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GAPS & CONTROVERSIES

The Hypoxia Response Pathway: A Potential Intervention Target in Parkinson's Disease?

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ABSTRACT: Parkinson's disease (PD) is a progressive neurodegenerative disorder for which only symptomatic treatments are available. Both preclinical and clinical studies suggest that moderate hypoxia induces evolutionarily conserved adaptive mechanisms that enhance neuronal viability and survival. Therefore, targeting the hypoxia response pathway might provide neuroprotection by ameliorating the deleterious effects of mitochondrial dysfunction and oxidative stress, which underlie neurodegeneration in PD. Here, we review experimental studies regarding the link between PD pathophysiology and neurophysiological adaptations to hypoxia. We highlight the mechanistic differences between the rescuing effects of chronic hypoxia in neurodegeneration and short-term moderate hypoxia to improve neuronal resilience, termed "hypoxic conditioning". Moreover, we interpret these preclinical observations regarding the pharmacological targeting of the hypoxia response pathway. Finally, we discuss controversies with respect to the differential effects of hypoxia response pathway activation across the PD spectrum, as well as intervention dosing in hypoxic conditioning and potential harmful effects of such interventions. We recommend that initial clinical studies in PD should focus on the safety, physiological responses, and mechanisms of hypoxic conditioning, as well as on repurposing of existing pharmacological compounds. © 2023 International Parkinson and Movement Disorder Society.

Key Words: hypoxia; hypoxia-inducible factor 1α; mitochondrial dysfunction; neuroprotection; Parkinson's disease

Parkinson's disease (PD) is the fastest-growing neurological disorder worldwide.[1] Clinically, PD presents with a gradually progressive variety of motor and nonmotor symptoms with debilitating effects on quality of life. Treatment options are limited to symptomatic therapies. In the past decade, several novel disease-modifying

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interventions have been investigated without proof of efficacy.[2]

Complex I is the first complex of the adenosine triphosphate (ATP)-producing mitochondrial oxidative phosphorylation (OXPHOS) system, and among the main producers of reactive oxygen species (ROS), especially during pathological conditions.[3-5] The fact that cellular energy shortage is a feature of PD,[6] combined with the observation that complex I deficiency can be a direct cause of progressive parkinsonism,[7] supports a key role for mitochondrial energy dysfunction in PD. In this context, exposure to chronic long-term hypoxia mitigated oxidative stress and rescued neurodegeneration in preclinical models of mitochondrial dysfunction.[8-10] Interestingly, evolutionarily conserved adaptive neuronal responses to hypoxia, including the hypoxia-inducible factor 1 (HIF-1) cascade, impact beneficially on pathophysiological mechanisms in PD.[11] Moreover, exposure to transient moderate hypoxia activates pathways that increase mitochondrial volume and decrease oxidative damage,[12] potentially increasing nigrostriatal dopamine (DA) concentration.[13,14] Furthermore, it is hypothesized that the potential neuroprotective and neuroplastic effects of exercise, for which there is preliminary evidence supporting its disease-modifying effect in PD, could be mediated by the hypoxia response pathway. The latter is supported by the observation that exercise induces the HIF-1α subunit,[15] and hypoxia-induced stabilization of HIF-1α appears necessary for exercise-induced nigral neuroprotection.[16] Furthermore, the protective effects of the hypoxia response pathway on brain energy rescue might be a prerequisite for targeting other energy-intensive processes of PD pathophysiology such as lysosomal dysfunction.[6] Finally, the broad interconnected action mechanism of hypoxia-mediated metabolic adaptations might overcome the single-pathway paradigm of most unsuccessful precision medicine approaches of recent years.[2] Taken together, targeting the hypoxia response pathway might be a promising novel treatment strategy in PD.[11]

We first inventorize the hypoxia-induced neurophysiological responses and adaptations to different hypoxic stimuli. Furthermore, we link these responses to PD-related pathophysiology and symptoms and discuss pharmacological compounds that induce the hypoxia response pathway. Finally, we address the controversies associated with targeting this pathway by discussing the safety, design, and differential effects across the PD spectrum of hypoxic conditioning trials.

The Connection between Hypoxia and PD

Mitochondria and Oxidative Stress Are Central to PD Pathophysiology

Although detailed etiological mechanisms are currently lacking, a central role for mitochondrial aberrations in PD is supported by various PD susceptibility genes as well as mitochondrial dysfunction-associated oxidative stress and neuroinflammation. Mitochondrial deficiency in PD is characterized by reduced neuronal OXPHOS functioning, impaired autophagic removal of damaged mitochondria (mitophagy), and dysfunctional signaling transduction cascades.[6] Neurons in the substantia nigra are particularly vulnerable to mitochondrial deficiency as they are among the most energy-consuming cells in the human brain and display a high ROS production integral to DA synthesis and their neuronal structure.[6] Furthermore, nigral neurons in PD have reduced antioxidant levels,[17] which further exacerbates ROS-induced damage, although nigral neurons can adapt to somatic mitochondrial DNA mutations to a considerable extent.[18] Mitochondrial dysfunction–induced oxidative stress disturbs metabolic homeostasis, causes neuroinflammation, accelerates cellular aging, and can induce programmed cell death (apoptosis).[19] In this context, it has been demonstrated that various genes associated with early-onset PD play a key role in (the regulation of) mitochondrial function and oxidative stress responses. These include leucine-rich repeat kinase 2 (*LRRK2*), protein deglycase DJ-1 (*PARK7*), PTEN-induced kinase 1 (*PINK1*), PARKIN (*PRKN*), and HtrA Serine peptidase A2 (*HTRA2* or *PARK13*).[19] This suggests that stimulating cellular adaptive pathways to mitochondrial dysfunction and oxidative stress might improve long-term neuronal resilience.[8,18]

Acute Hypoxia Induces Adaptive Responses That Maintain Mitochondrial Function and Counterbalance Oxidative Stress

Acute hypoxia induces an evolutionarily conserved response involving the HIF-1-mediated adaptation of neuronal metabolism to low-oxygen conditions (Fig. 1).[8,9,20-22] During normoxic conditions the HIF-1α degradation domain is hydroxylated by prolyl hydroxylase domain (PHD) and factor inhibiting HIF-1 (FIH). Subsequently, hydroxylated HIF-1α is ubiquitinated by the von Hippel-Lindau factor (pVHL), inducing HIF-1α breakdown.[22] On hypoxia induction, the enzymatic activity of PHD and FIH is decreased, HIF-1α hydroxylation is reduced, and pVHL binding is inhibited. As a consequence, HIF-1α is stabilized and accumulates in the nucleus,[23-25] where it associates with HIF-1β to bind to the hypoxia response element (HRE) in the promotor region of target genes. HIF-1 is involved in cellular bioenergetic homeostasis and protection against oxidative stress.[26] In concert with increased ROS production, which acts as a (co)signaling factor[27] and further stimulates HIF-1a stabilization,[27,28] the aforementioned pathways converge on pro-survival and antioxidant proteins. These include erythropoietin (EPO), vascular endothelial growth factor (VEGF), and brain-derived neurotrophic factor (BDNF). Importantly, HIF-1

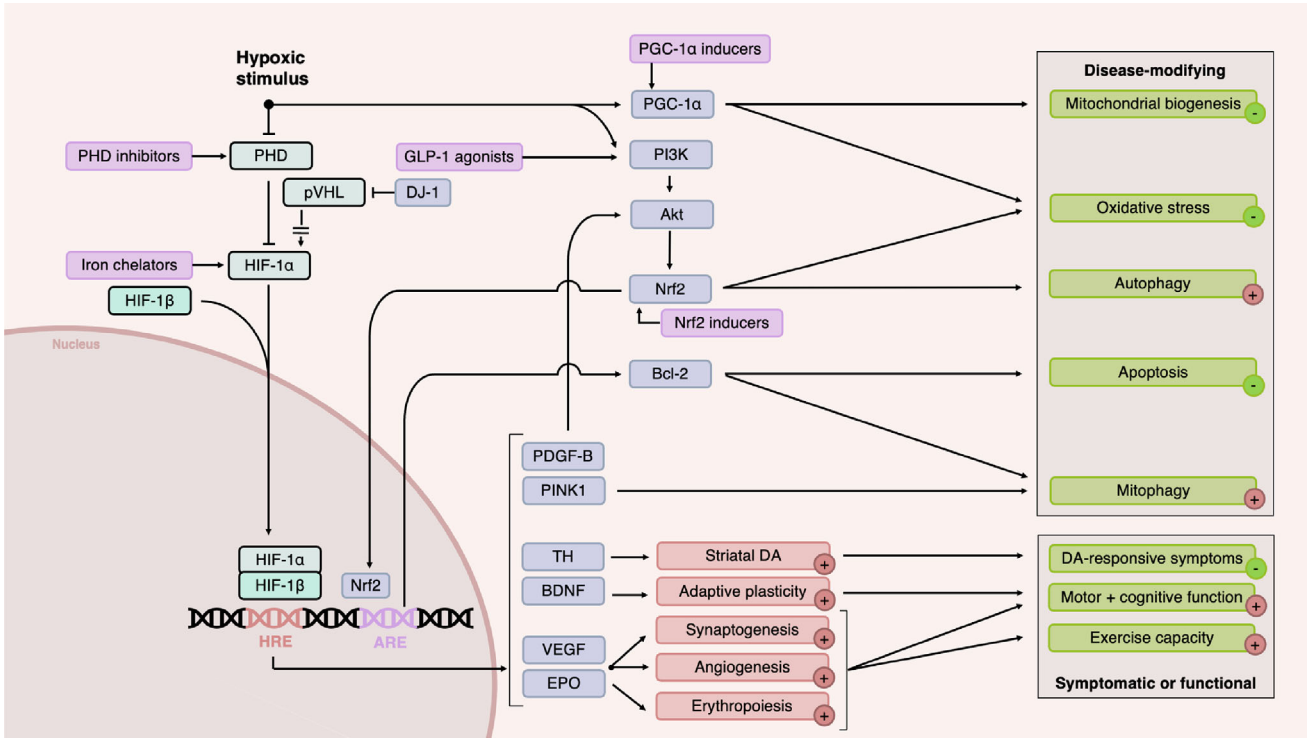

FIG. 1. Proposed chain of events for effects of disease-modifying (direct impact on pathophysiology) and symptomatic effects (no direct effect on pathophysiology) of hypoxic conditioning in PD (Parkinson's disease), including targets of pharmacological modifiers of hypoxia response (in purple). This is a simplified illustration and selection of the biochemical pathway as discussed in this manuscript. For example, interactive effects between HIF1-α, PGC-1α, and Nrf2 are not shown, and decreased oxidative stress and improved bioenergetic functioning also lead to decreased apoptosis. Downstream effects depend largely on the duration, intensity, and method of administration of the hypoxic stimulus. Akt, protein kinase B; ARE, antioxidant response element; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; DA, dopamine; EPO, erythropoietin; GLP-1, glucagon-like peptide-1; HIF-1, hypoxia-inducible factor 1; HRE, hypoxia response elements; Nrf2, nuclear factor erythroid 2-related factor 2; PDGF, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; pVHL, Von Hippel-Lindau tumor suppressor; TH, tyrosine hydroxylase; VEGF, vascular endothelial growth factor. [Color figure can be viewed at wileyonlinelibrary.com]

activation also interfaces with phosphatidylinositol-3-kinase (PI3K)/Akt-mediated signaling, which induces the transcription factor nuclear factor erythroid-2-related factor 2 (Nrf2). The latter binds to antioxidant response elements (AREs), thereby regulating the expression of oxidative stress response genes.[29-32] Other genetic targets of HIF-1α were comprehensively reviewed elsewhere.[26,33]

Role of the Hypoxia Response Pathway in PD

Various PD susceptibility genes are directly linked to the hypoxia response pathway. First, DJ-1 is a potent Nrf2 activator and inhibits VHL-mediated HIF-1α ubiquitination, and causes autosomal-recessive early-onset PD.[34] PD patients with *DJ-1* mutations have reduced HIF-1α levels and impaired cellular ROS defense. Conversely, HIF-1α stabilization protected against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a precursor of the neurotoxin and complex I inhibitor MPP^+ (1-methyl-4-phenylpyridinium) in *DJ-1*-deficient neurons.[35] Second, hypoxia stimulates specific PINK1-PARKIN-mediated autophagy of dysfunctional mitochondria (mitophagy), which improves mitochondrial function during stress and pathological conditions.[36,37] Both *PINK1* and *PARKIN* mutations cause autosomal-recessive PD.[38] PINK1 also regulates *HTRA2*, a mitochondrial serine protease that plays a role in the degradation of damaged/misfolded proteins as well as apoptosis induction.[39,40] Mutations in the *HTRA2* gene also cause autosomal-recessive PD,[40] and sustained hypoxia improves cellular functioning in a knockout model of *Htra2*.[41] However, there are no studies that have investigated whether this protective effect of hypoxia can be replicated in experimental models.

In addition to susceptibility genes, various hypoxia-induced mechanisms are linked to PD pathophysiology in preclinical models or associated with disease phenotype in humans (Fig. 1). First, although not a PD susceptibility gene, Nrf2 stimulates the expression of a large number of antioxidant response genes, and its loss in preclinical models is associated with excessive ROS levels and induction of parkinsonian pathology, including aggravation of α-synuclein aggregation, a pathological hallmark of PD.[42,43] Conversely, Nrf2 activation was paralleled by increased clearance of α-synuclein,[44] decreased nigrostriatal neurodegeneration, and mitigation

of oxidative damage induced by 6-hydroxydopamine (6-OHDA) and complex I inhibitors MPTP/MPP$^+$ and rotenone.[45-50] These protective effects are probably mediated by the PI3K/Akt/Nrf2 pathway,[25,51-54] which also appears to be involved in antioxidant effects of antidiabetics exenatide and liraglutide.[55,56] The latter are currently under investigation as disease-modifying drugs in PD.[57]

Second, peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) is a transcriptional coactivator for steroid and nuclear receptors involved in hypoxia-mediated neuroprotection through regulation of energy metabolism.[12,58] PGC-1α is intimately linked to *NRF2* expression[59] and is included in a feedback loop with HIF-1α,[60,61] but evidence indicates PGC-1α might act at least partly independent of HIF-1.[58,62] Although no pathogenic PGC-1α mutations have been reported (www.omim.org), PGC-1α polymorphisms are associated with disease onset in PD,[63] PGC-1α expression is reduced in PD,[64] and PGC-1α protein levels are lower in postmortem PD substantia nigra tissue.[65] The relevance of PGC-1α in protection against parkinsonian pathology is further supported by the fact that nigral neurons become more sensitive to α-synuclein[66] and MPTP/MPP$^+$[67] after PGC-1α knockout. Conversely, PGC-1α overexpression rescues mitochondrial structure and function induced by mutant α-synuclein or rotenone.[64] Finally, exercise-induced PGC-1α upregulation was associated with neuroprotection in a preclinical 6-OHDA model of PD.[68]

Targeting the Hypoxia Response Pathway in PD

Differences between Hypoxia Regimes

Importantly, most of the aforementioned preclinical studies in PD models are conducted in continuous (chronic) hypoxia, sometimes up to multiple months. This differs from hypoxic conditioning, which is defined as repeated exposure to a subtoxic hypoxic stimulus and is a strategy that can be extrapolated to human studies.[11,69] The limited experience with hypoxic exposure in people with PD is summarized in a recent review.[70] In the broader literature, hypoxia interventions deployed in the neuroscientific context can be divided into chronic hypoxia, (intermittent) hypoxic conditioning, and chronic intermittent hypoxia. These three types of hypoxia interventions are discussed in detail.

Continuous (Chronic) Hypoxia

Various in vitro and animal studies investigate whether chronic hypoxia mitigates neurodegeneration induced by complex I inhibitors (eg, rotenone, MPTP/MPP$^+$) or inherited mitochondrial disease. Examples of the latter include primary mitochondrial diseases such as Leigh syndrome,[8,9,71] Friedreich's ataxia,[72] and complex II deficiency.[10] However, such conditions are difficult to extrapolate to clinical studies. In addition to activation of neuroprotective pathways (Fig. 1), it is thought that HIF-1 mediates a shift from OXPHOS to glycolysis to reduce oxidative stress.[73,74] Similarly, fasting before a hypoxia bout increases adaptation to hypoxia by promoting the efficiency of ATP consumption and oxygen utilization.[75] Alternatively, chronic hypoxia might normalize oxygen overabundance (hyperoxia) during complex I deficiency, thereby ameliorating neuronal oxidative stress.[71] This theory is supported by the notion that contrary to hypoxia itself, pharmacological HIF activation in normoxia does not induce neuroprotection in some chronic hypoxia rescue models.[71,72] HIF activation during normoxic conditions might induce excessive oxidative stress due to formation of the highly reactive hydroxyl radical (HO$^\bullet$), leading to lipid peroxidation, protein damage/dysfunction, autophagy impairment, and cell death.[76] Alternatively, pharmacological left shifting of the oxygen dissociation curve has been proposed as a novel strategy to induce tissue hypoxia.[71]

Chronic Intermittent Hypoxia

This experimental model is primarily used to study the effects of obstructive sleep apnea (OSA) on neurodegeneration.[77] OSA is a disorder characterized by recurrent episodes of partial or complete airway obstruction, resulting in intermittent hypoxia during nocturnal sleep (thus typically imposed for 7 to 9 hours) where oxygen saturation below 80% is common.[78] Chronic intermittent hypoxia thereby simulates the detrimental impact of long-term reoxygenation, which causes oxidative stress and long-term sympathetic activation. Although a causal relation between sleep apnea and PD has not been established in humans, associations between OSA incidence and PD risk have been reported.[79] Moreover, preclinical evidence strongly suggests that sleep apnea induces nigrostriatal degeneration.[80,81]

Acute Intermittent Hypoxia (Conditioning)

In this approach hypoxia and normoxia are alternatingly applied for a few minutes. This avoids hypoxia tolerance and long-term stress and sympathetic activation caused by chronic intermittent hypoxia. Differences in effects between hypoxic conditioning and chronic (intermittent) hypoxia are exemplified in a few studies. For example, in mice, sustained hypoxia at a fraction of inspired oxygen (FiO_2) of 0.13 up to 3 days did not affect motor behavior and induced hippocampal neurogenesis, but longer-term exposure negatively affected movement, cognition, and balance.[82] This

coincided with upregulation of the pro-inflammatory markers interleukin-1β (IL-1β), IL-6 and tumor necrosis factor α, and hippocampal neurodegeneration.[82] Intermittent hypoxia at an FiO_2 of 0.10 reversed this pro-inflammatory and re-enabled neurogenesis, suggesting postconditioning effects, that is, inducible protection by hypoxia-based interventions after the toxic insult.[82] Through this mechanism, long-term intermittent hypoxia might rescue iron-induced oxidative injury in dopaminergic neurons,[83] a common finding in PD.[84] Similarly, a multiple-week protocol of 15-hour (chronic) hypoxia daily, untypical for hypoxic conditioning, did not ameliorate MPTP/MPP^+-induced neurodegeneration, although it still reduced indicators of oxidative stress.[85] Such ambiguous findings are also apparent in stroke studies, where moderate hypoxia at an FiO_2 of 0.10 shows neuroprotective effects, but lower FiO_2 levels cause increased oxidative stress.[86]

Hypoxic Conditioning Upregulates Symptomatic and Functional Pathways in PD

Hypoxic conditioning may induce disease-modifying effects but might also ameliorate symptoms directly.

Dopamine Release

HIF-1 stabilization stimulates tyrosine hydroxylase (TH) expression,[87,88] whereas *Hif-1α* knockout in mice reduced this expression.[89] As TH is the main rate-limiting enzyme in DA production, hypoxia- or HIF-1-induced TH upregulation augments striatal DA release[13,23,25] and may thereby mitigate parkinsonian symptoms.[90,91] Similarly, the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide might also induce TH.[25,92,93] Except anecdotal evidence of transient PD symptom improvement at high altitude,[94] it is unknown whether hypoxia interventions mitigate reduced striatal dopaminergic activity in PD. Furthermore, striatal DA release in mice with different levels of hypoxia is dose dependent,[13] and applying these hypoxic levels to humans is not feasible. In one nonblinded PD trial, a 14-day intermittent hypoxia protocol in 18 individuals resulted in decreased DOPA (DA precursor) and DA in serum.[95] However, it should be noted that the latter effect is not indicative of the dopaminergic state in the nigrostriatal pathway.

Adaptive Plasticity

Hypoxic conditioning induces adaptive plasticity in the central and peripheral respiratory motor network, meaning that hypoxia remodels neuronal networks and thereby improves breathing function.[21,96-104] One such study has been conducted in PD and demonstrated improved ventilatory responses to hypoxia.[105] This could be a novel addition to respiratory function training in PD, as complications of respiratory dysfunction are associated with high mortality.[106] Furthermore, there is evidence for motor cortex plasticity induced by hypoxia.[101,103,107-110] Supporting this idea, adaptive plasticity induced by exercise correlated with cognitive improvement and stabilization of motor symptoms in PD patients.[111,112]

Exercise-Related Effects

The effects of exercise and hypoxia are (partially) mediated by the same hypoxia response pathway. This is exemplified by HIF-1α being required for the neuroprotective effects of exercise in preclinical models and the fact that exercise and hypoxia both induce antioxidant responses and pathways involving EPO, VEGF, and PGC-1α.[15,16] Exercise also induces functional hypoxia in muscle, but it is unclear how this affects the cerebral hypoxia response. Recent studies suggest that BDNF has both nigrostriatal restorative effects[113-115] and mediates exercise-induced plasticity,[116] suggesting that this might be an important mediator of hypoxia- and exercise-induced plasticity and hypoxia- and exercise-related improvement in motor and cognitive functioning. To which extent respiratory and non-respiratory motor plasticity will translate to clinical improvement in PD remains to be determined.

Potential improvements in hypoxic conditioning in aerobic capacity[117] and exercise tolerance[118-121] may improve physical fitness of PD patients, which is especially important with regard to the progressive reduction in exercise after diagnosis.[122,123] Finally, higher EPO levels in the brain might increase the hypoxic ventilatory response[124] and, in concert with VEGF, increase synaptogenesis and angiogenesis.[125-127] This is beneficial because it enhances axonal regeneration[103] and increases the viability of dopaminergic neurons.[89] Some evidence indicates that EPO also increases mitochondrial volume and OXPHOS function in the brain.[128] It remains to be determined whether these effects positively impact on PD-related outcomes.

Platelet-Derived Growth Factor–Related Effects

Hypoxia stimulates platelet-derived growth factor BB (PDGF-BB) receptor and PDGF receptor β signaling.[51,129] PDGF-BB induces a conserved neuronal pro-survival pathway via the Akt pathway,[51,130] and preclinical studies suggest PDGF-BB-induced protective effects against 6-OHDA and increased dopaminergic activity.[130-132] In contrast, intraventricular PDGF-BB injection did not improve the clinical phenotype of PD patients in a first-in-human trial.[133]

Pharmacological Targeting of the Hypoxia Response Pathway

Various preclinical PD studies suggest that the hypoxia response pathway induces neuroprotection in

PD-relevant networks via the effects of either chronic hypoxia or hypoxic conditioning. The hypoxia response pathway can also be activated pharmacologically.[8,23,83,89] Table 1 summarizes the important studies that target the hypoxia response pathway in animal models or human studies relevant to PD. Prime advancements have been made with inhibitors of PHD, which augments HIF-1α stabilization, and iron chelators. Pretreatment with PHD inhibitors in dopaminergic cell models exposed to 6-OHDA or MPTP/MPP$^+$ protects against mitochondrial membrane potential decline, reduces oxidative stress, and increases cell viability.[25,35] Some PHD inhibitors protect against MPTP/MPP$^+$-induced cellular toxicity in the striatum,[134,135] paralleled by reduced ROS, increased Nrf2 and PGC-1α levels, and decreased apoptosis.[135] An important mediator for neuronal survival was ATP13A2, a PD susceptibility gene known as *PARK9*, through improved lysosomal iron homeostasis.[136] Dimethyloxalylglycine (DMOG) inhibits both PHD and FIH, and protects against dopaminergic cell death and parkinsonism in a mouse model of manganism.[137]

However, various challenges and limitations exist, including the occurrence of serious cardiovascular side effects with some PHD inhibitors[149] or inability to cross the blood–brain barrier (eg, DMOG). One exception is the competitive PHD inhibitor roxadustat, which has demonstrated target engagement by EPO upregulation in anemia patients on dialysis.[148] VHL small-molecule inhibitors have been developed but have not been tested in vivo.[182,183]

Table 1 does not cover pharmacological compounds that target specific components selectively, including PGC-1α,[64,184] PI3K (by GLP-1 agonists),[56] or the antioxidative pathway of Nrf2 selectively,[44-46,49,50,185,186] although these also show neuroprotective properties against preclinical parkinsonian cell models through anti-inflammatory and antioxidant effects. Some of these have been proposed in clinical trial protocols (NCT05855577, NCT05084365). It should be noted that these are not specific to hypoxia but can be activated by other transcription factors and ROS sources. It is unclear whether specific targeting of a single component of the hypoxia response pathway will be sufficiently neuroprotective, given the many other constituents of this pathway for which no (master) regulator(s) have been identified yet.[71] Future mechanistic research will likely guide more selective targeting of the hypoxia response pathway.

Controversies

Differential Effects across the PD Spectrum

Is the hypoxia response pathway a relevant target for everyone with PD? An important research gap of hypoxia applications in PD is that many studies investigated the mechanisms of hypoxia in preclinical PD models or with specific (often mitochondrial-related) mutations. This gap between preclinical models and the heterogeneous clinical population with multifactorial disease causes provides an important limitation to the translatability of those preclinical findings to clinical trials. For example, effects on adaptive plasticity and BDNF and target engagement markers such as EPO seem to be smaller in elderly individuals, suggesting smaller hypoxia-induced conditioning effects in PD.[187-190] Whether putative effects on mitochondrial function and oxidative stress decrease with increasing disease severity compared to common age-dependent decline is unknown. As previously noted, the various studies that deploy chronic hypoxia are not feasible to replicate in or extrapolate to human trials.[8,9,71] With regard to downstream effects and extrapolation to PD trials, preclinical evidence suggests that the HIF-1 response to hypoxia in the striatum may be reduced in parkinsonism models.[191] Dysfunction of OXPHOS, and complex I dysfunction specifically, even appears to reduce HIF-1α stabilization in severe hypoxia.[192,193] Indeed, gene expression of HIF-1α and its target genes is reduced in PD compared to age-matched controls, including VEGF. In postmortem substantia nigra pars compacta, PHD is upregulated, indicating reduced HIF-1α stabilization.[194,195] *DJ-1* or *PINK1* deficiency leads to increased ROS and HIF-1α stabilization in normoxia but to reduced HIF-1α stabilization in cancer cells under hypoxia[35,196] Gain-of-function *LRRK2* mutations are the most important causes for autosomal-dominant PD, and *LRRK2* has two HRE for HIF-1 to bind. This suggests that theoretically hypoxia could aggravate LRRK2 overactivity in people with *LRRK2* mutations.[197] In short, despite the fact that mutations in mitochondria-related susceptibility genes comprise only a small subset of individuals with PD, these observations suggest differential effects of hypoxia interventions by causative factors and disease severity. Gain-of-function *LRRK2* mutations are the most important causes for autosomal-dominant PD, and *LRRK2* has two HRE for HIF-1 to bind. This suggests that theoretically hypoxia could aggravate LRRK2 overactivity in people with *LRRK2* mutations.[197] Despite these limitations, evidence from both physiological and pharmacological activation of the hypoxia response pathway is promising and likely relevant for PD. The most common genetic risk factor for PD is glucocerebrosidase (GBA),[198] which is a primary lysosomal-related gene leading to dysfunctional autophagy. Although there are no experimental GBA models investigating hypoxia, moderate hypoxia upregulates mitochondrial-selective autophagy (mitophagy) through HIF-1α-induced BNIP3 expression, promoting Beclin-1 release from Bcl-2.[199] Upregulation of autophagy and Bcl-2 is

TABLE 1 *Pharmacological approaches in animals and humans to target the hypoxia response pathway*

	Target and mechanism	Animal/human	Outcomes	Challenges and limitations
PHD inhibitors				
Adaptaquin	Selective PHD2 inhibitor. Blocks stress-regulated heterodimeric transcription complex CHOP/ATF4 and increases neuronal survival protein *Parkin*. Additional metal-chelating ability.	6-OHDA-induced PD mouse model	Enhanced survival of dopaminergic neurons and protects the nigrostriatal system.[138]	Not tested in humans.
DMOG	HIF-1 prolyl-hydroxylase inhibitor, selective inhibition of PHD1 but not isoforms PHD2 or PHD3. Potent EPO and erythropoiesis response.[139] Results in upregulation of HIF-1α, Nrf2, heme-oxygenase-1, superoxide dismutase 2, VEGF,[135] reduction in oxidative death, independent of HIF activation.[140]	Traumatic brain injury mouse model Manganism mouse model (parkinsonism)	Reduces both cell death and lesion volume and stimulates angiogenesis after traumatic brain injury.[141] Dose-dependent rescue from manganese toxicity in mouse model, some dopaminergic restorative effect and significant behavioral improvement.[137]	Not tested in humans. Most important are (1) risk evaluation of cardiovascular events, depending on selectivity of compound, and (2) blood-barrier penetrance.[142]
Daprodustat (*GSK1278863*)	PHD inhibitor with highest potency for PHD1 and PHD3, less for PHD2.[143]	Human, anemia, and chronic kidney disease	Potent erythropoietic, mild and low-incident short-term adverse effects.[144]	Only 1-month drug exposure, no data on cardiovascular risks with longer treatment. Unclear whether exposure in brain.
FG-0041	Noncompetitive and nonspecific PHD inhibitor, potent at low concentrations.[145]	Wild-type male Sprague–Dawley and Wistar rats	Augmentation of TH expression and dopamine levels in rat brain.[23]	Only one in vivo study with brief exposure, not tested in humans.
IOX4, IOX2	Tricyclic triazole compounds that selectively inhibit PHD2.	Wild-type mice	IOX4 evokes potent cerebral HIF-1α and HIF-2α stabilization and downstream *Epo*, *Vegfa* induction compared to DMOG, IOX2.[142]	Evidence of cerebral target engagement, neuroprotective properties not tested. Not tested in humans.
Molidustat (*BAY85-3934*)	PHD inhibitor with lowest IC_{50} (half maximal inhibitory concentration) for PHD2, less for PHD1 and PHD3.	Human, nondialysis chronic kidney disease–associated anemia	Potent erythropoietic.[146]	More often chronic kidney disease worsening versus darbepoetin, more major cardiovascular side effects, but latter presumed unrelated. Larger PHD2

(Continues)

TABLE 1 *Continued*

	Target and mechanism	Animal/human	Outcomes	Challenges and limitations
				potency, unclear consequence for neuroprotective effects.
Roxadustat (*FG-4592*)	Induction of PGC-1α by increasing the phosphorylation of AMPK,[135] decreased oxidative stress via Akt/GSK-3β-mediated Nrf2 activation and induction of superoxide dismutase 2.[147]	MPTP-induced PD mouse model	Protection against MPTP-induced loss of TH-positive neurons of substantia nigra and attenuation of behavioral impairments.[135]	Tendency toward higher cardiovascular and upper-respiratory tract-related adverse effects.[148] Blood–brain barrier penetrance unclear.
		Human, anemia in long-term dialysis	More potent erythropoietic than epoetin-α, strong EPO response.[148]	
Vadadustat (*Vafseo*)	PHD inhibitor with similar inhibitory potence for PHD1, PHD2, and PHD3.	Human, symptomatic anemia + chronic kidney disease with or without dialysis	Potent erythropoietic, as effective as darbepoetin. High number of major cardiovascular events.[149,150]	High risk for thromboembolic events, higher than darbepoetin in nondialysis-dependent patients.[149] Unclear whether exposure in brain.
Iron chelators				
DFO	Iron chelation of nontransferrin-bound iron. Increases *Hif-1α* expression,[151] possibly through COX-2,[152] increases Bcl-2/Bax ratio and p-*ERK* (extracellular signal-regulated kinases) expression.[151] Induces angiogenesis and anti-inflammatory factors and reduces oxidative stress in vitro and in a rotenone cell model.[151,153,154]	6-OHDA-induced PD rat model (unilateral)	Improvement in apomorphine-induced rotational test, decreased limb asymmetry, increased dopaminergic neuronal integrity.[155]	Mechanism of HIF-1α induction not fully elucidated. Only subcutaneous compound available.
		6-OHDA-induced PD rat model	Increased glutathione, superoxide dismutase, increase in striatal dopamine.[156]	
		6-OHDA-induced PD rat model	Improvement in fore- and hindlimb retraction time and increase instriatal dopamine level.[157]	
		α-Synuclein rAAV PD rat model	Partial improvement in motor behavior, no improvement in dopaminergic cell death, reduction in terminal α-synuclein aggregation.[154]	
		MPTP-induced PD mouse model	Reduction in iron-positive staining in substantia nigra, increased dopaminergic neuronal survival, alleviation of behavioral deficits.[151]	

(Continues)

TABLE 1 *Continued*

	Target and mechanism	Animal/human	Outcomes	Challenges and limitations
		LPS-induced cognitive impairment mouse model	Cognitive performance (maze test) rescued by DFO pretreatment, prevented tumor necrosis factor-α and interleukin-1β release, reduced hippocampal iron accumulation.[158]	
		Human, spontaneous intracerebral hemorrhage	No treatment-related deaths or increased mortality or treatment-specific serious adverse events.[159]	
M30 (5-(*N*-methyl-*N*-propargyaminomethyl)-8-hydroxyquinoline)	Potent irreversible mitochondrial MAO-A and MAO-B inhibitor with iron-chelating properties, brain selective (striatum, hippocampus, cerebellum).	MPTP-induced PD mouse model	Attenuates MPTP-induced striatal degeneration and increased levels of dopamine.[160]	Not tested in humans.
Deferiprone	Reduction in labile iron and biological damage in oxidation-stressed cells and animals, improving motor functions while increasing striatal dopamine. Survival-promoting and antioxidant effects are HIF-1-mediated in fibroblasts.[161]	MPTP-induced PD model	Improvement in substantia nigra iron deposits.[162]	Incidental cases of rapidly resolving neutropenia and agranulocytosis, otherwise well tolerated. Adverse effects in largest trial to date, unclear whether effect on progression or symptomatic.[163]
		Human, early-stage PD	Reduced substantia nigra iron deposits and significant improvement in Unified Parkinson's Disease Rating Scale, Part III (motor scale).[162]	
		6-OHDA PD model in rats	Reduced loss of nigral TH-immunoreactive cells, increased striatal dopamine levels.[164]	
		Human, early-onset PD	Reduced dentate and caudate nucleus iron content, reduction in substantia nigra iron in only 3 of 22 patients.[165]	
		Human, de novo PD	Deferiprone-induced nigrostriatal iron reduction but was associated with symptom worsening and shorter time until dopaminergic therapy.[163]	

(Continues)

TABLE 1 *Continued*

	Target and mechanism	Animal/human	Outcomes	Challenges and limitations
(Apo-)lactoferrin	Stabilize HIF-1α and HIF-2α and high affinity for Fe^{3+}, upregulates EPO and Nrf2.[166] Potential mediators include ERK activation and putative HIF-1-mediated BDNF release.[167]	Rotenone-induced PD rat model	Reduced loss of nigral TH-immunoreactive cells and improved mobility and exploring activity in the open-field test.[166]	Mechanisms not fully elucidated. Limited high-quality in vivo evidence, not tested in humans.
		MPTP-induced PD mouse model	Reduction in MPTP-triggered apoptosis of dopaminergic neurons, neuroinflammation, and histological alterations and suppression of excessive iron accumulation.[167]	
Clioquinol	Bioavailable metal chelator, iodinated 8-hyxroyquinoline, antiparasitic agent. Mediating effects of HIF-1α.[134]	MPTP-induced PD mouse model	Reduction in substantia nigra iron levels and amelioration of striatal dopamine levels and neuronal nigral cell loss, possibly through reduced oxidative stress.[168]	Unclear mechanisms of action, despite long-term use.
HIF-1α inducers				
(Deoxy)gedunin	Anti-malaria agent, TrkB receptor agonist, potential mechanism of action through mitogen-activated protein kinase (MAPK)/PI3K, also p23 inhibition resulting in decrease in steady-state PHD2 protein.	6-OHDA- and MTPT-induced PD rat model	Pretreatment rescues dopaminergic neuron loss in substantia nigra and attenuates behavioral performance reduction in toxicity models.[169]	Limited in vivo evidence, not tested in humans, mechanism of action not elucidated.
Baicalein	Flavonoid with anti-inflammatory, antioxidative, antiviral, and antitumor actions. *Hif1a* expression implicated.[170] Neuroprotective effect involves PI3K/Akt, ERK, and PTEN (phosphatase and tensin homolog) signaling.	MPTP-induced PD mouse model	Improved neurogenesis, walking, and locomotor behavior.[170]	Studies mostly phenotypic screening, uncertain mechanisms of action. One study indicates that PHD inhibition rather than HIF-1α stabilization mediates neuroprotective effects.[140] Not tested in humans.
		Methamphetamine mouse model	Attenuation of the metamphetamine-induced striatal dopamine transporter loss as well as rescue of lipid peroxidation.[171]	
		MPTP-induced PD mouse model	Pretreatment rescues behavioral abnormalities and increased levels of striatal dopamine, potentially through antioxidant and ERK-mediated anti-astroglial effects.[172]	

(Continues)

TABLE 1 *Continued*

	Target and mechanism	Animal/human	Outcomes	Challenges and limitations
		Rotenone-induced PD mouse model	Reduction in further α-synuclein aggregation, restoration of striatal dopamine, and accompanying behavioral improvement.[173]	
		MPTP-induced PD rat model	Attenuation of MPP^+-induced reduction in striatal dopamine content, pro-inflammatory caspase-1, and α-synuclein aggregates in substantia nigra.[174]	
		MPTP-induced PD mouse model	Improvement in motor ability and prevention of dopaminergic neuron loss through anti-astroglial effects.[175]	
Hydralazine	Antihypertensive agent, potent inducer of nuclear translocation of *Nrf2* and thereby upregulates transcription of AREs, possibly mediating effects of increased HIF-1α protein expression in vitro.[176]	MPTP-induced PD mouse model	*Nrf2*-dependent amelioration of oxidative stress, loss of neurons of dopaminergic neurons in nigrostriatal circuit. Normalization of behavior.[177]	Antihypertensive agent. Unclear effective dosage and corresponding adverse effects for neurological effects in humans.
Agmatine	Endogenous arginine metabolite,[178] in vitro study suggests *Hif-1α*-dependent neuroprotective effects.[179]	MPTP-induced PD mouse model	No direct positive effect on dopamine uptake. Agmatine during MPTP infusion worsened MPP^+-induced toxicity, whereas post-MPTP administration protected against dopaminergic toxicity (~42% vs. 76% reduction).[180]	Unclear mechanisms for differential (pre-)conditioning and post-conditioning effects, unclear considerations in optimal dosing in humans.
		Rotenone-induced PD rat model	Reduced lipid peroxidation and loss of dopaminergic neurons. Better performance on quantitative motor tests.[178]	

(Continues)

TABLE 1 *Continued*

	Target and mechanism	Animal/human	Outcomes	Challenges and limitations
Albendazole	Anthelminthic benzimidazole. Promotes *Hif-1α* expression and nuclear-related receptor 1 (*Nurr1*), *Vegf* expression.[181]	Rotenone-induced PD rat model	Attenuated rotenone-induced substantia nigra degeneration, reduced pro-inflammatory factors, decreased the expression of α-synuclein, restored striatal dopamine level, and improved motor functions.[181]	Unclear adverse effects in man, unknown therapeutic window, mechanisms of neuroprotection uncertain.

Part of the compound selection is adapted from an earlier study.[26]
Abbreviations: PHD, prolyl hydroxylase domain; 6-OHDA, 6-hydroxydopamine; DMOG, dimethyloxalylglycine; HIF-1α, hypoxia-inducible factor 1α; EPO, erythropoietin; Nrf2, nuclear factor erythroid-2-related factor 2; VEGF, vascular endothelial growth factor; TH, tyrosine hydroxylase; AMPK, AMP-activated protein kinase; GSK-3β, glycogen synthase kinase-3 beta; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; DFO, deferoxamine; COX-2, cyclo-oxygenase 2; rAAV, recombinant-adeno-associated virus; LPS, lipopolysaccharide; MAO, monoamine oxidase; TrkB, tropomyosin receptor kinase B; MPP^+, 1-methyl-4-phenylpyridinium; ARE, antioxidant response element; BDNF, brain-derived neurotrophic factor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α.

associated with improved neuronal survival,[200] whereas pharmacological inhibition with chloroquine is associated with impaired mitochondrial function and increases oxidative stress and apoptosis in neurons.[201] This mitochondrial–lysosomal cross-talk through mitophagy to create a healthy mitochondrial turnover[202] is likely part of PD pathogenesis irrespective of causative factors, and has therefore been proposed as a prime disease-modifying target.[203,204] Indeed, in PD dopaminergic neurons, mitochondrial and autophagy-related genes are concomitantly downregulated.[194,195] In short, despite the fact that mutations in mitochondria-related susceptibility genes comprise only a small subset of individuals with PD, these observations suggest differential effects of hypoxia interventions by causative factors and disease severity.

Safety and Risk Profile of Hypoxic Conditioning in PD

Although most studies in geriatric and cardiorespiratory patients report no or mild and transient side effects of controlled intermittent hypoxia interventions,[115,119,120,205-210] cardiac and respiratory alterations in PD need to be considered. First, the hypoxic ventilatory response is substantially lower in elderly, and this response might be even lower in individuals with PD, potentially worsening with disease progression.[105,211] This suggests a risk of insufficient cardiopulmonary adaptation to hypoxia, resulting in severe hypoxemia, physical stress, and possibly exhaustion. In our recent trial (manuscript in preparation), we saw evidence for reduced hypoxic ventilatory response in PD and altered breathing patterns at rest. The reduction of hypoxic ventilatory response brought about by exogenic DA[212] additionally infers an interactive effect of hypoxia interventions and conventional PD therapy.

Individuals with PD in combination with cardiorespiratory comorbidities might be at increased risk of adverse respiratory responses such as larger-than-expected decreases in oxygen saturation[211] and speculatively adverse effects such as angina pectoris,[213] especially considering the fact that low hypoxic ventilatory response is associated with high-altitude illness with prolonged hypoxic exposure.[214] Next, prolonged hypoxia, contrary to acute intermittent hypoxia,[215] induces significant sympathetic activation,[216] especially in extracerebral systems,[217] and may cause increased blood pressure, dyslipidemia, and dysglycemia.[76,215] Chronic hypoxia also leads to increased risk of pulmonary edema, pulmonary hypertension, and right-sided heart failure. Sustained sympathetic overactivity could be especially harmful in PD, as high stress is speculated to negatively affect disease progression.[218] Although mechanisms are uncertain, excess stress may also inhibit various mediating mechanisms, such as neuroplasticity.[219] Dose-finding studies should take this sympathetic activity into account as outcome measure in

PD trials, even when deploying acute moderate normobaric hypoxia. Both hypoxic conditioning and dopaminergic medication may lower blood pressure[220] and cause transient dizziness,[221] increasing the risk of falls, although there is no evidence of hypoxic conditioning-induced blood pressure reduction in non-hypertensive individuals. Depending on the magnitude of symptomatic effects, we hypothesize the reducing impact on conventional drugs is limited. We envision hypoxic conditioning as an adjuvant intervention to dopaminergic therapy that putatively improves symptoms and potentially disease progression.

The HIF-1 pathway has received considerable interest from oncology, as HIF stabilization is also seen in various neoplasms and HIF inhibitors are therefore considered a putative oncological treatment. However, carcinogenicity evaluation of one PHD inhibitor does not demonstrate neoplastic effects, even at supra-maximal dosages.[222] Finally, chronic hypoxia, especially in chronic hypobaric hypoxia,[223-225] leads to increased ROS formation and is associated with increased α-synuclein misfolding.[226] Reoxygenation during the normoxic phase of acute intermittent hypoxia also causes ROS, although it seems that some ROS production is necessary for HIF-1α stabilization and activation of downstream targets and is likely not excessive in short-duration hypoxic conditioning.[27,28] Longer protocols do not appear to induce additional therapeutic benefit, despite their higher risk profile.[115,117]

Dose of Intervention

First, future hypoxia trials in PD should take the uncertainties regarding the hypoxia dosage into consideration with regard to safety as discussed. Second, evidence suggests the magnitude of activation of relevant mechanisms, such as neuroplasticity, is larger in brief minute-long bouts compared to sustained protocols with the same total duration.[227,228] As longer hypoxia bouts are associated with increased oxidative stress (see earlier), especially in PD due to reduced hypoxic ventilatory response, intermittent hypoxia with 3- to 5-minute exposures to hypoxia is likely optimal.[115,225] In our recent phase 1 trial (manuscript in preparation), we deployed a dose-finding protocol by administering four different hypoxic conditioning sessions once a week and compared it to placebo.[229] The low-frequency administration allowed for sufficient wash-off of potential lingering effects. We evaluated target engagement (eg, EPO) and measured the acute cardiovascular, respiratory, and symptomatic responses to all hypoxic conditioning sessions. We selected an average intervention duration of 45 minutes and 5-minute hypoxia-normoxia bouts, and FiO_2 levels that fall on the upper (FiO_2 0.16) and lower (0.127) boundaries of what is considered effective for conditioning effects and what is expected from markers of target engagement.[115,230,231] It remains uncertain to what extent such biomarkers reflect PD-relevant neuroprotective properties and how this translates to clinical benefits. In our follow-up trial, we deploy a thrice-a-week 4-week protocol. There is debate on whether hypoxia should be dosed based on the FiO_2 or based on the resultant oxygen saturation.[115,232] If activation of downstream mechanisms is ultimately determined by the resultant hypoxemia, dosage based on the resultant oxygen saturation might be superior for optimal individualized downstream effects.[232] In our first systematic hypoxic conditioning trial in PD however, we applied a fixed FiO_2 to determine intervention uniformity and study replicability, and to investigate whether inter-individual variability in target engagement or symptomatic outcomes can be explained by differences in physiological responses or target engagement. Finally, CO_2 clamping is a method often used to control CO_2 during hypoxic exposure to prevent onset of hypocapnia. However, due to the diminished ventilatory response in PD, physiological responses might differ.

Total treatment duration depends on the target mechanism and outcome (mechanistic or clinical). For clinical effects in cardiorespiratory applications, three-weekly[11,115,233-235] to five-weekly treatments are reported.[119,120,236] The minimum total protocol duration for cardiorespiratory effects is likely 3 to 4 weeks.[119,120] It is conceivable that the intervention period for long-term neurological effects, dependent on neuroplasticity, is substantially longer,[207] although improvement in walking distance and hand opening function was already measurable after five interventions in patients with spinal cord injury.[205,206] Trials investigating neuroprotective or even disease-modifying effects in PD will likely require at least a year of follow-up.

Conclusions

Following several decades of work on the effects of hypoxia in other disciplines, hypoxic conditioning has only recently been proposed for application in neurodegenerative disease. This application is further supported by mechanistic insights into exercise research in neurodegenerative disease. Through hypoxic conditioning, hypoxia may exert neuroprotective effects in PD, possibly through amelioration of mitochondrial dysfunction and oxidative stress. In addition, accumulating evidence suggests that hypoxic conditioning induces adaptive neuroplasticity and facilitates dopaminergic activation, subsequently translating to acute symptomatic effects in PD. Further opportunities exist for pharmacological approaches that target the hypoxia response pathway.

Although the predominant mechanisms and optimal dosage have yet to be elucidated and several lines of research suggest adverse effects of high-dose chronic hypoxia, well-controlled, randomized trials investigating hypoxic conditioning in PD are now warranted to establish its safety and to explore a wide range of possible clinical and mechanistic outcomes.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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