerebral malaria [122]. Since HIF1α regulates VEGF and EPO, HIF1α-targeted therapy effectively becomes a potential avenue for treatment for CM.

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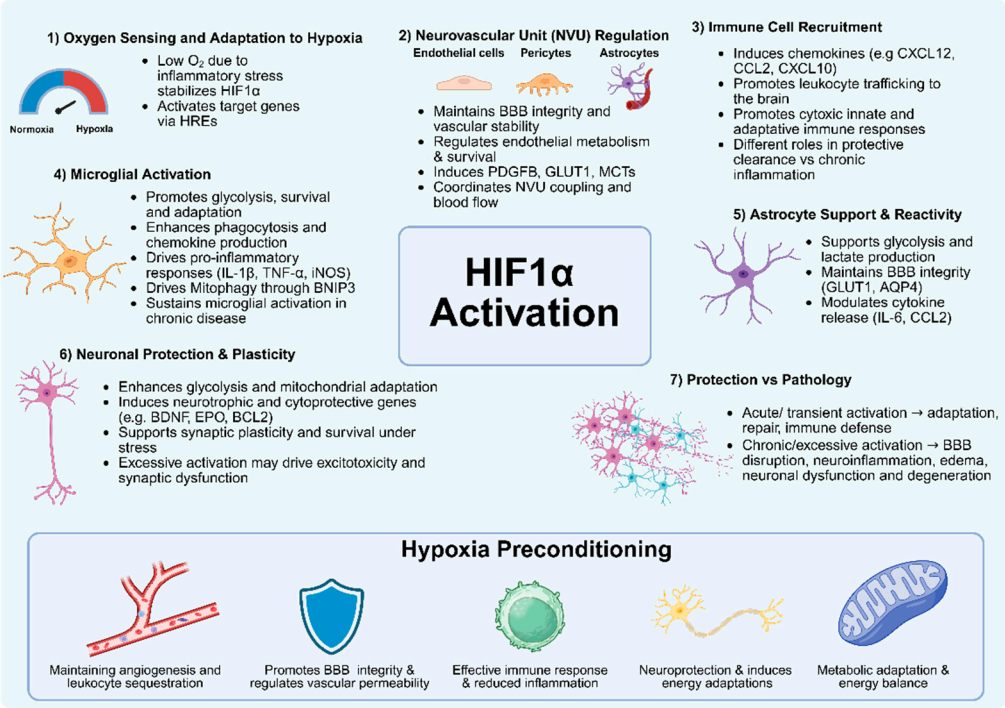

Figure 2. HIF1α activity in the CNS tightly regulates response to brain injury and infection. Under hypoxia, HIF1a coordinates neurovascular, immune, and metabolic responses that support CNS adaptation and survival, while prolonged activation can drive inflammation, BBB disruption and neurodegeneration. **1)** Adaptations to low oxygen conditions drive transcriptional activity of HIF1α, which **2)** maintains BBB integrity and regulates permeability. This regulates endothelial cells, pericyte activity, **3)** recruit immune cells and induces **4)** microglial activation. HIF1α activation works to enhance neurovascular unit (NVU) dynamics by improving **5)** astrocyte support and reactivity to maintain the barrier and respond to the neuronal microenvironment to **6)** promote neuronal **7)** protection and reduce pathogenicity. Under stress and extensive damage, these processes can become deleterious, however, hypoxia preconditioning has been proven to promote beneficial HIF1α transcriptional activity in neurological diseases and brain injury.

4. Discussion

This body of evidence highlights that HIF signaling, inflammatory and kinase signaling pathways create an intricate network of sensors designed to maintain homeostasis. By inducing hypoxia following organ insults, the body utilizes HIF1α activity to drive adaptations and metabolic shifts to promote neuroprotection in the brain. In this review, synthesizes current evidence on hypoxia-induced mechanisms that contribute to neuroprotection in ischemia, AD and infectious diseases. Overall, HIF1α transcriptional activity promotes neuroprotection through microglial inactivation, induction of mitophagy (BNIP3), suppression of pro-inflammatory cytokines (IL-1β, IL-6, TNFα) and chemokines (CCL2, CCL12) by CNS cells (Figure 2) and attenuating toxicity associated with neurological disease pathologies [123–125].

While current models have established a role for HIF1α signaling in neurological diseases, the spatial and cell-specific dynamics of this response remain poorly defined. Therefore, future work should aim to dissect the bidirectional interactions between CNS cells and CD8T cells, and how their interactions contribute to BBB disruption and neuronal death. Therefore, future studies should investigate the role of HIF1α activity in infiltrating immune cells and resident CNS cells in driving neurological complications linked to neuronal death and morbidity. Powerful tools such in vivo imaging and flow cytometric analysis can be paired with conditional gene ablation strategies in mouse models or AAV viral vector technologies to target specific cell types. Emerging clinical evidence indicates that intermittent hypoxia has therapeutic potential in brain injury and

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neurodegenerative disease. Accordingly, the modulation of HIF1α transcriptional activity presents a promising strategy to mitigate neuronal death and improve patient outcomes.

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