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FORUM REVIEW ARTICLE

Oxygen Sensing in Neurodegenerative Diseases: Current Mechanisms, Implication of Transcriptional Response, and Pharmacological Modulation

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Abstract

Significance: Oxygen (O_2) sensing is the fundamental process through which organisms respond to changes in O_2 levels. Complex networks exist allowing the maintenance of O_2 levels through the perception, capture, binding, transport, and delivery of molecular O_2. The brain extreme sensitivity to O_2 balance makes the dysregulation of related processes crucial players in the pathogenesis of neurodegenerative diseases (NDs). In this study, we wish to review the most relevant advances in O_2 sensing in relation to Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

Recent Advances: Over the years, it has been clarified that most NDs share common pathways, a great number of which are in relation to O_2 imbalance. These include hypoxia, hyperoxia, reactive oxygen species production, metabolism of metals, protein misfolding, and neuroinflammation.

Critical Issues: There is still a gap in knowledge concerning how O_2 sensing plays a role in the above indicated neurodegenerations. Specifically, O_2 concentrations are perceived in body sites that are not limited to the brain, but primarily reside in other organs. Moreover, the mechanisms of O_2 sensing, gene expression, and signal transduction seem to correlate with neurodegeneration, but many aspects are mechanistically still unexplained.

Future Directions: Future studies should focus on the precise characterization of O_2 level disruption and O_2 sensing mechanisms in NDs. Moreover, advances need to be made also concerning the techniques used to assess O_2 sensing dysfunctions in these diseases. There is also the need to develop innovative therapies targeting this precise mechanism rather than its secondary effects, as early intervention is necessary. *Antioxid. Redox Signal.* 38, 160–182.

Keywords: oxygen sensing, neurodegenerative diseases, gene expression, oxygen-targeting drugs, evaluation of oxygenation, HIF-1

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Introduction

THE CAPACITY TO perceive and respond to changes in oxygen (O_2) levels is fundamental for the survival of both prokaryotic and eukaryotic organisms. As the name suggests, O_2 sensing is defined as the ability to ''sense'' and, consequently, ''respond'' to changes in O_2 levels. In an organism, this is a key mechanism necessary to maintain cellular and tissue homeostasis (Giaccia et al, 2004). Changes in cellular O_2 availability, secondary to environmental challenges or diseases, stimulate a vastitude of adaptive responses that can be rapid (seconds) or more prolonged (weeks to months) (Wilson et al, 2020). The molecules and mechanisms involved in these versatile O_2 sensing signaling pathways are fundamental to the pathogenesis of highly prevalent medical conditions, among which are respiratory depression, hypertension, tumor progression, neurodegeneration, and inflammation (Liao and Zhang, 2020; Semenza, 2014; Sieck, 2004).

In 1931, Otto Warburg was awarded the Nobel Prize in medicine for identifying cytochrome aa3 (cytochrome oxidase) as the carbon monoxide (CO)-sensitive respiratory enzyme (Otto, 2016). Since then, many discoveries have been made elucidating the mechanisms through which organisms can perceive and adapt to O_2 levels, but many questions on this topic remain predominantly unanswered (Liao and Zhang, 2020). What is currently known is that complex networks exist, which allow to maintain O_2 homeostasis at the tissue level, through the capture, binding, transport, and delivery of molecular O_2 (Giaccia et al, 2004). Specifically, the alterations in O_2 levels can be perceived by ''O_2 sensing organs'' with a specific localization in the body and presenting molecular entities, with specific electrophysiological properties that enable O_2-dependent modulation of cell excitability and intracellular transduction mechanisms. These can then lead to a specific regulation of gene expression and cellular adaptations to O_2 imbalance (Wilson et al, 2020).

In this review, we are presenting a brief overview of mechanisms pertaining O_2 sensing both in the periphery and in the central nervous system (CNS). We also discuss O_2 sensing intracellular mechanisms in both a physiological state and in neurodegenerative diseases (NDs). Moreover, in a specific section, we aimed to assess what molecular signatures have been identified to be associated with ''O_2 sensing'' and NDs and current advances/limitations in techniques and therapeutic strategies for investigating O_2 imbalance in NDs. These are a heterogeneous class of disorders, typically characterized by the progressive degeneration of the structure and function of the CNS or peripheral nervous system. The investigation of O_2 sensing mechanisms appears to be relevant in numerous NDs, and in this review, we focus on three among the most studied diseases, namely Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS).

Overview of O_2 Sensing Mechanisms: Whole-Body Response to Changes in O_2 Levels

All living organisms can perceive changes in the partial pressure of O_2 (pO_2) and are thus able to trigger a compensatory response and avoid systemic damage. Specifically, the human body is a highly aerobic organism, with the necessity to match O_2 supply at the tissue level to the metabolic demand. To ensure this, there are numerous organs defined as ''O2 sensing'' that can detect changes in O_2 and thus elicit specific responses. These are reviewed in detail in the next section and include the carotid bodies (CBs), the pre-Bötzinger complex (preBötC) in the CNS, the pulmonary and cardiovascular system, and the kidneys (Fig. 1).

Acute neurological O_2 sensing: role of the CBs

The primary O_2 sensing mechanisms present in the human body rely on the detection of changes in pO_2. Small arterial changes of pO_2 are primarily detected in the CB, an organ made of glomus cells, the main O_2 sensing cells, and supporting cells, both surrounded by a network of thin vessels (López-Barneo et al, 2016). Glomus cells are electrically excitable and present O_2-sensitive potassium (K^+) channels in their membranes (Pardal and López-Barneo, 2002). The two CBs are situated bilaterally at the bifurcation of the common carotid artery. This anatomical structure favors the detection of changes in the arterial blood composition before the stimulus reaches the brain, which is highly dependent on O_2 and glucose (Teppema and Dahan, 2010). The blood supply to the CB thus originates mostly from the carotid artery, which supplies the highest blood flow per tissue weight in the whole body.

A low pO_2, also known as hypoxia, leads to the inhibition of K^+ channels in the plasma membrane of glomus cells, with the activation of cardiorespiratory reflexes through calcium (Ca^{2+}) entry, depolarization, and neurotransmitter release (López-Barneo et al, 1988; Pardal and López-Barneo, 2002). In turn, the CB activates the respiratory center in the brain stem to induce adaptive ventilatory responses. Intrastriatal grafting of the CB was performed in parkinsonian rats, an *in vivo* model obtained treating the animals with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Toledo-Aral et al, 2003; Villadiego et al, 2005). The rationale behind CB grafting relies on the fact that CB glomus cells are highly dopaminergic and express the glial cell line-derived neurotrophic factor (*GDNF*) (Mínguez-Castellanos et al, 2007; Toledo-Aral et al, 2003; Villadiego et al, 2005). In CB-transplanted parkinsonian rats, *GDNF* was still produced with an increased glomus cell survival rate after transplantation and a neurotrophic recovery of the treated animals.

This kind of approach was used in other murine and primate models of PD obtaining promising results (Espejo et al, 1998; Hao et al, 2002; Luquin et al, 1999; Shukla et al, 2004). With this preclinical evidence, a phase I-II clinical study was performed to assess the feasibility, long-term safety, and clinical and neurochemical effects of CB autotransplantation in PD patients (Mínguez-Castellanos et al, 2007). Blind tests highlighted a clinical amelioration in PD outcomes in 10 out of 12 patients, with a mean improvement of 23% after 6 months (Mínguez-Castellanos et al, 2007). Interestingly, the β-amyloid ($A\beta$) precursor protein cleaving enzyme 1 (*BACE1*) (Vassar et al, 1999) was recently found expressed in the rat CB, with a reversible reduced expression following cyclic intermittent hypoxia (Li et al, 2020a). *BACE1* is able to generate the $A\beta$ peptide, a crucial initiator of AD pathogenesis.

This evidence suggests that the CB may play a role in NDs, but the exact molecular dysregulation of this organ in the diseases is yet to be defined. These aspects are an interesting and understudied research topic and still need to be eviscerated with further studies.

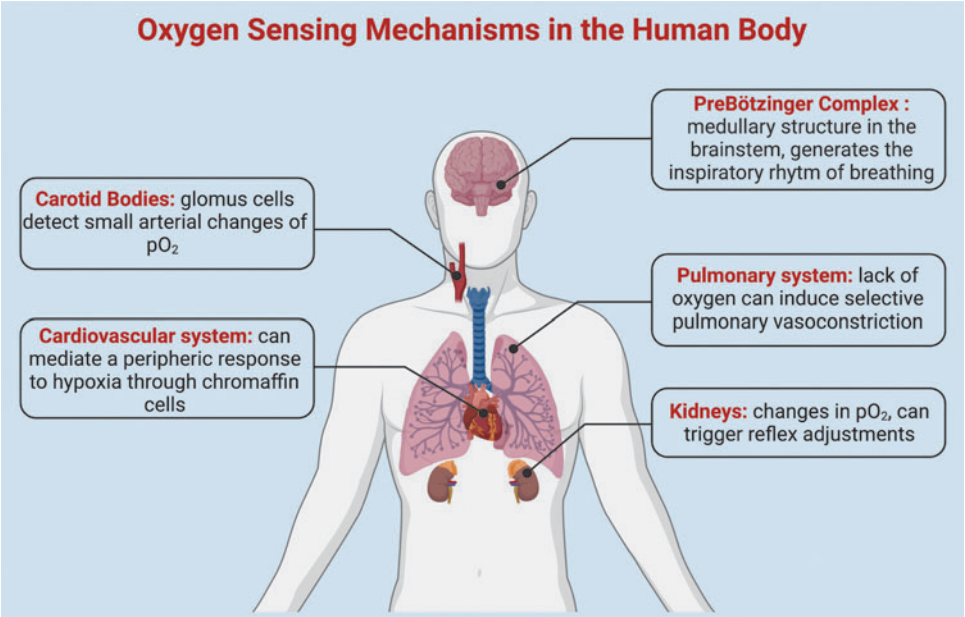

FIG. 1. The human body is a complex system that largely depends on O_2 for its correct functioning. To this end, numerous organs are able to sense changes in pO_2 and elicit responses to avoid systemic damage. These include the carotid bodies, the main organ with this function, made up of glomus (O_2-sensing) cells, the preBötzinger complex, a medullary structure in the brain stem able to generate the inspiratory rhythm of breathing, and the pulmonary, the cardiovascular, and the renal systems, which can induce peripheric responses to these changes. O_2, oxygen; pO_2, partial pressure of oxygen. Created with Biorender.com Color images are available online.

O_2 sensing in the brain

The brain is extremely sensitive to O_2 balance, as it is entirely aerobic (Bailey, 2019). Indeed, in humans, 20%–25% of the resting metabolic rate, meaning the energy needed when at rest, is reserved for brain functioning (Bailey, 2019). This is necessary to support the high rate of ATP formation and consumption, which allows the maintenance of ionic equilibria and neurotransmitter uptake, both necessary processes for synaptic transmission (Bailey, 2019). Even so, the brain has limited O_2 reserves, and if blood supply were to be interrupted, it would be able to sustain cerebral metabolism for 1 s only, subsequently resulting in neurodegeneration (Bailey, 2019; Leithner and Royl, 2014). Indeed, neurons require a constant supply of O_2 along with a removal of carbon dioxide (CO_2) and other metabolites (Gourine and Funk, 2017). For this reason, the oxygenation of the brain is strictly monitored by the CBs.

Even so, there are more aspects that need to be considered when thinking about the strict connection between the CNS and its associated NDs and O_2 intake and metabolism. Indeed, the inspiratory rhythm of breathing is generated at the level of a medullary structure in the brain stem called the preBötC (SheikhBahaei, 2020; Smith et al, 1991). The activity of this region is strictly regulated by inputs from other brain regions, which include functional inputs such as volitional, physiological, and emotional inputs, along with direct projections from neurons throughout the brain (Yang et al, 2020). Specifically, excitatory and inhibitory preBötC neurons receive projections from neurons in the breathing central pattern generator (bCPG), including the contralateral preBötC, the Bötzinger complex, the nucleus of the solitary tract, the parafacial region, and the parabrachial nuclei (Yang et al, 2020).

In NDs affecting the brain stem such as multiple system atrophy (MSA), preBötC neurons were reduced suggesting that the central respiratory network primarily contributes to breathing disorders in MSA (Schwarzacher et al, 2011). Moreover, the 6-hydroxydopamine hydrochloride (6-OHDA) rodent model of PD presents with a reduced respiratory frequency and NK1r-immunoreactivity in the preBötC, indicating that this decrease is an important contributor to the development of breathing abnormalities in PD (Oliveira et al, 2021).

Along with the CBs, there is now mounting evidence highlighting the existence of central respiratory O_2 chemosensors (Uchiyama et al, 2020). Interestingly, astrocytes have been found to rapidly respond to moderate hypoxia *via* the sensor cation channel transient receptor potential (*TRP*) *A1* (Uchiyama et al, 2020). These appear to specifically respond to a decrease of pO_2 as they do not respond to hyperoxia, carbon dioxide, and oxidant molecules (Uchiyama et al, 2020). Other evidences also highlight how changes in neuronal–glial interactions can contribute to the hypoxic ventilatory response, the ''coping'' mechanism that the brain utilizes to respond to a decrease of pO_2 (Angelova et al, 2015; Rajani et al, 2018; Sheikhbahaei et al, 2018).

Studies also highlight how astrocytes can respond to decreases in pO_2 with an elevation in intracellular Ca^{2+}, and interestingly, this ''sensor'' is in the mitochondria, the key organelle in O_2 metabolism (Angelova et al, 2015). Astrocyte–neuron interactions and mitochondria are relevant mechanisms in the pathogenesis of NDs (Mulica et al, 2021).

Specific brain areas affected in NDs can also play a role in O_2 sensing mechanisms. Indeed, the hippocampus, primarily implicated in AD, is extremely vulnerable to hypoxic insults, and an impaired hypoxia-inducible factor (*HIF*)-α signaling in this area may contribute to age-associated cognitive decline (Snyder et al, 2022). Moreover, blood flow, blood oxygenation, and neurovascular coupling were found to be decreased in the hippocampus compared with the neocortex, and features of the hippocampal vasculature may restrict O_2 availability thus explaining its sensitivity to damage in AD, where the brain's energy supply results also decreased (Shaw et al, 2021). PD loss of dopaminergic neurons in the substantia nigra (SN) is a primary hallmark of the disease, and this area is extremely vulnerable to oxidative stress (Trist et al, 2019).

Interestingly, even though this is surely true, and hypoxia plays a critical role in the pathogenesis of the disease, a novel computational model of SN cells highlights how hypoglycemia plays an even more crucial role in leading to ATP deficits (Muddapu and Chakravarthy, 2021).

Other mechanisms of O_2 sensing: implications for peripheral organs in NDs

Several organs can lead to changes in peripheral and central O_2 levels, with direct consequences in NDs. Peripheral organs include the kidneys, the cardiovascular circuitry, and the pulmonary system, each presenting a specific response to changes in O_2 levels (Table 1). First of all, the kidney is sensitive to falls in the pO_2, and in a hypoxic condition it can trigger reflex adjustments acting as an O_2 sensor, increasing perfusion pressure chronically (Patinha et al, 2017). A condition of hypoxia impairs hydrogen sulfide metabolism and increases its concentration, leading to vasodilation and stimulation of chemoreceptor afferent neurons, especially in the renal medulla (Bełtowski, 2010).

The kidney metabolism is also relevant in NDs, as kidney injury was found to be a risk factor for the development of both PD (Lin et al, 2016) and AD (Zhang et al, 2020). Moreover, the receptor for advanced glycation end products (*RAGE*), critical for chronic kidney disease progression, also mediates the transport of pathophysiologically relevant concentrations of Aβ into the CNS. *RAGE* has been found to be involved in both AD and hypertension, inducing plaque formation, Aβ deposition around blood vessels, and cognitive impairment (Carnevale et al, 2012). The *RAGE* pathway is tightly connected to the renin/angiotensin/aldosterone axis, which regulates systemic blood pressure, and it also has a role in oxidative stress (Gugliucci and Menini, 2014; Pickering et al, 2019).

Other peripheral organs relevant for O_2 sensing are the lungs, as it was also found that lack of O_2 induces selective pulmonary vasoconstriction to redirect blood flow to the most ventilated areas of the lung, promoting vascular angiogenesis and vasodilation in the brain (Wang et al, 2001). The genetic relationship between chronic obstructive pulmonary diseases, lung function, and AD was recently investigated without any specific evidence of association (Higbee et al, 2021). Acute respiratory distress syndrome, a syndrome characterized by severe hypoxia requiring intensive hospitalization, may result in long-term (at least 2 years) neurocognitive morbidity and decreased quality of life (Hopkins et al, 2005). Obstructive sleep apnea syndrome (OSAS), an example of pathological intermittent hypoxia, can also be associated with mild cognitive impairment.

Proteomic data suggest that OSAS and AD share biomarkers, which include insulin, angiopoietin-1, and *IL1B*, indicating also the possibility of a shared pathogenesis between these diseases (Lal et al, 2019). Ongoing studies are also investigating the relationship between COVID19 hypoxic condition and consequent neurological impairment, which, in the most severe cases, may resemble AD, or, as it has been suggested, predispose to AD future development (Almeria et al, 2020; Heneka et al, 2020).

Lastly, the cardiovascular response to hypoxia, similar to other stress situations, is peripherally mediated through chromaffin cells in the adrenal medulla. CB chemoreflex *via* increased sympathetic activity regulates the ensuing transcriptional regulation of pro- and antioxidant enzymes contributing to oxidative stress in the adrenal medulla (Kumar et al, 2015). Excessive afferent signaling from the CBs may lead to the development of pathological conditions such as hypertension (Patinha et al, 2017), a risk factor for NDs (Bergantin, 2019). Treatment-resistant hypertension has been

Table 1. Contributions of Peripheric Organs to Oxygen Sensing and Their Implications in Neurodegenerative Diseases

Organ	*Mechanism*	*Implication in NDs*	*References*
Kidney	It can act as O_2 sensor during hypoxia, increasing perfusion pressure chronically; erythropoietin production.	Kidney injury is a risk factor for PD and AD. Receptor for advanced glycation end products mediates the transport of Aβ into the CNS.	Carnevale et al (2012); Lin et al (2016); Zhang et al (2020)
Pulmonary system	Lack of O_2 induces selective pulmonary vasoconstriction.	Acute respiratory distress syndrome and obstructive sleep apnea syndrome can result in cognitive impairment. COVID19 hypoxic condition can lead to an AD-like phenotype.	Almeria et al (2020); Heneka et al (2020); Hopkins et al (2005); Lal et al (2019)
Cardiovascular system	Increased sympathetic activity regulates the ensuing transcriptional regulation of pro- and antioxidant enzymes, which contributes to oxidative stress in the adrenal medulla.	Excessive afferent signaling from the CBs may lead to the development of pathological conditions such as hypertension, a risk factor for NDs.	Bergantin (2019)

Aβ, β-amyloid; AD, Alzheimer's disease; CBs, carotid bodies; CNS, central nervous system; ND, neurodegenerative disease; O_2, oxygen; PD, Parkinson's disease.

shown to impact on blood–brain barrier integrity, inducing changes in O_2 delivery and altered neural signaling homeostasis (Katsi et al, 2020).

In conclusion, many districts of the body are implicated in sensing changes in O_2 levels. These include the CBs, the brain, and the pulmonary, cardiovascular, and renal system, which can also work cooperatively to avoid the induction of disruptive mechanisms. Alterations in these districts present some correlations with NDs, but this aspect is currently understudied and would need further investigation.

Cellular Response to Imbalance in O_2 Levels and Its Correlation with NDs

We so far presented the mechanisms of O_2 sensing at the ''whole-body'' level, attempting to eviscerate how our organism can respond to changes in O_2 levels and how this is connected to NDs. It is now worth focusing on the intracellular responses to O_2 as a signaling molecule, in normal physiological conditions and in conditions of reduced (hypoxia) O_2 levels (Fig. 2).

Membrane-associated mechanisms of O_2 sensing

The first question that needs to be answered is how O_2 can enter the cell, and as we previously mentioned, the cell membrane of O_2 sensing cells contains O_2-sensitive ion channels, specifically K^+ ion channels (López-Barneo et al, 1988). Following the first reported evidence, at least three families of O_2-sensitive K^+ channels have now been identified (Prabhakar and Peers, 2014; Vjotosh, 2020). Specifically, these channels are able to rapidly respond to a reduction in O_2 concentration.

Although to our knowledge, there is currently no direct association between these specific channels and NDs, many evidences connect K^+ ion channels to O_2 level imbalance and to the pathogenesis of these diseases. For example, the K(+) channels encoded by the Kv1.3 subtype of the voltage-dependent *Kv1* gene family, inactivated following an hypoxic signaling (Conforti et al, 2003) (Fig. 2), have been found to be highly expressed by activated and plaque-associated microglia in AD postmortem brains (Rangaraju et al, 2015). The selective inhibition of this channel through selective blockades with the small molecule PAP-1 leads to reduced

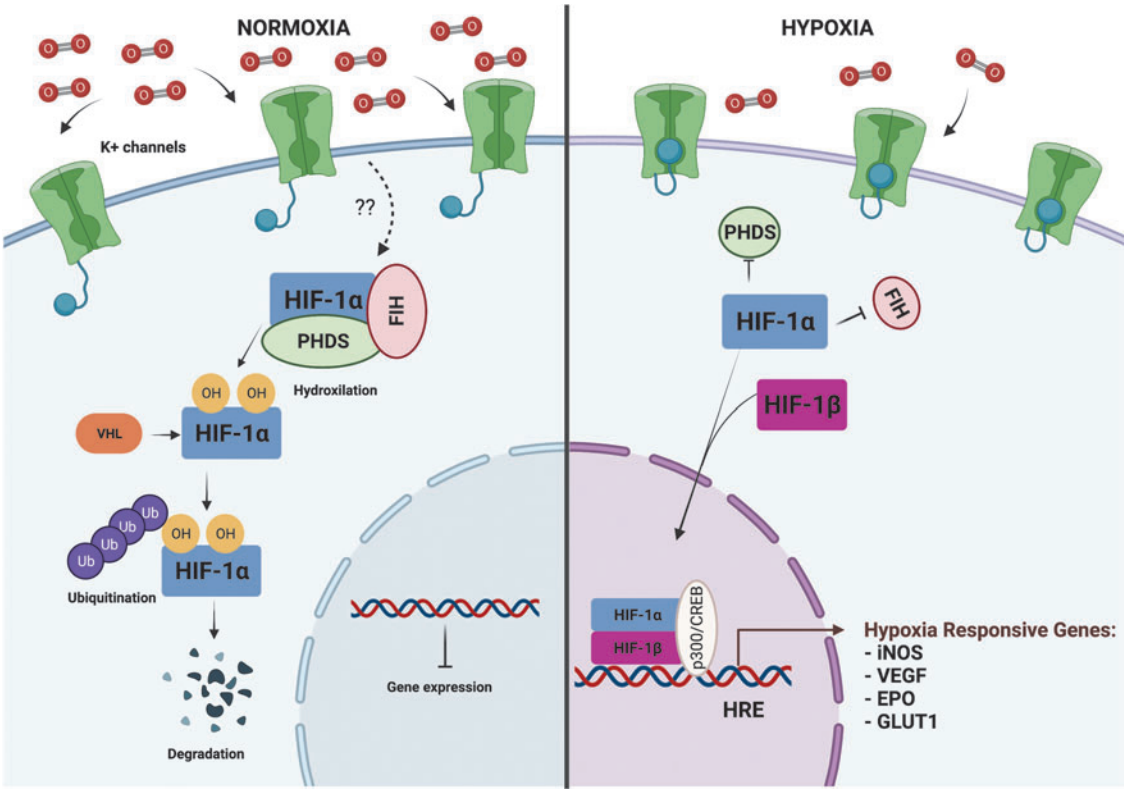

FIG. 2. Overview of O_2 sensing at the cellular level. The image depicts the two scenarios to which cells respond. On the *left*, at a normal O_2 concentration, the O_2-sensitive K^+ channels are active. *HIF-1*α is thus hydroxylated by O_2-PHDs that enhance its binding with VHL, and by *FIHs*, inhibiting the binding of *HIF* with coactivators p300/CREB-binding protein. The newly formed complex acts as substrate recognition component of the E3 ubiquitin ligase complex, which leads to proteasomal degradation of *HIF-1*α. Under hypoxic conditions, the O_2-sensitive K^+ channels are inactive. The activity of O_2-PHDs and FIHs are suppressed, and *HIF-1*α subunits translocate into the nucleus to bind with *HIF-1*β. The heterodimeric *HIF-1*α: *HIF-1*β transcription factor complex activates the HREs in *HIF* target genes to modulate their transcriptional upregulation. This activates transcription of *iNOS*, *VEGF*, *EPO*, *GLUT1*, glycolytic enzymes, and many other *HIF* target genes that are involved in glucose transport and metabolism. *EPO*, erythropoietin; *FIHs*, factors inhibiting hypoxia-inducible factors; *GLUT1*, glucose transporter 1; *HIF*, hypoxia-inducible factor; *HREs*, hypoxia-responsive elements; *iNOS*, inducible nitric oxide synthase; K^+, potassium; O_2-PHDs, O_2-dependent prolyl-4-hydroxylases; VEGF, vascular endothelial growth factor; VHL, von Hippel–Lindau protein. Created with Biorender.com Color images are available online.

neuroinflammation, decreased cerebral amyloid load, enhanced hippocampal neuronal plasticity, and improved behavioral deficits in murine models of the disease (Maezawa et al, 2018).

Along with Kv1.3, the inhibition of the cation channel *TRPV1* with 5-iodo-resiniferatoxin (I-RTX) leads to a reduction in microglial reactive oxygen species (ROS) production following acute stimulation of microglial cells with fibrillar or soluble amyloid fragments (Schilling and Eder, 2011). Modulation of *TRPV1* with the agonist capsaicin in an experimental model of PD also leads to a positive effect on the survival of dopaminergic neurons in the SN (Park et al, 2012). Furthermore, K^+ channels can be modified by oxidizing agents, and recent evidence has shown that they undergo an age-dependent oxidation, impairing neuronal functions (Cai and Sesti, 2009; Sesti, 2016).

Even if the importance of K^+ channels in O_2 sensing has been clarified, there is still a lot that needs to be discovered about this mechanism (Vjotosh, 2020) and how it is related to ND pathogenesis.

Cytoplasmic O_2 sensors: the role of HIF-1

Changes in O_2 levels typically converge to the activation of a specific transcriptional response aimed at counterbalancing this dysregulation. It is well known that the central elements of the cytoplasmic O_2 sensor pool are the *HIFs* (Liu et al, 2020). The human genome encodes three different HIF subtypes: *HIF-1*, *HIF-2*, and *HIF-3*, which are heterodimers composed of a functional α subunit and a stably expressed β subunit (Dengler et al, 2014). Specifically, *HIF-1*α is the main transcription factor involved in O_2 sensing as it targets genes that encode for proteins that increase O_2 delivery and mediate adaptive responses to O_2 deprivation (Lee et al, 2019; Semenza, 2010; Semenza, 2000; Vjotosh, 2020). At normal O_2 levels, *HIF-1*α is hydroxylated by O_2-dependent prolyl-4-hydroxylases (O_2-PHDs) that enhance its binding with the von Hippel–Lindau protein (*VHL*).

The newly formed complex can be recognized by the E3 ubiquitin ligase complex, and thus ultimately leads to *HIF* degradation by the proteasome (Sharp and Bernaudin, 2004). Moreover, *HIF-1*α subunits are also hydroxylated by factors inhibiting HIFs (FIHs), which inhibits the binding of HIF with coactivators p300/CREB-binding protein. Under hypoxic conditions, the activity of PHDs and FIHs is suppressed, and *HIF-1*α subunits translocate into the nucleus to bind with *HIF-1*β (Sharp and Bernaudin, 2004). The heterodimeric *HIF-1*α: *HIF-1*β transcription factor complex activates the hypoxia-responsive elements (HREs) in *HIF* target genes to modulate their transcriptional upregulation. This activates transcription of inducible nitric oxide synthase (*iNOS*), vascular endothelial growth factor (*VEGF*), and erythropoietin (*EPO*), which increases O_2 availability by promoting erythropoiesis and angiogenesis, and inducing glucose transporter 1 (*GLUT1*), glycolytic enzymes, and many other *HIF* target genes that are involved in glucose transport and metabolism (Lee et al, 2019; Sharp and Bernaudin, 2004) (Fig. 2).

Furthermore, the translation of *HIF-1*α messenger RNA (mRNA) into a protein is subjected to regulation by the *PI3K/Akt/mTOR* and *PI3K/Akt/FRAP* signaling pathways. Among the cellular processes activated in response to O_2 imbalance, a number of pathways are independent of *HIF*, such as the nuclear factor-κB (*NF-*κ*B*) pathway. Indeed, according to early studies, *I*κ*B*α is phosphorylated during hypoxia, allowing the degradation of *I*κ*B*α and the activation of *NF-*κ*B1* (Singh and Singh, 2020).

Since the brain is a great energy consumer it is particularly susceptible to O_2 imbalance and hypoxia. Consequently, the decrease of O_2 levels can contribute to brain damage by inducing cell death and NDs. Hypoxia may influence many pathological aspects of AD, including amyloid β metabolism, tau phosphorylation, autophagy, neuroinflammation, oxidative stress, endoplasmic reticulum stress, and mitochondrial and synaptic dysfunction, which may collectively result in neurodegeneration (Zhang et al, 2019). The activation of *HIF-1* through the repression of PHDs can provide neuroprotection, ameliorate the outcomes, or prevent the pathogenesis in these pathological conditions.

The beneficial effects of *HIF-1* arise mainly from the increased expression of *HIF-1* target genes, which combat oxidative stress, improve blood O_2 and glucose supply, promote glucose metabolism, regulate iron homeostasis, activate the synthesis of dopamine, and block cell death signal pathways (Merelli et al, 2018; Zhang et al, 2011). The *HIF-1* activation may be a potent strategy to ameliorate the outcomes of AD. An association between decreased *HIF-1* levels and an increase in tau protein and neurofilament presence has been reported (Mitroshina et al, 2021). These processes lead to a decreased presence of a panel of genes, including *HIF-1*, known for their role in maintaining the viability and synaptic transmission of nerve cells (Mitroshina et al, 2021). Specifically, M30, one of the *HIF-1*α activators, increases the *HIF-1*α protein expression and its target genes *VEGF* and *EPO*. Moreover, M30 also attenuates tau phosphorylation and protects neurons against Aβ (Snell et al, 2014).

Furthermore, deferoxamine (DFO), another *HIF-1* inducer, has been used in a clinical trial in AD showing a slowed cognitive decline, highlighting how an increased activity of HIF-1 can prevent neuron death and improve AD symptoms (Zhang et al, 2011). There are a high number of studies highlighting the neuroprotective role of *HIF-1*α and its subsequent signaling pathway, and for this reason, a novel therapeutic strategy in NDs worth investigating is that aimed at the stabilization of *HIF-1* (Merelli et al, 2018). Specifically, pharmacological activation of *HIF-1* might be used in therapy thanks to its neuroprotective effect. The increase in *HIF-1* activity, along with that of its target genes, has been shown to slow down the cognitive decline present in AD patients along with the progression of the disease (Iyalomhe et al, 2017).

Furthermore, lactoferrin administration leads to *ERK* signaling pathway transduction, activating *ADAM10* through the *HIF-1*α pathway (Mechlovich et al, 2014). This results in a non-amyloidogenic processing of APP, which ultimately leads to improved results in spatial learning tests and cognitive outcome assessment (Mechlovich et al, 2014). The most direct linkage between *HIF-1* and PD is the tyrosine hydroxylase (*TH*) activity, the rate-limiting enzyme in the synthesis of dopamine in dopaminergic neurons, also considered to be a hypoxia response element (Schnell et al, 2003). As widely explained, hypoxia and DFO activate *HIF-1*, which, in turn, has been seen to increase *TH* expression in rat brains. Meanwhile, the knockdown of *HIF-1*α in mice caused the decrease of *TH* expression in the SN (Milosevic et al, 2007).

Recent studies have shown that *HIF-1* has a fundamental role in both the differentiation and survival of dopaminergic neurons, and for this reason, a reduction in *HIF-1* could play a crucial role in PD pathogenesis. Subsequently, increasing the expression of *HIF-1*α could represent an innovative therapeutic approach for PD-affected patients (Mehrabani et al, 2020). These beneficial effects on dopaminergic neurons are found in both in *in vitro* and *in vivo* PD models, and they seem to be induced by *HIF-1* complex activation in relation to the expression of *EPO* and *VEGF* (Strowitzki et al, 2019). The administration of *EPO* appears to result in long-term synaptic plasticity, as well as an antioxidant effect, and a reduction in the inflammatory responses, thus highlighting the important role of *HIF*-mediated regulation of *EPO* in PD therapy (Thompson et al, 2020).

Moreover, recent studies have also demonstrated that the stabilization of *HIF-1* may protect dopaminergic neurons through the alteration in iron homeostasis and defense against oxidative stress and mitochondrial dysfunction. Specifically, the inhibition of PHD activities with 3,4-dihydroxybenzoate (DHB) results in HIF-1α protein stabilization and thus leads to the increase of *HIF-1* target gene expression, such as ferroportin and HO-1, in the SN (Zhang et al, 2011). In addition, *HIF-1* can directly influence the expression of leucine-rich repeat kinase 2 (*LRRK2*), involved in the pathogenesis of autosomal dominant PD, whereas hypoxia can trigger beta-synuclein accumulation (Bae et al, 2018). The proteins that lead to *HIF-1* degradation can be inhibited, thus allowing for a modulation of its subsequent signaling and improving the neuron protection from oxidative stress.

Several studies highlighted how it is possible to inhibit *HIF*-specific prolyl hydroxylases with interfering RNA or low-molecular-weight inhibitors (Aimé et al, 2020; Li et al, 2018; Mehrabani et al, 2020). Specifically, prolyl hydroxylase allows the activation of *TH*, and this leads to an enhancement in dopamine synthesis and release. Moreover, in *in vivo* models, the treatment with PHD inhibitors leads to a reduction in the loss of *TH*-positive neurons in the SN, attenuating behavioral deficits in murine models of the disease. The inhibition of HIF PHD can also lead to an amelioration in mitochondrial functions (Zhang et al, 2018). A decreased expression of *EPO* and *VEGF*, which results in tissue hypoxia, is also characteristic of ALS pathogenesis.

Thus, the lack of glucose and O_2 caused by hypoxia can lead to motor neuron death and to the occurrence of ALS. *HIF-1*α is highly expressed before the onset of clinical ALS symptoms, but its expression appears to be reduced in the later stages of the pathology (Nomura et al, 2019). The altered expression of *HIF-1*α leads to a subsequent dysregulation of its downstream signaling pathway, which, as it is implicated in the antihypoxic response, can worsen the motor neuron degeneration observed in ALS (Nagara et al, 2013). Many studies in the *SOD1G93A* animal model highlighted hypoxia as the major cause of motor neuron death (Tankersley et al, 2007). The *SOD1G93A* model is an *in vivo* murine model of genetically manipulated mice harboring the pathogenetic G93A mutation in the *SOD1* gene, causative of familial ALS (Marcuzzo et al, 2011; Rey et al, 2021a).

Indeed, *SOD1* is transcriptionally regulated in response to oxidative stress (Dell'Orco et al, 2016), and the activation of the *HIF-1-VEGF* pathway can induce angiogenesis and increase blood supply to motor neurons (Tankersley et al, 2007). Moreover, recent studies highlighted a negative correlation between *VEGF* levels in neurons and the severity of hypoxia in ALS patients, indicating a deregulation of VEGF in ALS and suggesting that an impaired *HIF-1-VEGF* pathway may contribute to the pathogenesis of ALS (Wang et al, 2007). The overexpression of *VEGF* in SOD1G93A mutant mice delays the degeneration of motor neurons and neuronal death and prolongs the survival of ALS mice (Wang et al, 2007).

Furthermore, numerous studies performed in *in vitro* and *in vivo* models of ALS highlight a neuroprotective effect of *HIF* activation. Indeed, the activation of *HIF1–1*α pathway of action in an *in vivo* model of ALS leads to a reduction in the hypoxic damage, ultimately resulting in neuroprotective and anti-inflammatory effects, with a subsequent reduction in motor neuron degeneration (Nomura et al, 2019). Researchers also showed that inhibiting PHD in an *in vitro* model of ALS can lead to the activation of HIF1–1α also in astrocytes, and this in turn leads to the expression of *VEGF* and *GLUT*, with an increased number of surviving neurons (Wiesner et al, 2013).

Even so, it is important to note that there is some controversial evidence, as the reduction of *HIF-1*α expression using an analog of prostacyclin named ONO-1301-MS was found to improve behavioral outcomes and survival in an *in vivo* model of the disease (Tada et al, 2019). Furthermore, a common shared pathway observed in the three NDs is the decrease of *HIF-1*α levels, and an understudied, worth-investigating part of research is represented by its potential use as a biomarker and it would thus be worthy to keep a lookout for studies analyzing *HIF-1*α expression in peripheral tissues.

Consequences of O_2 imbalance: implications for NDs

Another important aspect to consider within the context of O_2 sensing is how the cell can ''compensate'' a disbalance in O_2 levels and whether this is related to ND pathogenesis. To this end, it is worth mentioning what is the role of *HIF-1* activators, which are strictly correlated with a response to hypoxia (Bell et al, 2005). Among them, the mitochondrial electron transport chain surely plays a role, as it is required to regulate PHD activity and thus *HIF-1* signaling (Bell et al, 2005). Interestingly, among the complex I inhibitors that prevent hypoxic stabilization of *HIF-1*, there are MPTP and rotenone, both PD-causing neurotoxins (Agani et al, 2000; Bell et al, 2005).

These toxins, along with many others, can lead to the presence of deficits in the activity of the mitochondrial electron transport complex, reduce movement of mitochondria, increase the mitochondrial permeability transition, increase generation of ROS, and the activity of nitric oxide synthase in the mitochondria. Complex I activity results impaired not only in the SN but also in the skeletal muscles, platelets, and leukocytes of PD patients (Monzio Compagnoni et al, 2020). Indeed, studies suggest that mitochondrial dysfunctions may occur early in PD pathogenesis, and moreover, these are present in both sporadic and familial forms of PD (Malpartida et al, 2021).

The mitochondria are also relevant in *HIF-1* hypoxic stabilization as the electron transport chain can increase the production of ROS during hypoxia, stabilizing the

transcription factor (Brunelle et al, 2005; Chandel et al, 1998). This is also strictly related to the pathogenesis of NDs, as the role of oxidative stress has been well documented in the pathogenesis of AD and the first possible mechanisms concern the relationship of ROS production with Aβ plaques. Similarly, many evidences demonstrated that PD patients display increased levels of oxidized lipids, proteins, and DNA, along with reduced levels of glutathione in the SN (Nakabeppu et al, 2007).

Specifically, data collected from early-stage PD patients show that oxidative stress is a robust feature of initial disease stages, occurring before significant neuron loss (Ferrer et al, 2011). Lastly, evidence for ROS implication in ALS arose from multiple pathological studies that reported data of increased oxidative stress in ALS postmortem tissues compared with control samples (Islam, 2017). Specifically, markers for lipid oxidation were detected in the spinal cord from sporadic ALS patients, but were absent in controls (Shibata et al, 2001).

There are other consequences of O_2 disbalance that can then impact on ND pathogenesis (Fig. 3), and among them there is iron metabolism, as iron is the key component of hemoglobin. Indeed, following a condition of hypoxia, there is also an increased demand for iron, to limit the damage to the neuronal system. On one hand, intraerythrocytic hemoglobin, increased by *HIF*-induced *EPO* production, may protect neurons against hypoxia and hyperoxia (van der Kooij et al, 2008). On the other hand, extracellular free hemoglobin and its degradation products (such as heme and free iron) may trigger inflammatory immune and oxidative stress, and interact with pathological processes such as the Aβ deposition in AD (Atamna, 2006). Moreover, the increase in ROS production can lead at body level to the dysregulation of the inflammatory response.

Indeed, many studies demonstrate the role of neuroinflammation to be essential in neurodegenerative processes in all three NDs considered in this review (Carelli et al, 2018; Hirsch and Hunot, 2009; Kinney et al, 2018; Liu and Wang, 2017). Moreover, it is relevant to point out that the activation of *HIF-1*α may lead to the upregulation of proinflammatory cytokines and macrophage migration inhibitory factors, thus indicating that the rescue of *HIF-1*α needs to be well balanced to avoid excessive neuroinflammation (Basile et al, 2020).

Lastly, oxidative stress and ROS production can lead to impairment in processes such as calcium signaling, protein misfolding, and synaptic dysfunction, all crucial players in NDs (Merelli et al, 2018; Yeung et al, 2021). *Nrf2* is a master regulator in oxidative stress, as it is implicated in the *Nrf2-ARE* pathway, an intrinsic mechanism of defense against oxidative stress (Buendia et al, 2016). Compelling evidence suggests that oxidative stress increases the damage in NDs due to an increased production of oxidative species and the failure of antioxidant defenses. *Nrf2* is able to activate the phase II antioxidant response declines with aging, thus contributing to an exacerbated status of oxidative stress. Therefore, the activation of the *Nrf2–EpRE* pathway has been pointed as a key target for the development of new drugs for NDs (Buendia et al, 2016).

This evidence highlights how changes in O_2 levels can perturbate the cells in different areas. Specifically, these changes can be perceived primarily through the activation of O_2-sensitive K^+ ion channels, which then lead to an intracellular cascade through molecules associated with them termed as ''O_2-susceptible'' (heme oxygenase 2 [HO-2], nicotinamide adenine dinucleotide phosphate [NADPH], cystathionine-γ-lyase [CSE], guanine-cytosine content [GC], cyclin guanosine monophosphate [cGMP], and protein kinase G [PKG]). There are also other cytoplasmic O_2 sensors, of which HIF-1 is the most relevant for its transcriptional signature aimed at counteracting hypoxia. *HIF-1* can be activated by other intracellular organelles and mechanisms, such as mitochondria and ROS production, and these are tightly bound to ND pathogenesis.

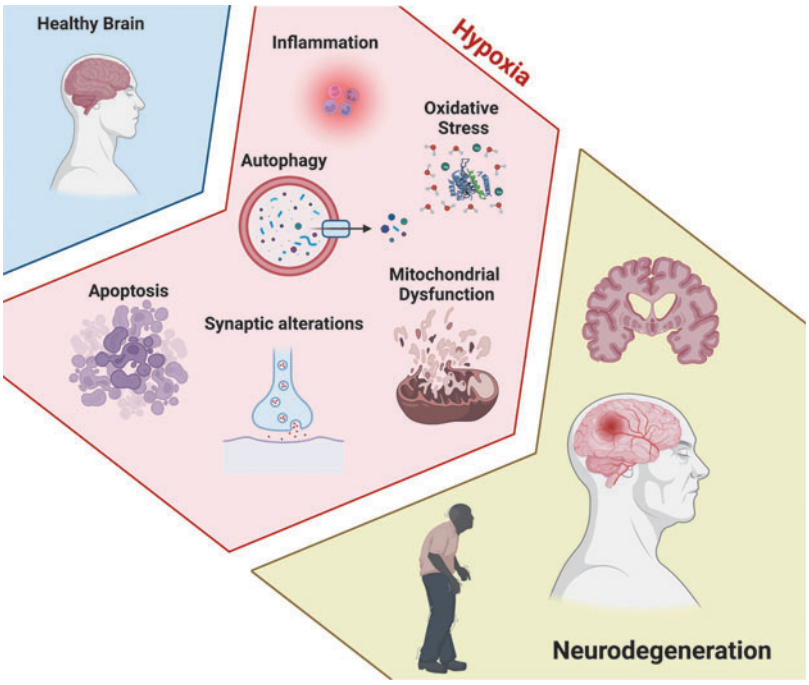

FIG. 3. A condition of hypoxia can lead to intracellular damages resulting in neurodegeneration. A condition of constant reduction in O_2 levels, specifically hypoxia, can lead to numerous intracellular perturbations. These include oxidative stress, mitochondrial dysfunctions, autophagy, synaptic alterations, inflammation, and, ultimately, cell death. The concomitance of these effects leads to neurodegeneration, and these pathways are often common players in NDs. NDs, neurodegenerative diseases. Created with Biorender.com Color images are available online.

Transcriptional Dysregulation of O_2 Sensing in NDs

There is currently a consistent amount of evidence highlighting the role of transcriptional dysregulation in NDs, and the impact that this has on their specific pathogenesis (Garofalo et al, 2020; La Cognata et al, 2021). Indeed, more and more studies are now aimed at highlighting changes in the gene expression signature in disease-affected patients, with the hope to identify novel disease players and possible biomarkers (La Cognata et al, 2021). Pathway analysis of differentially expressed genes allows the identification of those targets specifically involved in a certain process, and for this reason, with this review, we aim to identify also the transcriptional signature responsible for O_2 sensing dysregulation in the three NDs considered in this study (*i.e.*, AD, PD, and ALS).

Thus, the public RNA-Seq data stored on the GEO data sets were interrogated following the workflow reported in Figure 4A to search for dysregulated genes involved in O_2 imbalance in a previously published experimental data set (Butovsky et al, 2015; Simchovitz et al, 2020; Xicoy et al, 2020; Yang et al, 2021). The detailed analysis relative to data set processing and quality is reported in Supplementary Table S1.

The approach returned 104 dysregulated genes for PD, 53 for AD, and 187 for ALS. Among these, the analysis highlighted genes associated with *HIF-1* and changes in O_2 levels, as reported in Table 2. Interestingly, among the genes associated with *HIF-1* and O_2 imbalance, none of them was found dysregulated in ALS.

Adra2b emerged as upregulated in PD. This is a G protein-coupled receptor that regulates neurotransmitter release from sympathetic nerves and from adrenergic neurons in the CNS (Wang et al, 2002). Previous studies have demonstrated that Adra2b levels are increased in hypoxic hepatic stellate cells even if the upregulation occurred independently of *HIF-1α* (Copple et al, 2011). *Angpt2* emerged as upregulated in PD and it has been correlated with *HIF-1* as it is transcriptionally activated with other angiogenic genes and receptors by *HIF-1* expression during hypoxia (Zimna and Kurpisz, 2015).

Moreover, *Cxcr4*, found upregulated in PD, has been linked to hypoxia and *HIF-1* activation as it was observed that hypoxia increased *Cxcr4* expression through *HIF-1α* activation in human monocytes, macrophages, endothelial cells, and cancer cells, allowing the identification of a *Hyp–HIF-1α–CXCR4* pathway that controls cell migration and localization and with a relevance in the pathogenesis of different human diseases (Schioppa et al, 2003). *Gbe1* also emerged as deregulated in PD and it has been associated with hypoxia, as recent studies demonstrated that it is transcriptionally regulated by *HIF-1α* and that it affects tumor progression (Li et al, 2020b).

Lastly, *Cox2* and *Tph2* emerged as deregulated in AD, whereas no significant genes involved in O_2 sensing emerged in ALS. A condition of hypoxia leads to a *TNF-α*-induced regulation of *Cox2* in osteoblast, whereas the hypoxia-induced impairment of *Tph2* and serotonergic functions can be mediated by NOS, involving the generation of free radicals and decreasing the antioxidant status (Rahman and Thomas, 2014; Xing et al, 2015) (Table 2).

The pathways analysis of the dysregulated genes previously described allowed to extract those related to alterations due to O_2 imbalance. When considering NDs, there is often a common signature in the diseases as many pathways are shared among the conditions (see the Cellular Response to Imbalance in O_2 Levels and Its Correlation with NDs section), but a selective neurodegenerative pathogenetic mechanism is present, which leads to the degeneration of specific cell types in each disease. In support of this, it is interesting to note that alterations in O_2 levels cause the dysregulation of metabolic processes. Moreover, the pathway analysis highlights how O_2 imbalance alters not only processes involved in metabolism and signal transduction, but also disease related such as ''*GABA* receptor activation,'' ''*NOTCH* signaling,'' and ''dopamine receptors'' (Fig. 4B–D and Supplementary Table S2).

Furthermore, it is interesting to observe that most pathways linked to O_2 imbalance are specific for each disease (Fig. 5A), while three of them are common between PD and ALS (extracellular matrix organization, neutrophil degranulation, and metabolism of carbohydrates) and five between PD and AD [voltage gated K^+ channels, G alpha (q) signaling events, neuronal system, GPCR ligand binding, and signal transduction] (Fig. 5A). This is even more remarked when considering the gene signature responsible for the pathways' dysregulation (Fig. 5B). Indeed, no dysregulated gene is shared between the 3 NDs, while *DSP* (encoding for desmoplakin) is the only one shared between PD and ALS (Fig. 5B, C).

RNA-sequencing analyses provide researchers with an extremely high amount of information, but there is often

FIG. 4. Processing of RNA-Seq data sets for AD, PD, and ALS. (A) Workflow of processing pipeline: The GEO data sets was interrogated with the terms ''Alzheimer's Disease'' (AD), ''Parkinson's Disease'' (PD) and ''Amyotrophic Lateral Sclerosis'' (ALS), filtering for ''homo sapiens'' and expression studies (microarrays, high-throughput screening, and genome tilting arrays). The results were subsequently filtered for high-throughput studies and disease-specific affected tissues (*e.g.*, hippocampus for AD, substantia nigra for PD, and whole lumbar spinal cord for ALS) obtaining a final number of one AD data set, two PD data sets, and one ALS data sets. The data sets were reprocessed to obtain comparable and homogeneous data. Specifically, the quality of individual sequences was evaluated using FastQC software before and after overrepresented sequence removal with the Cutadapt software. Reads were computed using the STAR software using Gencode Release 38 (GRCh38). Reads abundance was inspected with FeatureCounts, whereas DGE analysis was performed through DESeq2 R package. Made with Biorender.com The dot plots report the pathways pertaining to O_2-sensing mechanisms in AD **(B)**, PD **(C)**, and ALS **(D)**. Gene enrichment analysis was then performed using g:Profiler, ranking terms according to their fold change, and using a Bonferroni–Hochberg false discovery rate (FDR) of 0.05 as threshold and the R software was used to generate dot plot graphs (ggplot2 library). The *y*-axis represents the name of the pathway, the *x*-axis represents the gene ratio, *dot size* represents the number of different genes, and the *color* indicates the adjusted *p* value. AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; DGE, differential gene expression analysis; FDR, false discovery rate; PD, Parkinson's disease. Color images are available online.

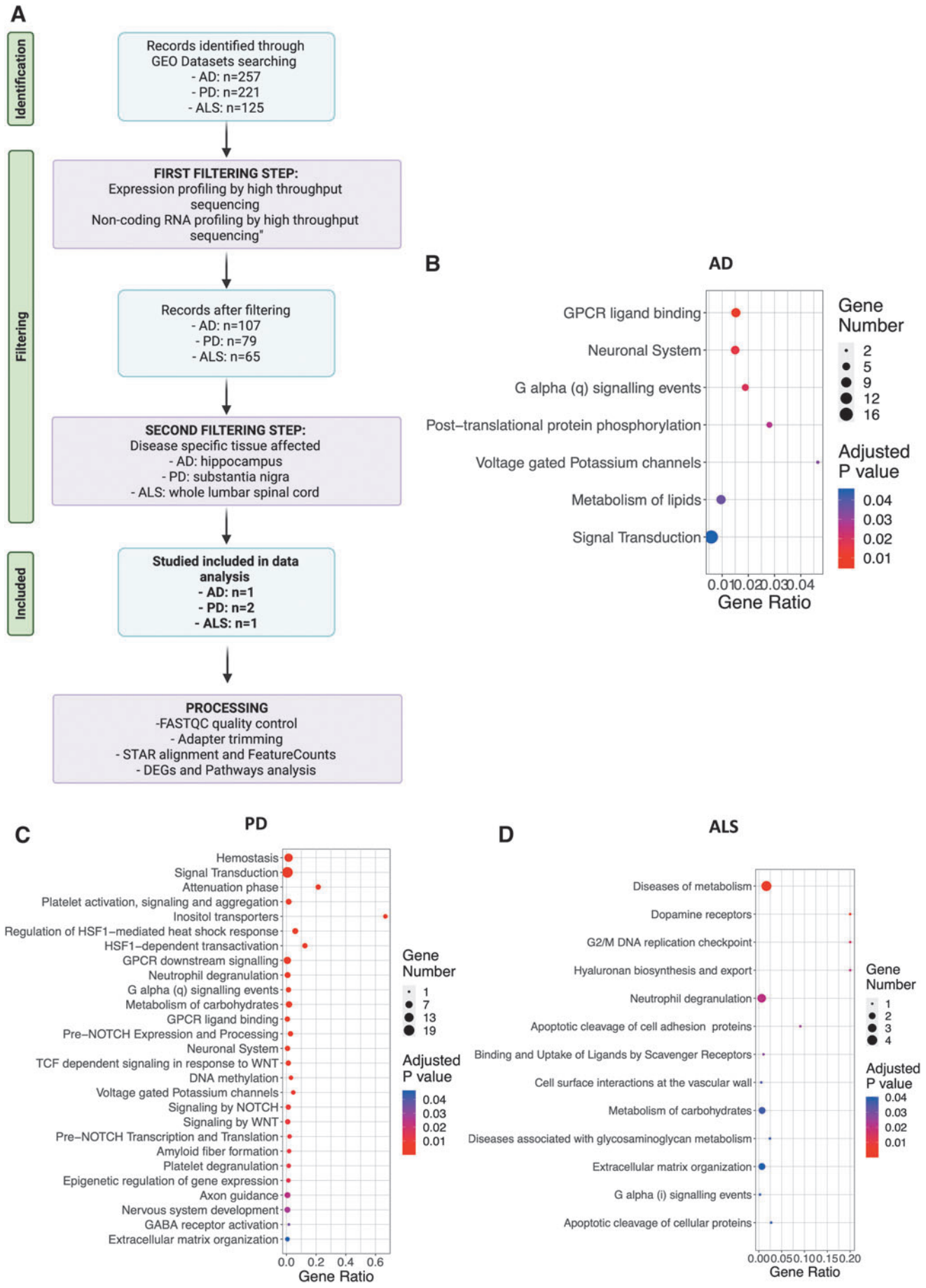

Table 2. Dysregulated Genes Associated with Hypoxia-Inducible Factor 1 and Changes in Oxygen Levels

Gene name	*AD*	*PD*	*Function*	*References*
Adra2b	//	↑	G protein-coupled receptor involved in neurotransmission.	Copple et al (2011)
Angpt2	//	↑	Angiopoietin family of growth factors, antagonist of angiopoietin 1. It is implicated in the direct control of inflammation-related signaling pathways.	Zimna and Kurpisz (2015)
Cxcr4	//	↑	CXC chemokine receptor specific for stromal cell-derived factor 1. It acts with the CD4 protein to support HIV entry into cells and is also highly expressed in breast cancer cells.	Schioppa et al (2003)
Gbe1	//	↓	Glycogen branching enzyme that catalyzes the transfer of alpha-1,4-linked glucosyl units from the outer end of a glycogen chain to an alpha-1,6 position on the same or a neighboring glycogen chain.	Li et al (2020b)
Cox2	↓	//	Also known as cyclooxygenase, it is the key enzyme in prostaglandin biosynthesis, and acts both as a dioxygenase and as a peroxidase.	Xing et al (2015, p. 2)
Tph2	↓	//	The encoded protein catalyzes the first and rate limiting step in the biosynthesis of serotonin, an important hormone and neurotransmitter.	Rahman and Thomas (2014)

Among all the deregulated genes found for the three specific NDs, six were related to *HIF* activation. The table reports the gene name, the ND where it emerged and the specific dysregulation in terms of up (↑) or downregulation (↓), the gene function, and the reference of source where the finding is reported. // Means no available information in the specific ND.

HIF, hypoxia-inducible factor.

a lack of subsequent validation or data integration. The data hereby presented provide a first inspection of the genes and pathways pertaining to O_2 sensing mechanisms in the three considered NDs (AD, PD, and ALS), with the aim to identify selective regulators for each disease, which can then be assessed functionally (see the Current Methodologies to Investigate O_2 Imbalance section) or even prove to be new pharmacological targets (see the Pharmacological Targeting of O_2 Imbalance in NDs section). These preliminary results shed light on the role of O_2 sensing in NDs, and also indicate a strong need for further studies to correlate these mechanisms with ND pathogenesis.

Current Methodologies to Investigate O_2 Imbalance

To gain further insights on O_2 sensing, it is necessary to discuss the possible approaches through which this can be investigated in NDs, and indeed, experimental techniques have been developed over the years to assess the level of oxygenation in cells and tissues (Silva and Oliveira, 2018). These techniques are depicted in Figure 6, and they can be subdivided in direct O_2 evaluation where microelectrodes and Seahorse technique are highlighted; fluorescence approaches, with particular attention to innovative techniques such as fluorescence lifetime imaging microscopy (FLIM) and MitoTracker, and finally, magnetic resonance approaches where the two most exploited techniques are pointed out.

Direct oxygenation evaluation

Microelectrodes are the most common method to measure directly O_2 consumption as they represent the gold standard for tissue oximetry (Springett and Swartz, 2007). They consist in an ultrafine tip of biopotential electrodes that can be inserted directly into biological cultures (Springett and Swartz, 2007). The O_2 tension is measured in a wide surface, and it is particularly used in neurophysiological studies.

In the recent years, extracellular flux (XF) analysis is becoming a gold standard method for the assessment of bioenergetics in adherent cell *in vitro* and *in vivo* tissues (Salabei et al, 2014). Furthermore, the mitochondrial activity can also be assessed *in vitro* in real time using Seahorse XF and this new setup is more suitable with primary neurons (Lejri et al, 2019; Rey et al, 2022). Seahorse XF analyzers measure O_2 consumption rate (OCR) and extracellular acidification rate (ECAR) of live cells in label-free conditions, evaluating cellular functions such as mitochondrial respiration and glycolysis. Sonntag et al exploited this innovative technique to investigate bioenergetic profiles in late-onset AD.

In this study, fibroblasts from patients exhibited a peculiar redox potential and an impaired mitochondrial metabolic potential, associated with reduced nicotinamide adenine dinucleotide metabolism. Indeed, the OCR, the ECAR, and proton production rate were increased in patients' fibroblasts respect to controls (Sonntag et al, 2017). Microglia activation metabolic profiles were tested in primary microglia obtained from murine brain using the Glycolysis Stress Test and Mito Stress Test Kits using the Seahorse XFe96 analyzer, demonstrating that higher levels of *GLUT1* were expressed in microglia (Wang et al, 2019).

Another interesting O_2 evaluation method *in vitro* is high-resolution respirometry to analyze mitochondrial respiratory pathways (Burtscher et al, 2015; Connolly et al, 2018; Djafarzadeh and Jakob, 2017). In particular, this technique was also exploited in ND studies. This technique can be applied to measure respiration in a wide range of cell types and also provides information on mitochondrial quality and integrity. A challenge is to understand why mitochondria fail in particular brain regions under specific pathological conditions. Risiglione et al (2020) deeply investigate O_2 consumption in

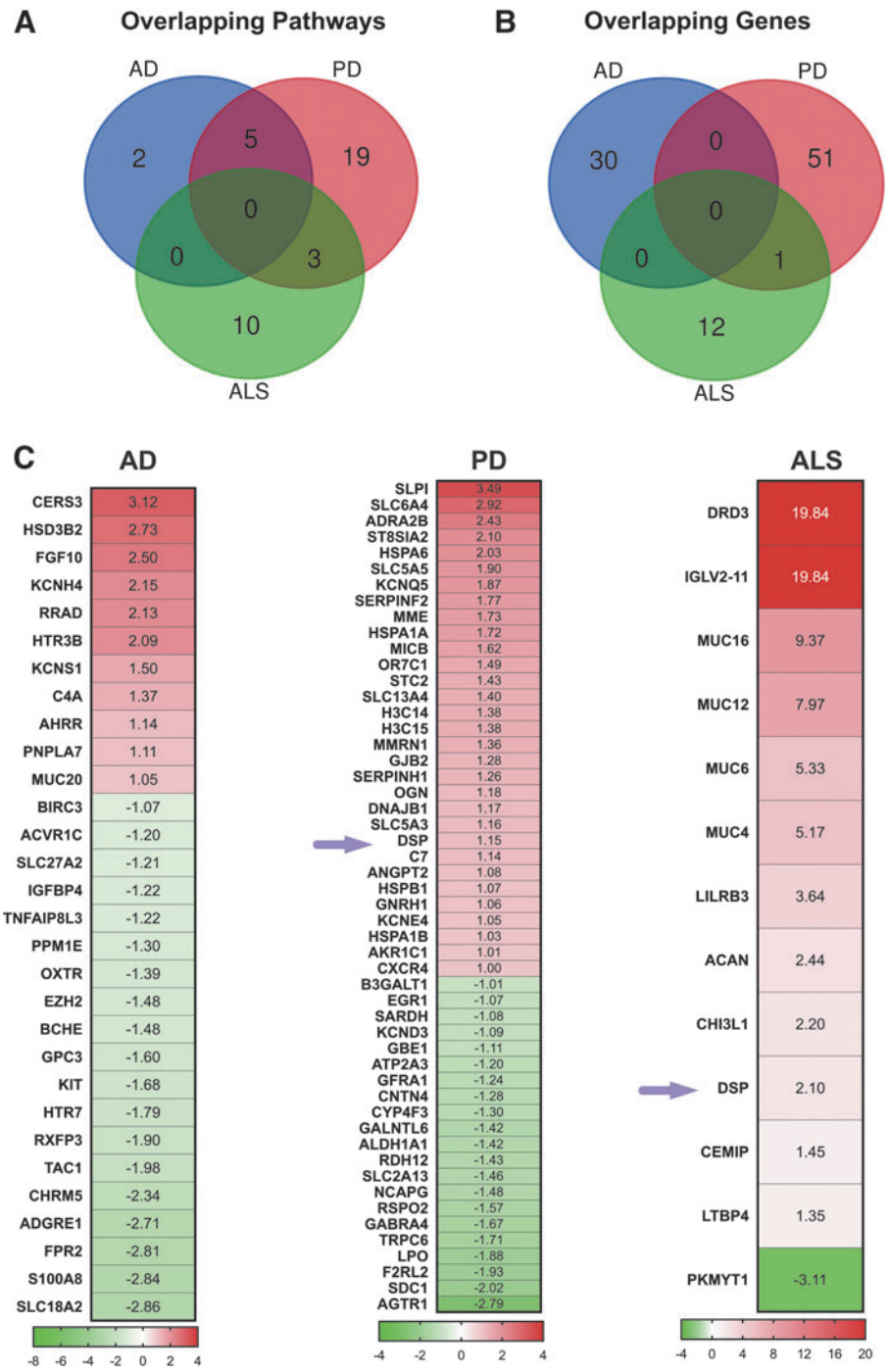

FIG. 5. The O_2-related signature is divergent in the three investigated NDs. (A) The Venn diagram displays how many pathways obtained with Reactome filtered for their relevance with O_2-sensing mechanisms are shared among conditions (http://bioinformatics.psb.ugent.be/webtools/Venn, last accessed on October 4, 2021). **(B)** Genes pertaining to O_2 sensing were extrapolated from the respective pathways. The Venn diagram displays how many of these genes are shared among conditions (http://bioinformatics.psb.ugent.be/webtools/Venn, last accessed on October 4, 2021). **(C)** Heatmap of DE RNAs related to O_2 sensing in AD, PD, and ALS. The *violet arrow* indicates the only term shared among PD and ALS. DE RNAs, differentially expressed RNAs. Color images are available online.

differentiated neuroblastoma cells exposed to the neurotoxin MPP+ and they highlighted the presence of mitochondrial damages at the inner membrane level.

Fluorescence techniques

Miniaturized optical sensors have been tested and optimized (Grist et al, 2010). These have as strongpoint the lack of contamination, the fact that they do not require a direct physical contact between the sensor and the optical detector, and, moreover, they do not consume O_2 (Papkovsky et al, 2000). They include fluorescence resonance energy transfer and two-photon imaging using luminescent quenching. Moreover, these methods are noninvasive and suitable for sequential monitoring. Nowadays, sensor technologies and advances in fiber optics improve the measurement of dissolved O_2 using stable phosphorescent dyes, such as ruthenium chloride, whose quenching is proportional to the surrounding O_2 level (Zeitouni et al, 2015). In 2021, Shin et al. studied oxide-sensitive fluorogenic molecular probes, benzenesulfonylated resorufin derivatives (BSRs), newly developed for optical bioimaging of oxidative events in neurodegenerative processes, in particular for AD.

The researchers demonstrated by immunofluorescence imaging the capability of this new probe to detect intracellular O_2 *in vitro* in inflammatory and microglia cells, and in

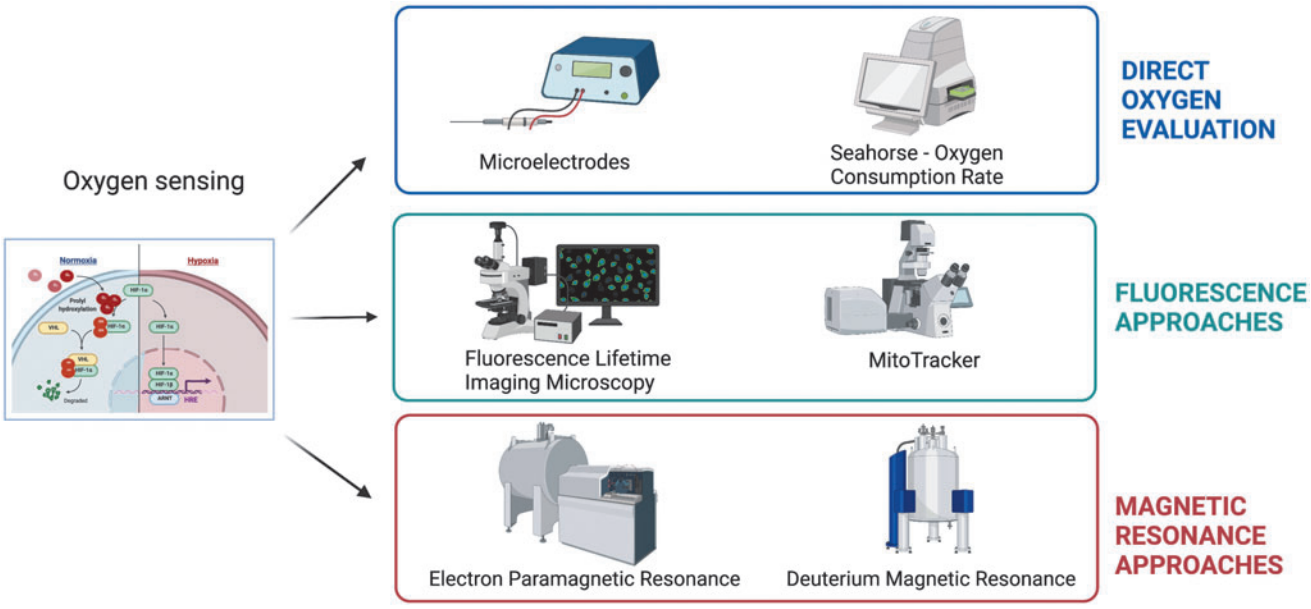

FIG. 6. Overview of techniques and approaches used to assess O_2 imbalance. These techniques can be subdivided in direct O_2 evaluation, where microelectrodes, Seahorse technique, and high-resolution respirometry are highlighted; fluorescence approaches, with particular attention to innovative techniques such as O_2 optodes, Fluorescence Lifetime Imaging Microscopy and MitoTracker, and finally, magnetic resonance approaches, with the two most exploited techniques being electron paramagnetic resonance and deuterium magnetic resonance. Created with Biorender.com Color images are available online.

animal models upon treatment with an oxidative stimulus (Aβ) or the by-product of oxidative stress (4-hydroxynonenal, HNE) (Shin et al, 2021).

The sensitivity of fluorescence O_2 optodes can be tuned to specific pO_2 values, resulting in a higher resolution (Ndubuizu and LaManna, 2007). Indeed, Lubbers et al used pyrene butyric acid to design a specific optode for the *in vivo* measurements of O_2 tension (Lübbers and Opitz, 1975; Opitz and Lübbers, 1987). Furthermore, Nguyen and Hong (2016) set a specific method based on functional near-infrared spectroscopy with bundled optode for detection of the changes of oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) concentrations to analyze brain activity with a higher spatial resolution.

In the recent years, FLIM has become increasingly relevant (Perottoni et al, 2021). Using this advanced imaging technique and an independent O_2 sensor, it is possible to evaluate and measure changes in fluorescence dye lifetime with corresponding changes in O_2 level, specifically in NDs (Sanchez et al, 2018). In this context, Pokusa and Kráľová Trančíková (2018) provide data on localization of intracellular changes of NADH associated with PD, finding a colocalization of the thioflavin fluorescence signal with those of mitochondria and NADH. Furthermore, these evidences corresponded to the accumulation of α-synuclein and of NADH in rotenone-treated cells. Moreover, interesting research published by Gomez-Virgilio et al investigated the translational potential of analyzing patient-derived olfactory neural precursors noninvasively isolated through NADH FLIM to reveal AD-related oxidative stress. This innovative technique permits to discriminate between the contribution of the cytoplasm and mitochondria (Gómez-Virgilio et al, 2021).

Another interesting approach to assess *in vitro* mitochondrial damage is the MitoTracker probe. MitoTracker is chemically reactive, linking to thiol groups in the mitochondria, and the analysis can be performed alternatively on both fixed samples and alive cells (Chazotte, 2011; Rey et al, 2022; Rey et al, 2021b). This approach was adopted to investigate mitochondrial dysfunction and mitophagy defects in PD patients with heterozygous GBA mutations, finding mitochondrial and autophagy deficits in brain tissues (Li et al, 2019). Moreover, a recent study by Sabogal-Guáqueta et al (2019) analyzed with the abovementioned technique the role of linalool on glutamate-induced mitochondrial oxidative stress in AD.

Magnetic resonance techniques

The above-described techniques are widely used in *in vitro* ND models, but are not exploited in preclinical studies. In this context, another innovative method to quantify the O_2 consumption of cells is the electron paramagnetic resonance (EPR) oximetry, widely used for mitochondria and submitochondrial particles (Hyodo et al, 2010). This method is extremely useful for detecting free radicals and ROS (He et al, 2014). ROS are reactive and they also have limited half-lives in biological environments. It is thus difficult to directly measure these species, but the new rapid-scan EPR methods can improve the sensitivity for these samples (Suzen et al, 2017).

Interesting research by Manabe et al. evaluated EPR combined with a mitochondria-targeted redox-sensitive nitroxide probe to elucidate the etiology of AD. With this technique, they demonstrated that an increased oxidative stress was observed in the brain mitochondria of a transgenic mouse model of AD (Manabe et al, 2019). Moreover, with the resonance technique, it is possible to evaluate O_2 consumption also *in vivo* in a preclinical animal model of AD under

noninvasive conditions that could be a potential key for early diagnosis and monitoring the progression of NDs. In this study, researchers observed that mitochondrial dysfunction and oxidative stress in early onset of AD and increased ROS levels associated with defects of mitochondrial and cognitive dysfunction (Fang et al, 2016).

A novel approach is based on deuterium magnetic resonance: this noninvasive technique allows the detection of stable deuterated compounds *in vivo* and therefore does not decay during biological processing (Hartmann et al, 2021). This technique was exploited by Vilaplana et al (2020) to investigate the neuroinflammatory mechanisms in early stages of AD and *in vivo* patterns of neuroinflammation, proteinopathies, and brain function in aging.

Clinical frontiers on O_2 sensing

In patients with NDs, different parameters are often evaluated, but to our knowledge, O_2 sensing is still understudied. In Israel, during 2014–2017, on a small group of patients with PD subjected to subthalamic deep brain stimulator surgery, the brain O_2 levels were measured with a noninvasive near-infrared spectroscopy device, with results yet to be published (NCT02278406).

In conclusion, several *in vitro* and *in vivo* studies exploit systems for O_2 detection. In particular, magnetic resonance techniques, widely used in preclinical research, are also used in different phases of clinical trials, allowing direct O_2 sensing evaluations also on patients.

Pharmacological Targeting of O_2 Imbalance in NDs

For years many researchers have been trying to develop new pharmacological procedures aimed at modulating O_2 sensing mechanisms in the brain, specifically targeting O_2-related pathways (Ferrara and Adamis, 2016; Li et al, 2018; Scheuermann et al, 2009). However, only few successes have been reported, especially concerning NDs (Fig. 7).

HIF-1 modulation as a potential therapeutic target in NDs

Even if specific drugs modulating O_2 sensing for NDs are not commercially available, in the last decade of basic and clinical research, a number of regulating responses (*e.g.*, HIF) have been found in cells exposed to hypoxia, which have a relevant role in O_2 metabolism. These processes have proven to be highly important for neurodevelopment, neuronal survival, and neurodegeneration (Schmidt-Kastner et al, 2006). It was first believed that as *HIF* acts as a DNA-binding transcription factor, it would not be druggable. As a consequence, for many years, researchers only tried to intervene downstream against components that are under the control of *HIF*, such as *VEGF* (Rey et al, 2022). This approach was successful in oncology and ophthalmology, where it allowed to develop many monoclonal antibodies (*e.g.*, ranibizumab, bevacizumab) and aptamers (*e.g.*, pegaptanib) (Ferrara and Adamis, 2016).

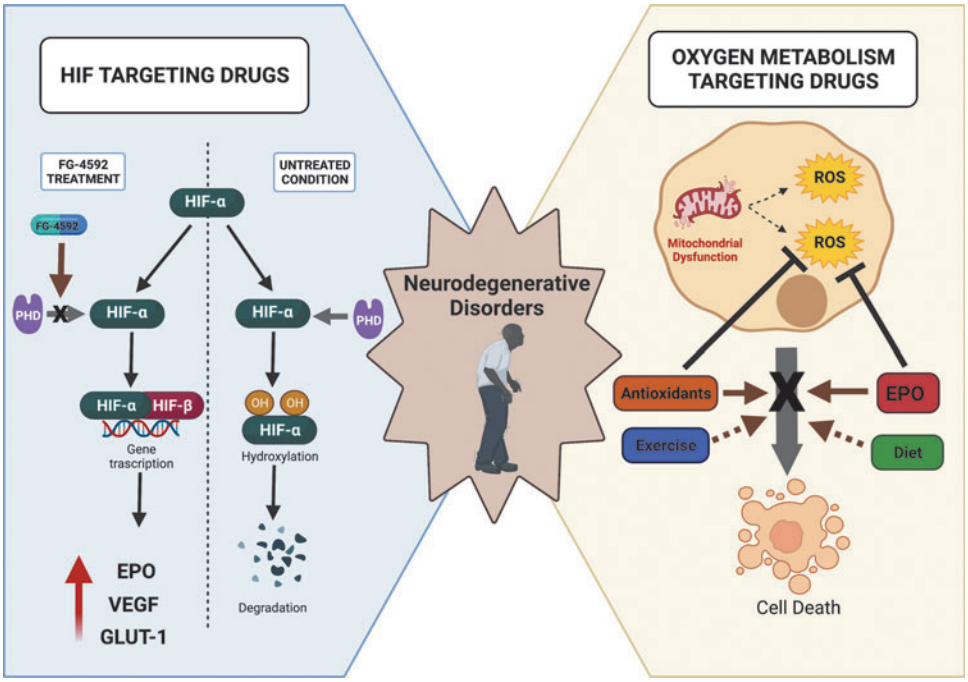

FIG. 7. Overview of possible innovative treatments for O_2 imbalance or its metabolism. These approaches can be classified into two main groups: HIF targeting drugs (*left*) and O_2 metabolism targeting drugs (*right*). As the name suggests, the first group acts on the HIF pathway, specifically on the activity of PHD protein. These drugs include FG-4592, which inhibits the hydroxylation (OH) and degradation of HIF-α subunit leading to transcription of gene targets. On the contrary, O_2 metabolism targeting drugs have broad mechanisms of action, which include a decrease of ROS production and a reduction of cellular senescence. This group includes drugs such as EPO, antioxidant nutrients, and nonpharmaceutical approaches (*e.g.*, diet and physical exercise) whose molecular effects are still to be fully discovered. FG-4592, roxadustat; PHD, prolyl hydroxylase domain; ROS, reactive oxygen species. Color images are available online.

On the contrary, it has been demonstrated, in preclinical experimental models, that VEGF administration inhibits loss of dopaminergic neurons (Kumar et al, 2022), while its antagonism leads to the reduction of synaptic functions and plasticity (Sharma et al, 2019). Indeed, it has been discovered that the use of *VEGF* inhibitors may be linked to PD-like events, dementia, or variants of these diseases (Sultana et al, 2020). Therefore, these approaches do not represent appropriate treatments for NDs. Experimental and clinical evidence has demonstrated that regulating *HIF-1* might ameliorate the cellular and tissue damage in the NDs. Thus, it would be interesting to consider HIF-1 inducers as potential strategies for NDs.

Specifically, iron chelators such as DFO and M30 provide neuroprotection by inhibiting the activation of PHDs. DFO prevents formation of a catalytically active center in the PHDs, thus enabling dopamine synthesis and secretion in PD and slowed cognitive decline in AD, as emerged in clinical trials. Moreover, M30, which upregulates *HIF-1* expression, protects NSC-34 motor neuron cells from oxidative damage *in vitro* and significantly delays the onset of ALS in SOD1-G93A mutant mice and simultaneously attenuates tau phosphorylation and protects cortical neurons against Aβ toxicity in AD experimental models (Zhang et al, 2011). These new findings suggest *HIF-1* as a potential medicinal target for the NDs.

In 2009, Scheuermann et al. published a landmark study in which they identified a druggable pocket in *HIF-2*α as well as a compound that could bind to this site. This led to the discovery of HIF-2 antagonists, such as roxadustat (FG-4592), a small molecule for the treatment of anemia, which has been recently approved by the EMA and currently under revision from the FDA. FG-4592 acts as an antagonist reversibly inhibiting the activity of PHD in normoxia. When PHD is inhibited, all the three subtypes (1, 2, and 3), which compose the HIF-α subunit, are not hydroxylated and degraded by the proteasome. Therefore, the more stable HIF-α enters the nucleus and forms heterodimers with HIF-2β (Haase, 2017; Haase, 2013), which activates target gene expression, including *EPO*, *VEGF*, and *GLUT1* (Semenza and Wang, 1992; Warnecke et al, 2004).

The effects of FG-4502 have been investigated also in PD experimental models. Specifically, FG-4592 is able to exert protective effects in the *in vivo* MPTP-induced PD model reducing both the loss of *TH*-positive neurons in the SN and the subsequent behavioral alterations in both *in vitro* and *in vivo* experiments (Li et al, 2018). These evidences suggest that this mechanism of action may lead to neuroprotective effects on PD patients. The role of dysbiosis and its effect on HIF have been investigated in AD experimental models, as oral bacteriotherapy appears to be a promising preventive and therapeutic strategy through the remodeling of gut microbiota. Indeed, this strategy appears to delay the onset and progression of AD through a reduction of neuroinflammation and protein aggregation.

Specifically, chronic supplementation with *SLAB51* enhances the expression of *HIF-1*α and decreases the levels of *PHD2* in the brain. Moreover, it successfully counteracts the increase of iNOS cerebral expression along with the nitric oxide plasma levels in AD mice, highlighting another mechanism through which *SLAB51* can exert its neuroprotective and anti-inflammatory effects (Bonfili et al, 2021). The implication for dysbiosis and gut microbiota highlights how the environment and nutritional dysregulation could impact on the O_2 sensing process, and indeed, antioxidant molecules and nutritional supplements could be used, in combination, to address O_2 dysfunctions in NDs.

Furthermore, given the importance of *HIF-1*, it would be interesting to evaluate potential strategies that envisage its production or availability in patients with NDs. To this end, Xue et al. proposed a rational drug design of *HIF-1*α*/VHL* inhibitors. Specifically, they developed an effective strategy to identify and design new inhibitors for protein–protein interaction targets. Through alanine scanning, site-directed mutagenesis, and molecular dynamic simulations, they observed that the interactions between Y565 and H110 played a key role in the binding of *VHL/HIF-1*α. Based on the interactions, they synthetized 8 derivates of VH032, 16a-h, by introducing various groups bounded to H110, that exhibited higher binding affinity to *VHL* and markable or modest improvement in stabilization of *HIF-1*α or HIF-1α-OH in HeLa cells (Xue et al, 2022).

In conclusion, novel drugs for NDs could be highly promising candidates in the treatment of these disorders, but still much work is needed to discover new potential biological targets.

Targeting of O_2 imbalance: consequences for the amelioration of ND symptoms

Since therapies that directly target O_2 sensing are limited, conventional drugs still remain the first-line treatment for NDs. Sometimes, these approaches include molecules that act against oxidative damage or its consequences, such as antioxidants or *EPO* itself (Ehrenreich et al, 2007; Moussa et al, 2017; Wüstenberg et al, 2011). Antioxidants are exogenous or endogenous molecules that can act against oxidative stress neutralizing ROS and other kinds of free radicals. These molecules are contained in numerous foods we consume, including flavonoids and phenolic compounds, lipoic acid (thioctic acid), ubiquinone and idebenone, β-carotene, and vitamin C (Chen et al, 2012).

Even if there is no FDA-approved antioxidant therapy for NDs yet, several clinical trials produced promising results in animal models of AD (Rajasekar et al, 2013; Sancheti et al, 2014) and in PD patients (Fahn, 1991). These trials include the use of vitamin E (alpha tocopherol) and vitamin C as strong antioxidant agents. This has been investigated to partially restore cognitive functions in individuals with early PD (Fahn, 1991) and in patients with mild-to-moderate AD (Dysken et al, 2014; Sano et al, 1997). Inconclusive results were also obtained when considering clinical trials with the polyphenolic compound curcumin, a molecule with antioxidant and anti-inflammatory effects (Ringman et al, 2012). Curcumin has indeed proved beneficial in multiple ND models and it has been suggested that the improvement of drug bioavailability could be effective in AD (Gagliardi et al, 2020; Gagliardi et al, 2018, Ringman et al, 2012).

Besides antioxidants, the research of molecules that act on mitochondria represents an innovative approach aimed at mitigating local ROS production or at reducing their induced damage (Brieger et al, 2012). These compounds include *EPO*, a cytokine induced by hypoxia expressed in the brain, that has been demonstrated to exert many fundamental effects

such as neuroprotection and neuroregeneration (Brines and Cerami, 2005; Carelli et al, 2018; Digicaylioglu et al, 1995; Rey et al, 2021b; Rey et al, 2019), neurodevelopment (Victor et al, 2022), and neuroplasticity (Brines and Cerami, 2005), when stimulated by mild local hypoxia (Wakhloo et al, 2020) or when administered as recombinant human *EPO* (*rhEPO*) in different *in vitro* and *in vivo* preclinical experimental models (Fernando et al, 2018; Maurice et al, 2013; Rey et al, 2021b; Rey et al, 2019).

The neuroprotective effects of *rhEPO* have been demonstrated also in two clinical trials in PD-affected patients (Jang et al, 2014; Pedroso et al, 2012).

Moreover, *EPO* and its receptor (*EPOR*) were found in catecholaminergic glomus cell type I of CB (Soliz et al, 2005) where they have been shown to regulate also the activity of carotid sinus. Research highlights that systemic *EPO* can activate the CB chemosensory activity after a hypoxic and hypercapnic stimulation (Andrade et al, 2018). Recent findings also suggest a dual effect of *EPO* in Carotid Sinus Nerve (CSN) in mice, as it stimulates the CSN hypoxic response at low concentrations (<0.5 IU/mL), while it inhibits hypoxic and hypercapnic CSN activation at higher concentrations (>1 IU/mL) following an increase in NO production by type I cells (Arias-Reyes et al, 2021). In conclusion, divergent results have been achieved during EPO and antioxidant research on NDs, and many aspects regarding their role in the CNS remain elusive and need to be elucidated.

Nonpharmacological treatments and lifestyle interventions, which include exercise and caloric restriction, are gaining increasing attention due to their overall beneficial effect on O_2 imbalance, health, and life span (Mendiola-Precoma et al, 2016). Specifically, grounded on a population-based perspective, the Alzheimer's Association has identified regular physical exercise as one of the strategies to reduce the risk of cognitive decline and the development of dementia (Baumgart et al, 2015). Indeed, regular physical activity was associated with reduced oxidative stress, increased antioxidant capacity, and anti-inflammatory effects (Baumgart et al, 2015). To sum up, the molecular mechanisms implicated in the beneficial effects of exercise are not fully understood. Therefore, a better understanding of lifestyle modifications is needed to develop integrated strategies effective in the counteraction of the evolution of neurodegenerations.

Concluding Remarks

O_2 sensing mechanisms in the brain are crucial to maintain tissue homeostasis and organ functionality. Even so, these mechanisms do not strictly occur in the brain, but rather are the result of the cooperation among different organs, which primarily include the CB, preBötC, and the cardiovascular, renal, and pulmonary systems. It is thus of course necessary to consider the whole-body regulation of O_2 sensing and its implication in NDs, but there is also a need to identify the cellular responses to these changes. Specifically, even if more and more evidence is mounting each year concerning the physiology of O_2 sensing, the number of researches correlating these evidences with the three NDs considered in this review article, AD, PD, and ALS, is still limited.

On the contrary, literature evidence primarily focuses on the dysfunctions induced by these processes, which include the production of ROS, mitochondria's health, protein misfolding, and neuroinflammation, all pathways characteristic of NDs. These pathways are strongly altered also when considering the transcriptional deregulation present in AD, PD, and ALS. There is thus a crucial need to investigate O_2 sensing mechanisms, and to identify novel strategies for the detection of these altered pathways and their correlation with specific NDs. Moreover, therapeutic approaches currently primarily focus on the ''correction'' of the abovementioned secondary effects of the dysfunction rather than the O_2 sensing pathway itself. In our opinion, novel approaches targeting this aspect would be of fundamental relevance.

Authors' Contributions

F.R.: Conceptualization, writing—original draft, writing—review and editing, and investigation. L.M.: Formal analysis, investigation, writing—original draft, and writing—review and editing. E.M.: Data curation and writing—original draft. G.C.: Investigation, writing—original draft, and writing—review and editing. S.O. and B.B.: Investigation and writing—original draft. M.T.R., C.C., S.C., and G.Z.: Funding acquisition and writing—review and editing. E.E. and I.P. Project administration and writing—review and editing. S.C.: Conceptualization, writing—original draft, writing—review and editing, and project administration. All authors have contributed to this study and read, edited (where needed), and approved the article as submitted.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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Abbreviations Used

Aβ = β-amyloid
AD = Alzheimer's disease
ALS = amyotrophic lateral sclerosis
BACE1 = β-amyloid precursor protein cleaving enzyme 1
Ca^{2+} = calcium
CBs = carotid bodies
CNS = central nervous system
DGE = differential gene expression analysis
DE RNAs = differentially expressed RNAs
DFO = deferoxamine
ECAR = extracellular acidification rate
EPO = erythropoietin
EPR = electron paramagnetic resonance
FDR = false discovery rate
FG-4592 = roxadustat
FIHs = factors inhibiting hypoxia-inducible factors
FLIM = fluorescence lifetime imaging microscopy
GC = guanine-cytosine content
GDNF = glial cell line-derived neurotrophic factor
GLUT1 = glucose transporter 1
HIFs = hypoxia-inducible factors
HREs = hypoxia-responsive elements
iNOS = inducible nitric oxide synthase
K^+ = potassium
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine
MSA = multiple system atrophy
NDs = neurodegenerative diseases
NF-κB = nuclear factor-κB
O_2 = oxygen
OCR = oxygen consumption rate
OSAS = obstructive sleep apnea syndrome
PD = Parkinson's disease
PHD = prolyl hydroxylase domain
O_2-PHDs = O_2-dependent prolyl-4-hydroxylases
pO_2 = partial pressure of oxygen
preBötC = preBötzinger complex
RAGE = receptor for advanced glycation end products
rhEPO = recombinant human erythropoietin
ROS = reactive oxygen species
SN = substantia nigra
TH = tyrosine hydroxylase
TRP = transient receptor potential
VEGF = vascular endothelial growth factor
VHL = von Hippel–Lindau protein
XF = extracellular flux