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REVIEW

A Hypoxia-Inflammation Cycle and Multiple Sclerosis: Mechanisms and Therapeutic Implications

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Abstract

Purpose of Review Multiple sclerosis (MS) is a complex neurodegenerative disease characterized by inflammation, demyelination, and neurodegeneration. Significant hypoxia exists in brain of people with MS (pwMS), likely contributing to inflammatory, neurodegenerative, and vascular impairments. In this review, we explore the concept of a negative feedback loop between hypoxia and inflammation, discussing its potential role in disease progression based on evidence of hypoxia, and its implications for therapeutic targets.

Recent Findings In the experimental autoimmune encephalomyelitis (EAE) model, hypoxia has been detected in gray matter (GM) using histological stains, susceptibility MRI and implanted oxygen sensitive probes. In pwMS, hypoxia has been quantified using near-infrared spectroscopy (NIRS) to measure cortical tissue oxygen saturation (StO_2), as well as through blood-based biomarkers such as Glucose Transporter-1 (GLUT-1). We outline the potential for the hypoxia-inflammation cycle to drive tissue damage even in the absence of plaques. Inflammation can drive hypoxia through blood–brain barrier (BBB) disruption and edema, mitochondrial dysfunction, oxidative stress, vessel blockage and vascular abnormalities. The hypoxia can, in turn, drive more inflammation.

Summary The hypoxia-inflammation cycle could exacerbate neuroinflammation and disease progression. We explore therapeutic approaches that target this cycle, providing information about potential treatments in MS. There are many therapeutic approaches that could block this cycle, including inhibiting hypoxia-inducible factor 1-α (HIF-1α), blocking cell adhesion or using vasodilators or oxygen, which could reduce either inflammation or hypoxia. This review highlights the potential significance of the hypoxia-inflammation pathway in MS and suggests strategies to break the cycle. Such treatments could improve quality of life or reduce rates of progression.

Keywords Inflammation · Hypoxia · Multiple sclerosis · Hypoxia-inducible factor · Treatment

Introduction

Multiple sclerosis (MS) is a complex disease that involves both inflammation and autoimmunity [1]. Historically, it was considered a disease of the nerves, as it involves demyelination and loss of function of the central nervous system (CNS) [2, 3]. As more evidence is gathered, it has become clear that the pathophysiology is highly complex, involving various cell types and multiple forms of cellular damage [3]. This includes inflammatory cell invasion, as well as damage to oligodendrocytes, astrocytes and cells associated with blood vessels and the blood–brain barrier (BBB).

Given this complexity, treatment approaches have evolved as well. Currently, three categories of disease treatment are being considered [4]. One is a treatment that will cure people with MS (pwMS) such that there is no further cell damage,

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and function is restored. This represents the ultimate goal. A second type is a treatment that will prevent progression to more severe symptoms. The third includes treatments that address symptoms and improve quality of life. In some cases, the latter two types of treatment may overlap.

An example of overlap includes many of the anti-inflammatory treatments. Those that reduce specific types of inflammatory responses, such as blocking T-cell activation, were expected to fall under the second category, where periods of relapse are reduced, and symptoms appear to stabilize. We now find that people on some of these treatments still had an inexorable loss of brain volume. Thus, atrophy persisted even with a lack of relapses [4]. Short of a cure for MS, there remains a critical need for treatments that reduce both symptoms and progression. To find such treatments, targets are required and to find the targets, a greater understanding of the basic pathophysiology of the disease is required.

This paper focuses on the occurrence of oxygen deficiency (hypoxia) in many pwMS and MS animal models. Evidence also suggests an interaction between hypoxia and inflammation. We will present evidence for a hypoxia-inflammation cycle that may contribute to MS pathogenesis and discuss its potential as a treatment target.

Inflammation-Induced Hypoxia

Inflammation and hypoxia are now recognized to be integral to the phenotypes of MS. It is important to determine whether inflammation or hypoxia occurs first [5]. In the current review, we discuss a negative hypoxia-inflammation cycle, and assume inflammation comes first. However, this is not critical for the existence of such a cycle. In the experimental autoimmune encephalomyelitis (EAE) model of MS, inflammation is certainly the initial step, as it is triggered with an adjuvant often accompanied by pertussis toxin. Even before motor symptoms and demyelination occurs, there is elevation of pro-inflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α) in the hypothalamus, and IL-6 and TNF-α in normal appearing cortical gray matter (GM) [6, 7]. Thus, although most work on the EAE model is in the spinal cord, there is diffuse CNS inflammation.

There is strong evidence that inflammation can cause both hypoxia and upregulation of hypoxia-response genes. Using the hypoxia marker EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide], the endothelial area of intestinal mucosa shows significant hypoxia [8]. Inflammation may cause hypoxia through multiple pathways. Research on Coronavirus disease 2019 (COVID-19) supports this hypothesis and may have identified a similar negative feedback loop to that which we propose for MS: *"a vicious cycle, as infection- and hypoxia-related inflammation cause capillary function to deteriorate, which in turn accelerates hypoxia-related inflammation and tissue damage."* [9]. Similar damage also occurs in sepsis [10].

Abnormal oxygen delivery, where it no longer meets demand, will cause hypoxia. Inflammation can result in both physical blockage of the microvasculature and abnormal regulation in the vasculature [11, 12]. The phenomenon called "*vascular stalling*" halts capillary perfusion possibly in association with pericyte constriction or leukocyte adhesion [13]. BBB disruption occurs with inflammation, followed by edema. Edema, and changes in regulation can shift flow from gas exchanging small vessels to less effective microvascular shunts [12]. Inflammation-induced edema, and therefore hypoxia, may be regional, as lipopolysaccharide (LPS) induced CNS inflammation in a mouse model causes periventricular edema [14]. Periventricular lesions are recognized as a phenotype of MS, perhaps relating to this link between inflammation and hypoxia [15].

Impairment in blood flow regulation with inflammation can also cause hypoxia [16, 17]. Astrocytes are certain to play a role in inflammation-induced hypoxia. They are associated with inflammation related disruption of the BBB and development of edema [18]. This may involve pericyte constriction [19].

Also, hypoxia could occur if oxygen utilization increases without an appropriate increase in perfusion. Inflammation is associated with changes in the metabolism of inflammatory cells that could cause an imbalance in oxygen delivery. In theory, demyelinated neurons may also have a higher metabolic rate for a given action potential. Thus, inflammation could cause the hypoxia observed in MS.

Evidence for Hypoxia in MS

The hypothesis that hypoxia plays a role in MS pathogenesis was first proposed in 1990, suggesting that MS might be characterized, at least in part, as a cerebrovascular condition [20]. This vascular injury triggers a cascade of biochemical and physiological events, ultimately leading to ischemic hypoxia, phagocytosis of endothelial cells, and consequent demyelination. This process is then compounded by a secondary immune response that exacerbates the damage. However, in many cases, such inflammation-induced hypoxic-like lesions occur in the absence of significant vascular damage, and thus certain inflammatory mediators, in particular reactive oxygen species (ROS), nitric oxide (NO), or their combined products may induce mitochondrial dysfunction [21]. Structural and functional mitochondrial damage in acute lesions has been confirmed, while in inactive plaques, increased mitochondrial activity indicates higher energy

demand in demyelinated axons [22, 23]. Additionally, MS samples show suppressed mitochondrial respiratory chain complexes in axonal pathology [24]. Further supporting this concept, a multi-center European study demonstrated that serum lactate levels—an indicator of anaerobic metabolism—were significantly higher in individuals with MS compared to healthy controls, with the highest levels correlating with disease progression [25]. The strong positive correlations between lactate levels, Expanded Disability Status Scale (EDSS) scores, and various clinical and radiological outcomes underscore the potential link between mitochondrial dysfunction and MS progression [25, 26]. As evidence accumulated, the idea of *"virtual hypoxia"* was identified as a significant mechanism in MS, while highlighting various methods to quantify it [5, 27]. This, however, is a potentially related but distinct concept from true hypoxia, which involves actual oxygen deficiency [5].

Hypoxia in MS Animal Models

Over the past decade, studies on MS animal models like EAE have consistently quantified hypoxia using a range of in vitro and in vivo techniques. Researchers discovered significant hypoxia in the lumbar spinal cord of EAE rats using two independent methods: pimonidazole labeling and oxygen probes. In this study, severity of hypoxia closely mirrored the extent of neurological impairment [28]. Notably, partial pressure of oxygen (PO_2) levels normalized during periods of disease remission but dropped sharply again during relapses. Furthermore, they demonstrated that hypoxia was linked to increased labelling of hypoxia-inducible factor 1α (HIF-1α) in neurons. The blood vessels in the spinal cord also showed changes consistent with the body's action to compensate for this hypoxia. Specifically, during relapse periods, rats with neurological impairments had larger and more numerous blood vessels in the lumbar and sacral areas. Additionally, the overall size of the spinal cord increased during periods of disease activity, further supporting the presence of hypoxic conditions. These findings imply that hypoxia may not only reflect but also drive pathological changes in the spinal cord, potentially setting the stage for early inflammatory events that contribute to demyelination.

More recently, researchers used a LPS injection to mimic the molecular events of inflammatory demyelination, identified early-stage transient hypoxia in the spinal cord [29]. This hypoxia was particularly prominent at the white matter (WM)/GM junction and in the dorsal white column and was associated with elevated levels of reactive oxygen species (ROS) and NO, preceding the onset of demyelination. Based on these findings, the researchers proposed a model where the activation of innate immune responses triggers transient hypoxia in susceptible vascular regions, initiating pathological changes that contribute to disease progression. This concept was further studied in the other part of the CNS, using mixes of in vivo and in vitro techniques.

In one study, susceptibility-weighted imaging (SWI) was used to detect hypointense lesions in the spinal cord and cerebellum of EAE and control mice [30]. Blood was then removed through perfusion with saline. The rationale was that if the SWI lesions disappeared following the removal of blood from vessels, this would indicate they were caused by deoxyhemoglobin, suggesting that these areas were relatively hypoxic. In the spinal cord, SWI lesions were primarily located at the WM/GM boundary, with some found in the ventral WM. In the cerebellum, SWI lesions were largely observed in the WM tracts, mostly in regions with perivascular cuffs. Moreover, results showed that many SWI lesions, especially at the WM/GM boundary of the lumbar spinal cord and in the cerebellum, disappeared after perfusion, suggesting that these lesions were associated with deoxyhemoglobin and hypoxia. This was a groundbreaking approach to identifying hypoxic lesions; however, a more practical method was needed that did not require sacrificing animals.

A solution was to modify the inspired oxygen content during SWI imaging to identify deoxyhemoglobin-driven hypointensities in vivo [31]. SWI was performed on the lumbar spinal cords of naïve control and EAE mice using 30% O_2, followed by 100% O_2. In some mice, imaging was also conducted after perfusion. Most SWI lesions observed with 30% O_2 changed in appearance with 100% O_2 and were no longer visible after perfusion. Those lesion changes upon O_2 alteration, indicates that they were most likely driven by deoxyhemoglobin and hypoxia. This research suggest that future studies could employ this method to assess the impact of vascular hypointensities with SWI in tracking the progression of EAE and MS over time.

In vivo oxygen measurements were conducted over time in the cerebellum and cortex of awake EAE mice [32]. Fiber-optic-based PO_2 sensors were implanted to allow continuous measurement over several weeks. The study revealed a marked increase in PO_2 variance following the induction of autoimmunity, with a pattern that was primarily hypoxic. Notably, significant hypoxia was observed in the GM of both the cerebellum and cortex, with cortical hypoxia occurring in approximately 75% of the measurements. The diminished PO_2, in the cerebellum and in the cortex, was sufficient to potentially stimulate a hypoxic response, which may influence immune modulation. Furthermore, the study suggested that greater behavioral impairment correlates with increased hypoxia and PO_2 variance. The cerebellum was identified as becoming hypoxic earlier than the cortex, implying a rostral progression of hypoxia from the spinal cord to the cortex in EAE model.

In order to assess oxygenation and vascular integrity in the spinal cord of EAE animals, light sheet fluorescence

microscopy and optoacoustic imaging was used in real-time and non-invasively [33]. Comparing the spinal cords of EAE mice to those of healthy mice, the researchers discovered decreased hemoglobin content and oxygen saturation, which may indicate hypoxia and impaired perfusion in the cord.

Evidence for hypoxia was also seen in the optic nerves of the EAE model [34]. Acutely inflamed optic nerves were marked by significant hypoxia, which was tightly associated with the upregulation of several innate immune factors, including superoxide, NO, and peroxynitrite. These results suggest that the hypoxia may be caused by insufficient perfusion of blood vessels, likely driven by vasoconstriction, increased tissue pressure from edema, and compression of blood vessels by extravasated cells. In their review on tissue energy dynamics in MS, Desai and Smith concluded that recent findings suggest hypoxia plays a significant role in MS pathogenesis and neurological dysfunction [35].

Hypoxia in People with MS

For years, researchers have suggested that hypoxia plays a role in MS pathophysiology, drawing parallels between the histological features of types III and IV lesions and ischemic lesions [36]. According to recent research, lower metabolic rates in MS appear to be widespread, especially in GM, rather than localized [37]. These findings imply that hypoxia in MS may be a diffuse phenomenon, affecting multiple regions of the brain, beyond just the plaques, emphasizing the importance of considering GM when quantifying hypoxia. The first direct measurement of hypoxia in human volunteers was done using frequency-domain near-infrared spectroscopy (fdNIRS). This method indirectly assessed cortical hypoxia by measuring tissue oxyhemoglobin saturation (StO_2) within the microvasculature.

Studies demonstrated that 42% of pwMS had statistically lower StO_2 values compared to healthy controls, with this threshold defined as two standard deviations below the control mean [38]. A significant correlation was found between StO_2 values and clinical disability, as measured by the EDSS. These findings were pioneering in showing how quantitative NIRS can be utilized to detect reduced StO_2 in pwMS. Subsequent studies have confirmed low values for StO_2 in cortical GM of pwMS [39–42].

Research shows that hypoxia persists for at least a year in 80% of cases [39]. The fact that more individuals remained hypoxic rather than returning to normoxia suggests that hypoxia development may be tied to disease progression. Functional imaging studies using functional NIRS showed that normoxic pwMS exhibit higher brain coherence—a measure of brain function—compared to hypoxic subtypes [40]. This finding suggests that hypoxia may be associated with alterations in brain function and other disease-related functional changes. Although hypoxia in MS persists chronically for at least a year and impacts brain coherence, only a weak correlation was observed between cognitive functioning and brain StO_2 [39]. These findings, which suggest a weak correlation between brain hypoxia and cognitive function as well as disease severity, are consistent with later studies [42]. This limited association may be attributed to the heterogeneous nature of MS and the intricate factors influencing levels of hypoxia. Further investigation into brain StO_2 values in the progressed MS subtype revealed that individuals with secondary progressive MS (SPMS) have significantly lower cortical StO_2 compared to age-matched controls, reinforcing the role of hypoxia in the pathogenesis of SPMS. These studies underscore the potential of using NIRS to quantify hypoxia in MS, offering invaluable insights.

Blood-based biomarkers and other non-imaging methods have also been used to look into hypoxia and progression in pwMS [43]. People with SPMS have considerably greater concentrations of Glucose Transporter-1 (GLUT-1) than healthy controls. GLUT-1 is a known marker of hypoxia and affects glucose metabolism. Furthermore, more impairment has been linked to low levels of angiogenesis biomarkers, such as hepatocyte growth factor (HGF) and angiopoietin-2 (APN2), indicating the possible involvement of vascular components in hypoxia and its connection to the advancement of disease.

Sleep apnea research also provides evidence of increased hypoxia [44]. Increased cognitive impairments are correlated with varying levels of apnea severity in pwMS. Specifically, apnea severity was linked to deficits in processing speed, attention, working memory, visual memory, psychomotor speed, cognitive flexibility, and manual dexterity. These findings highlight the significance of considering relevant factors, like sleep disruptions, while studying hypoxia in MS.

The Hypoxia-Inflammation Cycle

The concept is that inflammation can induce hypoxia, which leads to the upregulation of hypoxia-response genes. This, in turn, triggers a negative hypoxia-inflammation cycle [45]. The fact that there is an interaction between hypoxia and inflammation responses is now well established [46]. Once a hypoxic condition exists, a multitude of responses occur which can further increase inflammation (Fig. 1).

A master regulator of hypoxia associated gene transcription is the HIF pathway. HIF-1β is steadily expressed. HIF-1α is also produced but is rapidly degraded under normal oxygen conditions through the ubiquinone pathway and prolylydroxylases (PHD). This pathway is inhibited under hypoxic conditions, resulting in a build-up of HIF-1α. This binds to HIF-1β, resulting dimer translocates to the nucleus,

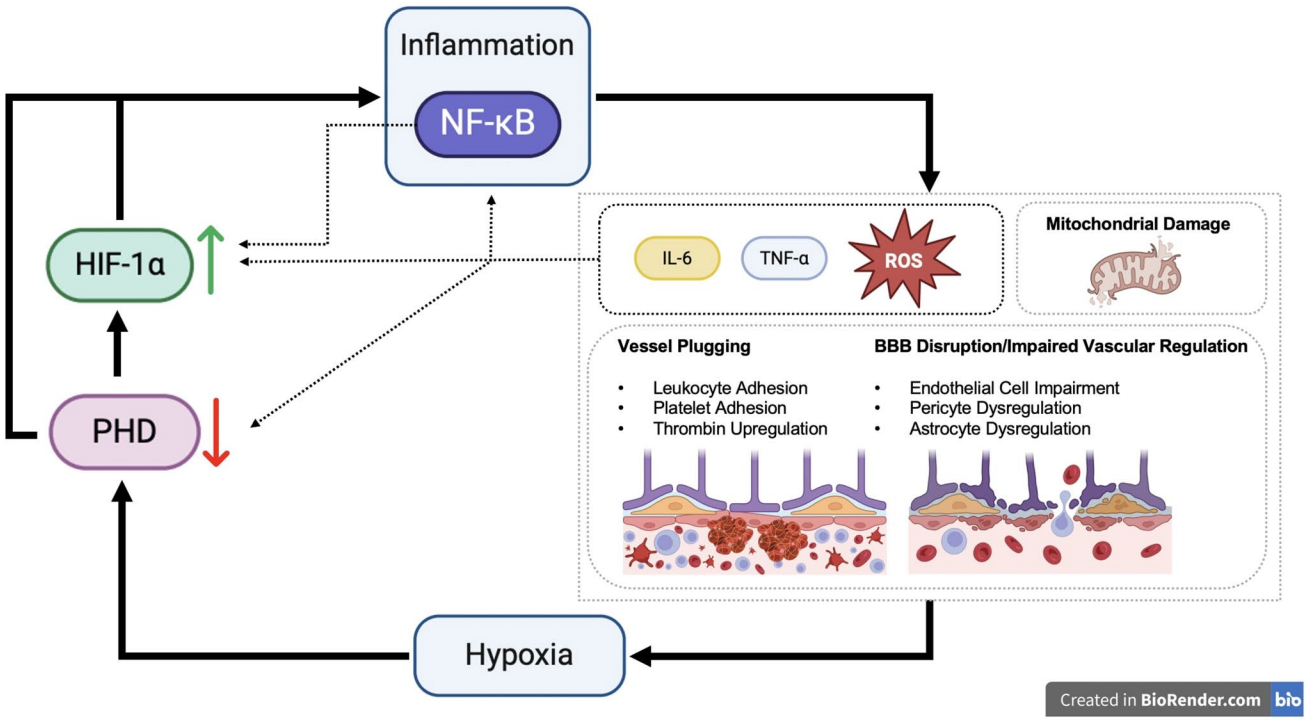

Fig. 1 A Hypoxia-Inflammation Cycle. Inflammation triggers numerous responses that lead to hypoxia and upregulate hypoxia-response genes. These inflammatory factors contribute to vessel plugging through mechanisms like leukocyte and platelet adhesion and thrombin upregulation, as well as blood–brain barrier (BBB) disruption via the dysregulation of endothelial cells, pericytes, and astrocytes. Furthermore, inflammation can independently upregulate hypoxia-responsive genes, even in the absence of low oxygen conditions. In turns, many hypoxia-related gene responses can, in turn, amplify inflammation. Major regulatory targets of this feedback loop include prolyl hydroxylase domain (PHD) enzymes, hypoxia-inducible factor 1-alpha (HIF-1α), and nuclear factor kappa B (NF-κB). Image created using Biorender.com

where it results in transcription of hundreds of hypoxia-associated genes [47].

Inflammatory responses can also stabilize HIF-1α in an oxygen-independent fashion [48]. For instance, human pulmonary epithelia cultured with respiratory syncytial virus showed stabilization of HIF-1α without a decrease in oxygen levels [49]. Mechanisms are complex but can involve protein kinase A [50]. After LPS-induced inflammation, HIF-1α stabilization may also involve sirtuin 1 (SIRT1) or the 60-kDa Tat-interactive protein (Tip60) [51, 52].

The master regulator of inflammation is NF-κB through either the canonical or non-canonical pathway. There is evidence that the canonical pathway is stimulated by hypoxia through inhibition of the PHDs, leading to the activation of IκB kinase (IKK). This results in the degradation of IKK, allowing for upregulation of NF-κB [53, 54]. Hypoxia induction of inflammation often involves disorders where there is a question of what comes first—hypoxia or inflammation [5]. High altitude adaptation research is helpful as hypoxia is likely the driving event. A range of inflammatory response genes are activated in humans during high altitude exposure including Toll-like receptor 4 (TLR4) and genes associated with active neutrophils and phagocytes [55].

Inflammation can also stimulate a hypoxia-associated gene response through oxygen-independent stabilization of HIF-1α during inflammation may also involve factors such as ROS production, TNFα and IL-1β, as well as changes in PHD regulation [56, 57].

Thus, inflammation can cause hypoxia, resulting in two outcomes: the upregulation of the hypoxia-response genes through HIF-1α stabilization, and the upregulation of inflammation-associated genes through both the oxygen-sensing PHD system and HIF stimulated transcription of inflammatory genes. Some of these inflammatory products further stabilize HIF in a non-oxygen sensitive mechanism.

Specific Hypoxia-Inflammation Interactions

The key point is that there is a complex interaction between hypoxia, and inflammatory gene responses. There is a clear link between HIF and TLR4, as HIF can stimulate the production of TLR4 [58]. The oxygen-independent stabilization of HIF may be facilitated by TLR4, which in turn stimulates further TLR4 production, establishing a positive feedback loop [56]. TLR4 production is associated with increases in the inflammatory products such as TNFα and

IL-1β, Inducible nitric oxide synthase (iNOS), ROS and NO [59].

The complexity of the interaction between HIF, hypoxia, and inflammation is exemplified by myeloid cell activation, which is particularly important in MS, as cells like macrophages migrate to sites of injury and plaque formation. The response may vary depending on the cell type. Increased neutrophil activity may require HIF-2α and, depending on the state of the myeloid cell, HIF can either enhance or supress inflammation [48].

SIRT-1 is induced by hyperoxia and reduced by hypoxia [51]. SIRT-1 deficiency increases activity of NF-κB. There is an interaction between SIRT-1 and HIF-1α that impacts regulation of both the innate and adaptive immune responses [60].

Extracellular matrix metalloproteinase inducer (EMMPRIN) is induced by HIF-1α, vascular endothelial growth factor (VEGF), and MMP-1 expression in human retinal microvascular endothelial cells [61]. EMMPRIN upregulation is associated with both hypoxia and inflammation, and is elevated in a range of diseases, such as MS and Alzheimer's disease [62].

Hypoxia can stimulate conversion of microglia to the pro-inflammatory type 1 phenotype [63, 64]. HIF-1α plays multifactorial role in regulating macrophage activity, including reducing macrophage autophagy [64].

The monocyte plugging and vascular blockage are linked to increased TNF-α and thrombin as well as platelet metabolism. For example, the endothelial protein C receptor inhibits leucocyte extravasation, but TNF-α downregulates this receptor, promoting cell adhesion. Thrombin, platelets, and fibrinogen together contribute to microvascular damage [65].

This short list of examples highlights the growing awareness, and therefore critical importance, of the interaction between immune responses and hypoxia [5, 46, 66–68].

Potential Therapeutic Approaches Associated with the Hypoxia-Inflammation Cycle

There are various therapeutic approaches that could target different aspects of the hypoxia-inflammation pathway. As shown in Table 1, the upregulation of HIF-1α, pro-inflammatory cytokines (e.g., NF-κB), inflammatory mediators (e.g., ROS), mitochondrial dysfunction, and leukocyte adhesion represent potential initial targets for studying these treatment options, though they are not the only possibilities. However, given the complexity of the hypoxia-inflammation cycle, this review primarily focuses on these factors. These molecules and drugs are not proposed as a cure but may help improve quality of life or slow the progression associated with this cycle.

Table 1 Potential therapeutic targets and corresponding molecules/drugs for addressing upregulated pathways in hypoxia-related inflammatory conditions

Initial target	Molecule/Drug	Reference
HIF-1α upregulation	2-methoxyestradiol (2MeO-E2)	[69]
	Digoxin	[70]
	Topotecan	[71]
	PX-478	[72]
	Cyclo-CLLFVY	[73]
	RO7070179 (EZN-2968)	[74]
	D-mannose	[75]
	Tanshinone IIA (Tan-IIA)	[76]
	Curcumin	[77]
	Hydroxychloroquine	[78]
	Roxadustat (FG-4592)	[79]
	Cyclosporine	[80]
	Sevoflurane	[81]
	4-octyl itaconate (4-OI)	[82]
	YC-1	[83]
	Echinomycin	[84]
	Metformin	[85]
TNF-α upregulation	Infliximab	[86]
	Adalimumab	[86]
	Clemastine	[87]
Leukocyte adhesion	SR1001	[88]
	Lipoxins	[89]
	Eplerenone	[90]
NF-κB upregulation	Dimethyl fumarate (DMF)	[91]
ROS upregulation	Resveratrol	[92]
Mitochondrial dysfunction	Biotin	[93]
Vascular dysregulation	Nicardipine	[94]
	Nimodipine	[95]

The table is a short list of the many potential agents that target hypoxia-inducible factor 1-alpha (HIF-1α), tumor necrosis factor-alpha (TNF-α), leukocyte adhesion, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), reactive oxygen species (ROS), and mitochondrial dysfunction

Regulation of HIF-1α can be achieved through inhibition or stabilization, which respectively aim to suppress inflammatory genes or activate hypoxia-responsive elements, facilitating adaptation in ischemic conditions [96]. There are various HIF-1α inhibitors. Non-specific inhibitors include 2-methoxyestradiol (2MeO-E2), which targets HIF-1α at the mRNA and protein levels, and cardiac glycosides like digoxin, which inhibit HIF-1α synthesis and show potential benefits in ischemic tissues [69, 70]. Specific small-molecule inhibitors such as Topotecan, PX-478 (*S*-2-amino-3-[4′-*N,N*,-bis (2-chloroethyl) amino]-phenyl propionic acid *N*-oxide dihydrochloride), and cyclo-CLLFVY have been identified, each working through different

mechanisms like inhibiting translation, reducing mRNA levels, or preventing HIF-1α dimerization [71–73]. Additionally, RO7070179 (EZN-2968), a locked nucleic acid antisense oligonucleotide, inhibits HIF-1α expression and downregulates target genes [74]. While these inhibitors show promise, further research is needed to evaluate their safety and efficacy in humans and potential in treating hypoxia in MS [96]. Several drugs inhibit HIF-1α or modify its bindings to directly impact immune cells towards anti-inflammatory phenotypes. This can occur without involving the HIF-1α as well. The mechanisms can vary depending on the targets [97].

Inhibiting HIF-1α promotes an anti-inflammatory macrophage phenotype by disrupting glycolysis and related pathways. Compounds like D-mannose, and Tanshinone IIA (Tan IIA) reduce HIF-1α activation, altering macrophage polarization from the pro-inflammatory M1 type to the anti-inflammatory M2 type [75, 76, 98]. Curcumin and hydroxychloroquine also reduce HIF-1α levels and inflammation, contributing to improved macrophage function and decreased inflammatory cytokine release [77, 78].

Anti-inflammatory drugs also suppress inflammation by inhibiting inflammatory cytokines and neutrophil activity, with HIF-1α as a key target. Roxadustat (FG-4592), a PHD inhibitor, stabilizes HIF-1α to prevent neutrophil infiltration and reduce hypoxia-induced inflammation [79]. Cyclosporine enhances neutrophil HIF-1α expression, aiding glycolysis and reducing migration in conditions like ulcerative colitis [80]. Sevoflurane inhibits neutrophil adhesion by stabilizing HIF-1α and the Adenosine A2B receptor [81]. Itaconic acid and its derivative, 4-octyl itaconate (4-OI), reduce pro-inflammatory cytokines and inhibit neutrophil extracellular traps (NET) formation by suppressing HIF-1α [82]. Additionally, HIF-1α inhibitors like YC-1[3-(5′-hydroxymethyl-2′-furyl)-1-benzyl indazole] block inflammatory signaling pathways, specifically involving NF-κB, reducing neutrophil infiltration [83].

Under hypoxic conditions, the imbalance between regulatory T (Treg) and T helper 17 (Th17) cells drives inflammation, with Th17 cells promoting cytokine release, including TNF, IL-6, and IL-17. TNF and IL-17 inhibitors, such as infliximab and adalimumab, are used to treat inflammatory diseases and may influence the hypoxia-inflammation pathway [86]. Compounds like SR1001, reduces Th17 differentiation and function [88]. HIF-1α modulates inflammation and T cell interactions, and inhibitors like echinomycin improve Treg development while suppressing Th17 activity [84].

Other drugs can shift immune cells toward anti-inflammatory phenotypes in broader, less specific ways. Eplerenone, for instance, downregulates leukocyte adhesion and inhibits vessel plugging [90]. Lipoxin is a pro-resolving lipid mediator that inhibits neutrophil recruitment and activation while promoting the clearance of apoptotic neutrophils by macrophages [89]. This process helps shift macrophages toward an anti-inflammatory M2 phenotype and reduces inflammatory responses. Similarly, clemastine, an antihistamine, shows immunomodulatory effects by reducing microglial activation, which is crucial in neuroinflammation [99]. In MS, clemastine aids remyelination and indirectly affects T cell responses by mitigating neuroinflammation [87].

There are substances influence the inflammation-hypoxia pathway through more direct anti-inflammation and antioxidant mechanisms. For instance, dimethyl fumarate activates oxidative stress responses by upregulating Nrf2 and is currently used in treating RRMS [91]. Resveratrol shows antioxidant effects by reducing intracellular ROS and mitigating hypoxia-induced apoptosis but has negative effects on demyelination and inflammation in MS [92, 100]. Metformin inhibits HIF1α-driven inflammation in macrophages by inducing its degradation through mitochondrial complex I inhibition, reducing oxygen consumption independently of ROS [85]. It also inhibits Th17 cells and enhances Treg activity, while suppressing dendritic cell activation, thereby reducing T cell-mediated inflammation [101]. Biotin, used in progressive MS, supports mitochondrial function by regulating fatty acid synthesis and energy production, indirectly influencing the hypoxia-response [93]. Similarly, dihydropyridines like nicardipine, calcium channel blockers, modulate calcium levels in cells, including mitochondria [94]. By maintaining calcium homeostasis, nicardipine reduces oxidative stress and prevents mitochondrial dysfunction and ROS production, ultimately affecting hypoxia levels. Dihydropyridines, as vasodilators, have the potential to reduce vascular resistance and address hypoxia related to vascular dysfunction [102]. Notably, nimodipine, which has been studied in the EAE model of MS, has demonstrated the ability to restore spinal oxygenation, improve neurological function, and reduce demyelination [95]. These effects contribute to improved oxygen delivery and may alleviate hypoxic conditions caused by impaired blood flow [102].

In animal models of MS, research has demonstrated the potential effects of normobaric oxygen therapy in reversing hypoxia, partially restoring function, and reducing disease severity. Studies using the LPS rat model have shown that breathing normobaric oxygen not only reduces demyelination but, in some instances, prevents it altogether [28, 29]. This includes initially addressing the HIF-1α upregulation and inflammatory pathway, mitochondrial dysfunction, vasodilation impairment, or energy demand alterations [45]. In human MS, the objective has been to explore the relationship between oxygen therapies and disease outcomes. However, no human study to date has controlled for hypoxia levels when administering oxygen. Many of these studies have shown moderate or limited success [103, 104]. However, considering that only approximately 40% of pwMS exhibit

hypoxia in GM at any given time, it would be valuable to control for brain oxygenation levels in future trials.

Conclusion

The evidence in this review highlights the important role hypoxia plays in MS pathogenesis, as seen in both pwMS and MS animal models. The hypoxia-inflammation cycle emerges as a potential key driver of disease progression, leading to tissue damage even in the absence of overt inflammation. This hypoxia-inflammation cycle likely drives many of the pathological changes seen in MS, including BBB disruption, oxidative stress, mitochondrial dysfunction, vascular abnormalities, and heightened inflammatory responses. The uncertainty surrounding whether hypoxia or inflammation occurs first in real-world MS adds complexity to this phenomenon. We present evidence supporting the presence of hypoxia in both MS animal models and pwMS. The ability to perform non-invasive, real-time quantification of hypoxia is a groundbreaking step toward understanding this phenomenon. However, these techniques are not without limitations. Optical-based imaging tools, such as fdNIRS, have shown promise in quantifying microvasculature hypoxia and hold potential for clinical application. Still, further research is necessary to identify a direct biomarker for hypoxia in the CNS of pwMS. Further, targeting the hypoxia-inflammation cycle offers a promising opportunity for therapeutic interventions that may not only alleviate symptoms but also slow disease progression. By categorizing individuals based on their oxygenation status, treatments can be more precisely tailored, potentially improving outcomes for those with hypoxia-driven disease characteristics. Moreover, given the complexity of the cycles and the broad spectrum of potential treatments (only some of which are noted in this paper), combining therapeutic approaches could yield significant benefits. Overall, the hypoxia-inflammation pathway presents a new target for treatment strategies.

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  - This study offers insights into targeting the hypoxia-inflammation cycle in MS by studying the biochemical mechanisms that regulate Hypoxia-inducible factor (HIF) stabilization and exploring molecular strategies to pharmacologically inhibit HIF-1α, a crucial mediator in the hypoxia-inflammation cycle.

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  - This study examines how immune cells are altered under hypoxic conditions and proposes treatment options targeting different immune cells. These options may directly affect immune cell function or indirectly involve other elements of the hypoxia-inflammation cycle.

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Declarations

Competing Interests The authors declare no competing interests.

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