Ageing Research Reviews 68 (2021) 101343

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Hypoxia and brain aging: Neurodegeneration or neuroprotection?

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ARTICLE INFO

Keywords:
Aging
Dementia
HIF
Hippocampus
Intermittent hypoxia
Mitochondria

ABSTRACT

The absolute reliance of the mammalian brain on oxygen to generate ATP renders it acutely vulnerable to hypoxia, whether at high altitude or in clinical settings of anemia or pulmonary disease. Hypoxia is pivotal to the pathogeneses of myriad neurological disorders, including Alzheimer's, Parkinson's and other age-related neurodegenerative diseases. Conversely, reduced environmental oxygen, *e.g.* sojourns or residing at high altitudes, may impart favorable effects on aging and mortality. Moreover, controlled hypoxia exposure may represent a treatment strategy for age-related neurological disorders. This review discusses evidence of hypoxia's beneficial *vs.* detrimental impacts on the aging brain and the molecular mechanisms that mediate these divergent effects. It draws upon an extensive literature search on the effects of hypoxia/altitude on brain aging, and detailed analysis of all identified studies directly comparing brain responses to hypoxia in young *vs.* aged humans or rodents. Special attention is directed toward the risks *vs.* benefits of hypoxia exposure to the elderly, and potential therapeutic applications of hypoxia for neurodegenerative diseases. Finally, important questions for future research are discussed.

1. Beneficial or detrimental effects of hypoxia in the brain – a matter of dose

The adverse neurologic consequences of acute exposure to high altitudes (hypobaric hypoxia) when climbing high mountains or during balloon flights have been known since the 19th Century. In 1862, James Glaisher and Henry Coxwell ascended to 8,839 m in an open hot-air balloon, an altitude near that of Mt. Everest (Glaisher, 1862). After barely surviving, the balloonists described severe neurologic symptoms including appendicular and later truncal paralysis, blindness, initially preserved cognition, and subsequent loss of consciousness (Glaisher, 1862). Several weeks acclimatization (West, 1988), however, can enable humans to climb Mt. Everest without supplemental oxygen (O_2), as demonstrated by Reinhold Messner and Peter Habeler in 1978. Without acclimatization, exposure to much lower altitudes can cause life-threatening illnesses due to cerebral and/or lung edema (Hackett and Roach, 2001), mood disturbances (Nelson, 1982), mild cognitive impairments impacting, for example, learning (Pagani et al., 1998) or verbal memory (Pelamatti et al., 2003; Nelson, 1982; Wilson et al., 2009). Even neurological symptoms resembling age-related neurodegenerative diseases, such as parkinsonism (Hur, 2015; Park and Yang, 2013; Swaminath et al., 2006) have been observed following high altitude ascents. At high altitudes the decreased partial pressure of O_2 attenuates the O_2 supply to the brain. The resulting hypoxia is the main determinant of high altitude effects on the brain. Although the low-pressure environment per se might slightly modulate those symptoms (Millet and Debevec, 2020), hypoxia associated with rapid gain in altitude constitutes the primary cause (West and Richalet, 2013).

Molecular O_2 is indispensable for oxidative metabolism and therefore vital to aerobic organisms. However, reliance upon O_2 for aerobic

Abbreviations: AMS, acute mountain sickness; BDNF, brain-derived neurotropic factor; CIH, chronic intermittent hypoxia; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DOPA, dihydroxyphenylalanine; GSH, glutathione; GSK-3β, glycogen synthase kinase-3β; HIF, hypoxia inducible factor; HRE, hypoxia response element; IHC, intermittent hypoxia conditioning; IHHC, intermittent hypoxia-hyperoxia conditioning; Keap1, Kelch-like ECH-associated protein 1; MCI, mild cognitive impairment; miRNA, microRNA; NOS, nitric oxide synthase; eNOS, endothelial NOS; iNOS, inducible NOS; nNOS, neuronal NOS; Nrf2, nuclear factor erythroid 2-related factor 2; OGD, O_2-glucose deprivation; OSA, obstructive sleep apnea; PI3K, phosphatidylinositol 3-kinase; ROS, reactive O_2 species; VEGF, vascular endothelial growth factor; VHL, Van Hippel-Lindau tumor suppressor; VO_{2max}, maximal O_2 uptake.

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https://doi.org/10.1016/j.arr.2021.101343
Received 23 February 2021; Received in revised form 6 April 2021; Accepted 9 April 2021

metabolism is also associated with the production of potentially harmful reactive O_2 molecules, against which organisms must protect themselves (Bunn and Poyton, 1996). The balancing act of avoiding both O_2 deprivation and O_2 toxicity has been compared to Ulysses' perilous navigation between the *Scylla* and *Charybdis* (Bunn and Poyton, 1996).

As the most O_2-dependent organ (Kann and Kovács, 2007), the brain accounts for 20 % of resting O_2 consumption in humans (Silver and Erecińska, 1998), making it exquisitely vulnerable to hypoxia. Systemic hypoxia occurs in numerous pathological states, including infections, inflammation, pulmonary diseases, cancer, stroke and ischemic heart disease. Severe, episodic or sustained hypoxia also is caused by reduced O_2 intake, as in obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) (Daulatzai, 2015; Dodd et al., 2010; Kerner and Roose, 2016). Effective treatment of neurological disorders by O_2 replacement strategies, *e.g.* continuous positive airway pressure (CPAP), underscores the pivotal role of hypoxia in the pathogeneses of these disorders.

Conversely, brief and repeated exposures to mild or moderate hypoxia trigger cellular and physiological adaptations, the phenomenon of intermittent hypoxia conditioning (IHC), rendering organisms more resistant to subsequent hypoxic or ischemic insults (Mayfield et al., 1994). The cardio- and neuroprotective effects of IHC (Manukhina et al., 2016) were first demonstrated in rat brain by Dahl and Balfour (1964). IHC is potentially beneficial in many pathological conditions (Aleshin et al., 1997; Burtscher et al., 1999; Tkatchouk et al., 1994; Zhuang and Zhou, 1999), and has proven effective against cardiovascular (Burtscher et al., 2004; Dudnik et al., 2018; Saeed et al., 2012) and pulmonary diseases (Haider et al., 2009). As reviewed herein, IHC also protects the brain against many neuropathological conditions.

Several factors determine the ultimate risks *vs.* benefits of hypoxia conditioning. These factors include the hypoxia regimen parameters: the application of normobaric (*i.e.*, decreased fraction of inspired O_2, (F_IO_2) at barometric pressures near sea-level) *vs.* hypobaric ($F_IO_2 = 20.93$ % at decreased partial pressure of O_2 in a high altitude or hypobaric chamber) hypoxia (Millet and Debevec, 2020) and the intensity, duration, number and frequency of hypoxia exposures (collectively referred to as hypoxia "dose"). The subject's hypoxia tolerance, physiological capacity, physical conditioning, genetic makeup and nutritional status (Richalet and Lhuissier, 2015), as well as meteorological high altitude variables like wind and temperature (Burtscher et al., 2018) also affect outcomes of hypoxia conditioning.

Intermittent hypoxia typically is administered in cycles of alternating hypoxia-normoxia (Neubauer, 2001) or hypoxia-hyperoxia (Bayer et al., 2017). Depending on the hypoxia dose, intermittent hypoxia either elicits beneficial adaptations (*i.e.*, IHC) or models pulmonary disease (*e.g.*, chronic intermittent hypoxia (CIH) modeling of OSA). Of particular interest as a potential intervention for aging-related brain disease is intermittent hypoxic-hyperoxic conditioning (IHHC), in which hypoxic episodes are alternated with moderate hyperoxia (Bayer et al., 2017). This refinement has proven to be therapeutically effective, particularly for overtraining syndrome (Susta et al., 2017), coronary artery disease (Glazachev et al., 2017), and cognitive impairment (Bayer et al., 2017; Serebrovska et al., 2019b). Relative to IHC, IHHC may afford more robust protection from oxidative stress (Sazontova et al., 2012) and improved post-hypoxic recovery (Serebrovska et al., 2019a). Moreover, IHHC has proven to be safe when applied in at-risk cardiac patients with clinically significant comorbidities (Dudnik et al., 2018). Transient hyperoxia also may prevent detrimental hypoxic pulmonary remodeling (Lyu et al., 2020).

This review examines the risks *vs.* rewards of hypoxia applications for aging and neurodegenerative diseases, where hypoxia may be neurotoxic or neuroprotective. To this end we first provide a mechanistic overview on hypoxia adaptations, followed by a discussion of the effects of hypoxia on aging with a focus on the brain. Reports of direct comparisons of hypoxia intervention in young *vs.* aging animals and humans are analyzed systematically to define current knowledge of hypoxic conditioning and the aging brain. Finally, we integrate our results in an attempt to contribute to an elucidation of the role of hypoxia – and the potential of hypoxic conditioning – in brain pathologies with a particular emphasis on neurodegenerative diseases, exemplified with Alzheimer's disease and Parkinson's disease. To delineate the underlying causes of the divergent outcomes of hypoxia on the brain, first the adaptations to hypoxia of the brain parenchyma, intact brain and the organism are discussed in Section 2.

2. Adaptations to hypoxia: mechanistic aspects

Hypoxia imposes severe challenges to the human organism depending on the applied dose, and can trigger the onset and/or promote the progression of neurological diseases. A potentially increased vulnerability to hypoxia during aging is of particular relevance for age-related neurodegenerative diseases.

The organism addresses hypoxic challenges by various adaptations that are summarized briefly in this section with a focus on aspects relevant to aging and neurodegenerative diseases. Several in-depth reviews on adaptations and maladaptations to hypoxia are available (Beaudin et al., 2017b; Dempsey and Morgan, 2015; Mateika and Komnenov, 2017; McKenna et al., 2020; Prabhakar and Semenza, 2012).

2.1. Molecular responses to hypoxia and hypoxia conditioning

For the purpose of this review it is important to distinguish hypoxia conditioning from the related phenomena of hypoxic pre- and post-conditioning. All three interventions utilize moderate, non-injurious hypoxia to mobilize and/or modulate molecular signaling pathways that increase neuronal or brain tolerance to adverse stress. Hypoxic pre- and postconditioning are well-defined and imparted by single sessions of continuous or intermittent hypoxia, administered before (preconditioning) or shortly after (postconditioning) an acute ischemic-hypoxic insult, *e.g.* ischemic stroke or myocardial infarction. The more broadly used term "hypoxia conditioning" includes hypoxia pre- and postconditioning and describes programs of hypoxia exposures that are commonly administered repeatedly and in intermittent form, however, in contrast to pre- and postconditioning, also often over days or weeks. Hypoxia conditioning does not necessarily refer to a specific ischemic-hypoxic insult and can be performed for example during the prodromal phases of chronic neurological conditions such as late-onset neurodegenerative diseases, which usually lack such identifiable, targetable and acute insults. As indicated above, the quality and dose of the hypoxic stimulus, as well as environment, species, age, health status, autonomic activity and other factors collectively determine the effectiveness of the molecular adaptations.

Hypoxia conditioning modulates gene and protein expression in the brain in 2 distinct phases (Rybnikova and Samoilov, 2015). First, *induction of tolerance*, in which immediate early genes and the molecular machinery to synthesize and post-translationally regulate proteins are mobilized, develops within minutes to several hours after hypoxia. Later *expression of tolerance*, involving additional gene expression and protein synthesis, imparts to neurons protracted resistance to subsequent insults.

2.1.1. Gene expression regulation in response to hypoxia

Adaptive responses to hypoxia at the cellular level are initiated by signaling molecules, primarily reactive O_2 species, *i.e.* ROS (Sies and Jones, 2020) and transcription factors, such as hypoxia inducible factors (HIFs), the central regulators of O_2 homeostasis (Semenza, 1999), and nuclear factor erythroid 2-related factor 2 (Nrf2) (Leonard et al., 2006).

2.1.1.1. Hypoxia-inducible factor (HIF). At normoxic O_2 concentrations and in the presence of α-ketoglutarate and ferrous iron, the α-subunits of HIF are hydroxylated by prolyl hydroxylases (members of the

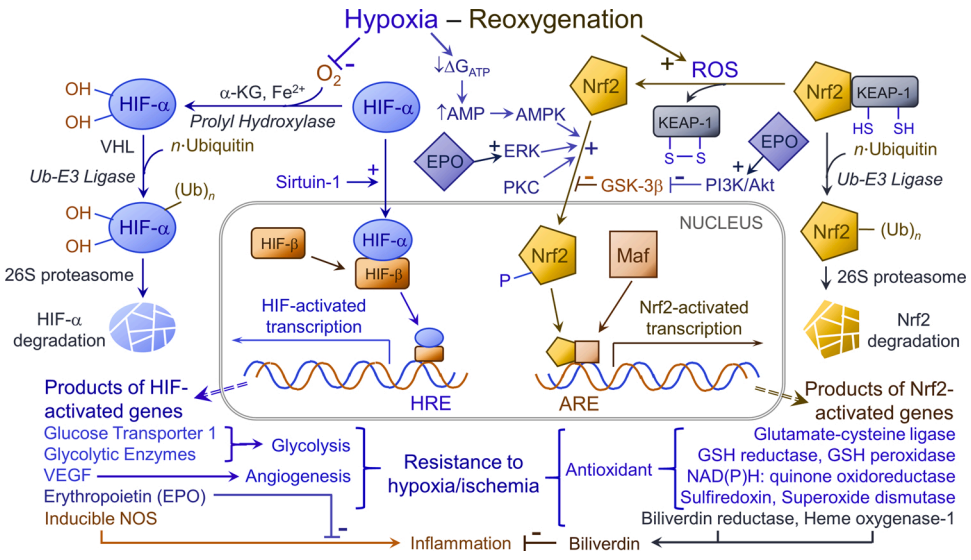

Fig. 1. *Induction of neuroprotective gene expression by intermittent hypoxia-reoxygenation.* During IHC or IHHC, cyclic hypoxia-reoxygenation activates transcription factors HIF (left) and Nrf2 (right). During normoxia, HIF's α-subunit undergoes O_2-dependent prolyl hydroxylation, whereupon VHL recruits ubiquitin-E3 ligase to polyubiquitinylate HIF-α, enabling its proteasomal degradation. Hypoxia and sirtuin-1 stabilize HIF-α, which enters the nucleus and binds the constitutive HIF-β subunit. HIF heterodimers interact with hypoxia-response elements (HRE) in the promoters of genes encoding glucose transporters, glycolytic enzymes, VEGF, erythropoietin (EPO), and others. Synthesis of these proteins increases the cell's capacity to catabolize glucose, activates angiogenesis and suppresses inflammation. Kelch-like ECH-associated protein 1 (Keap1) holds Nrf2 in the cytosol, promoting Nrf2 ubiquitinylation and degradation. Reoxygenation generates ROS, which oxidize Keap1's vicinal sulfhydryls, releasing Nrf2 to enter the nucleus and, with coactivator Maf, bind antioxidant response elements (ARE) to activate antioxidant and anti-inflammatory gene transcription. Unbound Nrf2 also is regulated by protein kinases. AMP kinase, protein kinase C and ERK increase Nrf2's transcriptional activity, while GSK-3β, itself inhibited by PI3K/Akt, inactivates Nrf2. HIF's gene product EPO augments Nrf2's transcriptional activity *via* ERK and PI3K/Akt. Collectively, HIF- and Nrf2-activated gene expression bolsters cellular resistance to severe hypoxia or ischemia. GSH: glutathione; ΔG_{ATP}: Gibbs free energy of ATP hydrolysis. Other acronyms are defined in the text. HIF-α represents HIF-α 1, 2 and 3.

α-ketoglutarate dioxygenase superfamily) at prolyl residues in the α-subunit's O_2-dependent degradation domain. Van Hippel-Lindau proteins (VHL) interact with the hydroxylated α-subunits, facilitating their poly-ubiquitinylation, which targets them for degradation by 26 s proteasomes (Kaelin and Ratcliffe, 2008; Lee et al., 2020; Lendahl et al., 2009). Also under normoxic conditions, the factor inhibiting HIF-1 represses HIF transactivation by hydroxylating an asparagyl residue in the transactivation domain of the α-subunit.

Low O_2 conditions stabilize HIF α-subunits, which dimerize with their β-subunit counterparts, whereupon the HIF heterodimers bind hypoxia responsive elements (HREs) in the promoters of HIF-regulated genes (Fig. 1). This HIF-driven gene expression initiates molecular remodelling to lower cellular O_2 demand by increasing glycolytic capacity, and attenuating hypoxia-induced cell death (Almohanna and Wray, 2018). Erythropoiesis, angiogenesis and alterations related to energy metabolism are among the best-studied HRE-mediated adaptations. Hypoxemia-induced erythropoiesis, well-characterized in rodents (Moore-Gillon and Cameron, 1985) and humans (Knaupp et al., 1992), is orchestrated principally by HIF-1 activation of erythropoietin gene expression in the kidney and liver (Haase, 2013). In the brain parenchyma, erythropoietin serves a neuroprotective function as an anti-inflammatory factor and activator of the transcription factor Nrf2, and its antioxidant and anti-inflammatory gene program (Fig. 1).

2.1.1.2. Nuclear factor erythroid 2-related factor 2 (Nrf2). The master regulator of cellular redox states, Nrf2 activates transcription of an extensive portfolio of antioxidant and anti-inflammatory genes (Baird and Yamamoto, 2020; Sharma et al., 2020; Vasconcelos et al., 2019; Yang and Zhang, 2020). Specifically, Nrf2 activates genes encoding amino acid transporters and enzymes necessary for synthesis, utilization and regeneration of the principal intracellular antioxidant molecule glutathione (Zhang et al., 2013a), the ROS-detoxifying enzymes superoxide dismutase, catalase, sulfiredoxin and NAD(P)H dehydrogenase [quinone] 1, and the enzymes heme oxygenase-1 and biliverdin reductase (Inose et al., 2020; Syapin, 2008), which degrade heme to an anti-inflammatory metabolite, bilirubin (Fig. 1).

While hypoxia activates HIF, Nrf2 is activated by ROS generated upon reoxygenation. ROS release Nrf2 from its suppressor Kelch-like ECH-associated protein 1, *i.e.*, Keap1 (Baird and Yamamoto, 2020; Sharma et al., 2020), whereupon Nrf2 enters the nucleus and, with its partner musculoaponeurotic fibrosarcoma protein (Maf), activates expression of its gene program. Nrf2 also is regulated by several protein kinases including AMP kinase, ERK and protein kinase C (Fão et al., 2019). Glycogen synthase kinase-3β (GSK-3β) phosphorylation inhibits Nrf2 (Culbreth and Aschner, 2018; Sharma et al., 2020), yet GSK-3β is itself inactivated by phosphatidylinositol 3-kinase (PI3K)/Akt (Sharma et al., 2020). These protein kinases mediate crosstalk between the HIF and Nrf2 systems: a HIF product, erythropoietin, activates ERK and PI3K/Akt, which in turn activate Nrf2 (Fig. 1).

2.1.2. Energy metabolism and other adaptations

Molecular responses to hypoxia-reoxygenation are not limited to HIF's and Nrf2's gene programs, but comprise other adaptations involving the epigenome, metabolome, noncoding RNAs and numerous signaling pathways and biochemical adjustments (for a recent review see Lee et al., 2020). In response to hypoxia, brain cells temper their reliance on oxidative phosphorylation, the brain's predominant source of ATP. Concomitant upregulation of glycolytic enzymes and glucose transporters enables glycolysis to assume a more prominent role in cellular ATP production (Lendahl et al., 2009) and lowering reliance on oxidative metabolism to meet cellular energy requirements. The downregulation of both ATP demand and supply is an important mechanism of hypoxia tolerance (Hochachka et al., 1996) and the resulting attenuated electron flux through the mitochondrial respiratory chain has been demonstrated to be at least partially due to inhibition of complex I activity (Tello et al., 2011).

2.2. Systemic adaptations to sustained and intermittent hypoxia

Systemic adaptations to hypoxia include increased alveolar ventilation and cardiac output, erythropoiesis and angiogenesis. Teppema and Dahan (Teppema and Dahan, 2010) provided an extensive review of the ventilatory responses to hypoxia. Acute reductions in the brain's O_2 supply are detected by central (ventrolateral medulla) and peripheral (carotid bodies) chemoreceptors that drive the ventilatory response and activate the sympathetic nervous system to increase cardiac output,

Table 1
Effects of hypoxia on brain function in relation to aging.

Subjects	Age (number)	Hypoxia conditions	Main results	Citation
Mice (wild type)	2 mo (39), 18 mo (19)	NH: $FIO_2 = 10$ % (moderate) or 5 % (severe) for 35 days	GABAergic neurons ↑ in aged and young males after severe IH, but not in young males after moderate IH; parvalbumin neurons ↓ and somatostatin neurons ↑ in young males only after severe IH. Females: no change in total GABAergic neurons, but subgroups differed	(Rubin et al., 2020)
Healthy humans	20−30 yr (16), 60−70 yr (15)	NH: $FIO_2 = 12$ % for 10 min at rest and incremental cycling tests	Cerebral oxygenation was lower in the older subjects; no effect of hypoxia	(Puthon et al., 2017)
Healthy humans	24 ± 3 yr (13), 71 ± 2 yr (12)	NH: 5 min/cycle x 5 cycles: $FIO_2 = 10\%$	Older subjects: lower ScO_2 and resting V_{MCA} pre-hypoxia; reduced heart rate, SaO_2, ScO_2 and cerebrovascular conductance responses to hypoxia	(Liu et al., 2020)
Healthy humans	23 ± 2 yr (7), 61 ± 1.4 yr (9)	Sea level → 2200 m	Blood dopamine and DOPA contents higher in older people at sea level. Altitude effects on dopamine and DOPA contents were blunted in older people	(Serebrovskaya et al., 2000)

DOPA: dihydroxyphenylalanine; FIO_2: inspired O_2 fraction; IH: intermittent hypoxia; NH: normobaric hypoxia; SaO_2: arterial O_2 saturation; ScO_2: cerebral tissue O_2 saturation; V_{MCA}: middle cerebral arterial flow velocity.

peripheral resistance and systemic arterial pressure (Serebrovskaya et al., 2008). Erythropoiesis augments the blood's O_2-carrying capacity, but also increases blood viscosity and coagulability, which may impair cerebral function and increase risk of ischemic stroke (Peacock, 1998). Prolonged hypoxia elicits resetting of the carotid chemoreflex to augment the hypoxia ventilatory response (Carroll and Kim, 2013). Hypoxia exposures lasting several days or more trigger the aforementioned ventilatory, cardiovascular and hematological adaptations that collectively defend O_2 supply:demand balance and effect tolerance to hypoxia (Guillemin and Krasnow, 1997).

Intermittent hypoxia evokes cardiovascular responses which benefit the brain by improving cerebral blood flow, lipid profiles and cerebrovascular functions. It also lowers several cardiovascular risk factors of Alzheimer's disease and other neurodegenerative diseases, namely obesity, hypertension, metabolic syndrome and ischemia (Kivipelto et al., 2005; Navarrete-Opazo and Mitchell, 2014). The frequency, in particular continuous *vs.* intermittent hypoxia, and number of hypoxia-reoxygenation cycles likely determines how long the effects of hypoxia persist. Recently, Tobin et al. (2020) reported moderate (12–15 %) increases in the hematocrit and hemoglobin content of healthy, 67 ± 7 year-old men and women in response to intermittent (cyclic peripheral O_2 desaturation to 85 %) but not continuous hypoxia.

Interventional hypoxia studies typically use chronic intermittent hypoxia (CIH) protocols to study detrimental effects of severe hypoxia, often to model OSA in animals. CIH elicits robust oxidative stress and resultant oxidative damage of biomolecules (Lavie, 2003), mitochondrial dysfunction (Duranteau et al., 1998) and the detrimental activation of inducible NO synthase (iNOS) (Manukhina et al., 2000, 2006). These effects are pro-inflammatory, may be aggravated at advanced age, and may compromise membrane integrity, enzyme efficiency and ATP production, culminating in the development of various pathologies, including OSA (Lévy et al., 2015). In IHC, on the other hand, more moderate ROS and NO formation (Goryacheva et al., 2010; Manukhina et al., 1999) have been found to evoke favorable adaptations (Neubauer, 2001), including upregulation of antioxidant defense systems (Zhuang and Zhou, 1999), increased mitochondrial resilience and efficiency (Mela et al., 1976) and HIF-activated gene expression (Bernaudin et al., 2002), which collectively oppose development of pathogenic cellular environments. Oxidative stress and/or inflammation associated with chronic diseases and aging are potent modulators of the adaptive response to intermittent hypoxia.

3. Hypoxia and aging

Aging is characterized by progressive functional decline (Kauppila et al., 2017), which may be modified by varying O_2 availability. Despite the essential role of O_2 in oxidative metabolism, moderately reduced O_2 concentrations can benefit aging organisms. Hypoxic environments are associated with unusually long life-spans in some mammals, including the naked mole rat (Kim et al., 2011) and bowhead whale (Keane et al., 2015). Mild reductions of mitochondrial respiration, *i.e.*, decreased O_2 utilization – also prolong the viability of cultured cells (Packer and Fuehr, 1977), and lifespan of *Caenorabditis elegans* (Feng et al., 2001; Kayser et al., 2004; Lee et al., 2003; Mehta et al., 2009), *Drosophila melanogaster* (Copeland et al., 2009) and mice (Dell'agnello et al., 2007; Lapointe and Hekimi, 2008), concordant with the proposed inverse relationship between metabolic rate and life span (Kenyon, 2010). On the other hand, severe hypoxia may accelerate aging, possibly by increasing oxidative stress, inflammation and mitochondrial dysfunction. Intense, episodic hypoxia is also associated with decreased telomere length – another indicator of aging – in leukocytes of OSA patients (Kim et al., 2016a).

3.1. The role of HIF in aging

The HIF system activates adaptive responses that oppose aging, yet HIF itself may be downregulated with advancing age (Katschinski, 2006). HIF-1 has been identified as a potent modulator of aging in *C. elegans* (Leiser and Kaeberlein, 2010), an effect mediated by acyl coenzyme A binding proteins (Shamalnasab et al., 2017), and dependent on temperature (Leiser et al., 2011) and oxidative stress (Hwang and Lee, 2011). Moreover, Kim et al. (Kim et al., 2003) demonstrated impaired HIF-1 binding to HREs in aged human diploid fibroblasts. Diminished HIF-1 function also was demonstrated in aging mice (Frenkel-Denkberg et al., 1999). Concordant with these findings, cardioprotective effects of hypoxia conditioning were less pronounced in older *vs.* young rats (Honma et al., 2002).

Collectively, these findings demonstrate a reciprocal relationship between HIF activity and age, which augurs reduced capacity of the HIF system in the elderly. Impairment of the molecular machinery for hypoxia adaptations may increase the vulnerability of older adults to severe hypoxia and/or ischemia.

3.2. The hypoxic ventilatory response in aging

In addition to the HIF system, aging alters O_2 sensing and ventilatory responses to hypoxia. Aging is associated with a reduced breathing capacity due to alterations in peripheral and central chemoreceptor function (Teppema and Dahan, 2010) and diminished capacity of the ventilatory pump due to decreased respiratory muscle strength and chest wall compliance (Janssens, 2005). Carotid bodies of older rats were found to have reduced mitochondrial content and lower numbers of O_2-sensing glomus cells (Pokorski et al., 2004). Also in rats, aging was associated with increased carotid body catecholamine content but decreased hypoxia-induced catecholamine release (Conde et al., 2006). Moreover, hypoxia-induced enhancement of HIF-1α content and expression of HIF's gene products, VEGF and iNOS, declined with age (Di Giulio et al., 2003, 2005). In aging humans the ratio of connective tissue to neurons in the carotid bodies increases (Sarrat-Torres et al., 2020) and sustentacular cells and infiltrating lymphocytes replace the

Table 2
Impact of aging on rodent brain vulnerability to hypoxia.

Species	Age	Hypoxia conditions	Main results	Citation
Mice	2, 18 months	NH cycles (40 s 20 % FIO_2 + 20 s 6 % FIO_2), 6 h/day for 8 weeks	Neither chronic intermittent hypoxia mimicking OSA nor aging modified brain tissue stiffness	(Jorba et al., 2017)
Rats	3, 24 months	Hypobaric hypoxia: simulated altitude 7620 m for 1, 2 or 3 weeks	Hypoxia and aging were associated with lipofuscin deposition, altered aging-related protein contents and mitochondrial ultrastructure in hippocampal neurons, learning and memory impairment	(Biswal et al., 2016)
Mice	4, 24 months	Chronic hypobaric hypoxia (290 mm Hg) for 3 weeks	HIF-1α and VEGF responses were delayed in aged mice; cyclooxygenase-2, angiotensin II and PGC1α unaffected by age	(Benderro and LaManna, 2011)
Rats	8 days-2 years	NH preconditioning (95 % N_2/5 % for 1–10 min) before 10 min OGD	Age-related loss of HPC effects may be due to altered intracellular Ca^{2+} homeostasis and prevents critical elements of neuroprotective signaling.	(Bickler et al., 2010)
Rats	3, 24 months	12 h $FIO_2 = 10$ % followed by 12 h $FIO_2 = 21$%, 8 days	HIF-1α cytoplasmic accumulation was associated with cell death in cerebral cortex of old rats exposed to intermittent hypoxia	(Rapino et al., 2005)
Rats	3–4, 20–22 months	$FIO_2 = 10$ % O_2 every 90 s for 12 h/day, 3 or 14 days	Increased susceptibility to intermittent hypoxia in aging rats: decreases in proteasomal activity, increased neuronal apoptosis. Reduced pCREB and impaired spatial function (Morris water maze)	(Gozal et al., 2003)
Rats	3, 24 months	12 h $FIO_2 = 10$ % or 8.5 % followed by 12 h $FIO_2 = 21$ %, 28 days	Hypoxia inactivated synaptosomal ATPases in both age-groups, except low-affinity Ca^{2+} ATPase decreased only in 24 month-old rats.	(Benzi et al., 1994a, 1994b)

All of these studies were conducted in wild-type rodents. FIO_2: inspired fraction of O_2; HIF-1α: α-subunit of hypoxia inducible factor 1; NH: normobaric hypoxia; OGD: O_2 -glucose deprivation; pCREB: phosphorylated cyclic AMP response element-binding protein; VEGF: vascular endothelial growth factor.

chemosensory glomus cells (Hurst et al., 1985). Central chemoreceptors may partially compensate for deteriorating carotid bodies (Pokorski et al., 2004), as the hypoxia ventilatory response in elderly, although attenuated *vs.* that of young adults (Liu et al., 2020) is not severely impaired (Teppema and Dahan, 2010).

4. Hypoxia conditioning of the aging brain

Hypoxia conditioning, especially IHC, exerts a number of beneficial effects on the brain and has proven an efficient intervention for numerous experimental brain pathologies (Manukhina et al., 2016), but aging modulates these benefits. Decreased HIF signaling may be a central factor in age-related neurodegenerative disorders (Correia et al., 2013; Correia and Moreira, 2010). The paucity of systematic investigations of the reciprocal interaction of hypoxia and aging on the brain prompted a literature search to identify reports shedding light on the potential risks and benefits of hypoxia preconditioning in age related neurological disease. Sixteen controlled studies in humans and rodents were identified that addressed the effects of aging on brain responses to hypoxia by directly comparing younger *vs.* older subjects. Tables 1–3 present these studies. Other studies not reporting such direct comparisons but which address other aspects of hypoxia and brain aging also are discussed herein.

4.1. Hypoxia changes blood flow and activity in the aging brain

Hypoxia's pronounced effects on cerebral blood flow and oxygenation first were reported in mountaineers (Rootwelt et al., 1986). Cerebral deoxygenation assessed by transcranial Doppler and diffuse correlation spectroscopy was more persistent than peripheral deoxygenation in 22−80-year-olds ascending to 4559 m (Sanborn et al., 2015). The effect of altitude on cerebral blood flow velocity varies among different brain regions. Feddersen et al. (2015) reported increased flow velocity in the anterior and middle cerebral arteries of mountaineers (age: 43.5 ± 2.2 years) ascending from 100 to 3440 m, while flow velocity in the posterior cerebral arteries decreased up to 5050 m. Further increases in middle cerebral artery flow during ascent to 5050 m were associated with the development of acute mountain sickness (AMS).

Acute hypoxia compromises cerebral oxygenation, particularly during exercise at altitude. At low altitudes cerebral O_2 delivery was maintained in unacclimatized adults exercising on a cycle ergometer until maximal O_2 uptake (VO_{2max}) was attained, but at 5260 m O_2 delivery was highest at 30 % of VO_{2max} and thereafter declined progressively at increasing exercise intensities (Imray et al., 2005). Conversely, intermittent hypoxia has the potential to increase cerebral oxygenation in men and women (Iwamoto et al., 2020; Liu et al., 2017).

Concordant with the high altitude effects, several studies showed cerebral blood flow and cerebrovascular regulation also to be altered in OSA patients (Beaudin et al., 2017a, b; Yadav et al., 2013). In heart failure patients, increased carotid artery flow suggests a compensatory mechanism to preserve cerebral blood flow (Mansur et al., 2018). On the other hand, COPD patients experienced severe deterioration of systemic and cerebral oxygenation, which correlated with decreased cycling performance, already at a moderate altitude of 2590 m (Furian et al., 2018).

Several other studies confirm effects of high altitude sojourns on increased cerebral vasodilation (Jensen et al., 1996) and circulating markers of blood brain barrier disruption (Bjursten et al., 2010; Winter et al., 2016). The small sample sizes and disparate demographics (*e.g.*, age ranges of participants) underscore the need for detailed studies about the influence of aging on incidence and severity of AMS, cerebral edema, cognitive impairment and other adverse effects of high altitude. The development of methods and biomarkers to reliably detect alterations of brain structure at high altitudes will facilitate such studies. Recently, the extracellular vesicles $CD31^{neg}$ and $CD42b^{low/neg}$, which are required for platelet-endothelial cell interactions and that appear in the circulation at extreme altitudes, were proposed as early markers of hypoxia-induced vascular dysfunction and blood brain barrier disruption (Utermöhlen et al., 2019).

Brain injury in OSA patients was accompanied by altered concentrations of *N*-acetylaspartate (indicating neuronal injury), glutamate

Table 3
Modulation of cognitive function in humans by hypoxia conditioning.

Health status	Mean age ± SD (number)	Hypoxia conditions	Main results	Citation
Healthy but physically inactive	Hypoxia: 63.7 ± 3.4 (17); Normoxia: 63.6 ± 3.2 (17)	NH: 10 min hypoxia (SpO_2 90 % weeks 1–2, 85 % week 3, 80 % weeks 4–6) + 5 min normoxia, 4 cycles/day, and 30 min full body strength-endurance training	Improved cognitive performance and sleep quality in hypoxia	(Schega et al., 2013)
Physically active	Hypoxia: 66.4 ± 3.3 (18); Normoxia: 67.9 ± 4.4 (18)	NH: SpO_2 90–85 % week 1, 80 % weeks 2–4, 90 min/session + 30 min aerobic bicycle training (week 1: 65–70 % HR_{max}; weeks 2–4: 70–75 % HR_{max}), 3x/week for 4 weeks	Hematological parameters, time to exhaustion (load test) and cognitive function improved only in hypoxia. VO_{2max} and serum BDNF unchanged in both groups	(Schega et al., 2016)
Multi-morbidity due to advanced age	Hypoxia: 80.9 ± 7.8 (18); Normoxia: 83.4 ± 5.5 (16)	IHHC: 4–6 min FIO_2 12 %, 1–2 min FIO_2 35 %, 2–3x/week, total 15–16x in 5–6 weeks. Multimodal rehabilitation (2–3x/week, total 16–20 sessions)	Improved cognitive performance (dementia and clock drawing tests) only in IHHC. 6 min walking test improved in both groups, significantly more in IHHC	(Bayer et al., 2017)
Patients with MCI	Healthy: 63.0 ± 10 (7); MCI + sham: 72.6 ± 6.9 (6); MCI + IHHC: 68.2 ± 7.2 (8)	IHHC: 5x/week for 3 weeks: 4 × 5-min FIO_2 12 %, followed by 3-min hyperoxia (F_IO_2 33 %)	Slight cognitive improvement immediately post-IHHC; ERPs unchanged. Better amyloid precursor protein ratio, reduced amyloid β and neutrophil extracellular traps in IHHC	(Serebrovska et al., 2019b)
Patients with amnestic MCI	Hypoxia: 69 ± 3 (7)	NH: 5 min FIO_2 10% + 5 min room-air, 8 cycles/session, 3 sessions/week for 8 weeks	Resting arterial pressures fell by 5–7 mm Hg, ScO_2 increased after IHC. IHC enhanced hypoxemia-induced cerebral vasodilation, improved mini-mental status exam and digit span scores	(Wang et al., 2020a)

BDNF: brain derived neurotrophic factor; ERP: event related potential; FIO_2: fractional inspired O_2; HR: heart rate; HR_{max}: maximum heart rate; IHC: intermittent hypoxia conditioning; IHHC: intermittent hypoxic hyperoxic conditioning; MCI: mild cognitive impairment; NH: normobaric hypoxia; SA: simulated altitude; SaO_2: arterial O_2 saturation; ScO_2: cerebral O_2 saturation; SpO_2: O_2 saturation; VO_{2max}: maximum O_2 uptake.

(suggesting ongoing excitotoxicity or astrocyte activation) and ascorbate (a putative indication of oxidative stress) in limbic brain structures, including hippocampus, thalamus and putamen (Sarma et al., 2014, 2016), and in midbrain (Macey et al., 2017). Evidence of compromised structural integrity also emerged from studies in mice, where chronic (12 week) exposure to hypobaric hypoxia (equivalent to 5000 m) altered synaptic and astroglial protein contents in specific brain regions, which coincided with cognitive deficits in fear conditioning tests (Sharma et al., 2019).

Not surprisingly, hypoxia-induced changes in brain permeability and blood supply are associated with altered brain electrical activity. In healthy 26–57-year-old men and women ascending to 2700 m, discrete changes in brain electrical activity were detected by event-related synchronization tests (Guger et al., 2005). Changes in the brain's electrical activity also were detected by electromagnetic tomography in OSA patients (Toth et al., 2009, 2016) and were reversible by CPAP (Toth et al., 2012).

Animal experimentation has advanced our understanding of the responses to hypoxia which may confer protection to the brain despite its critical dependence on a robust O_2 supply for ATP production. LaManna et al. (1992) demonstrated two phases of cerebrovascular adaptations to chronic, hypobaric hypoxia (5500 m) in 3–6 month-old rats. First, cerebral blood flow increased within the first hours of hypoxia and subsided after 3 weeks (LaManna et al., 1992). Second, 3-week hypoxia elicited angiogenesis in a brain-region specific manner (LaManna et al., 1992) while also augmenting erythropoiesis and hematocrit. Chronic hypoxia (Boero et al., 1999; Kalaria et al., 2004; LaManna et al., 2004) and – albeit less pronounced – intermittent hypoxia (Kalaria et al., 2004) also increased angiogenesis and brain capillary densities. Adequate brain perfusion is maintained by metabolic autoregulation and neurovascular coupling (Lourenço et al., 2017; Toth et al., 2017). Vasodilation is effected by nitric oxide (NO) production and signaling, which are impaired in neurodegenerative diseases (Lourenço et al., 2017; Steinert et al., 2010). Intermittent hypoxia has been shown to increase vasoactive NO (Goryacheva et al., 2010; Manukhina et al., 1999), as well as *S*-nitrosothiol and dinitrosyl iron complexes which provide releasable cerebrovascular stores of neuroprotective NO (Manukhina et al., 1999, 2011).

HIF-1-induced and vascular endothelial growth factor (VEGF)-mediated angiogenesis may be particularly important in astrocytic endfeet, which report neuronal activity to the vasculature to effect neurovascular coupling (Chávez et al., 2000; LaManna et al., 2004). Together with HIF-1-activated upregulation of glucose transporter GLUT1, increased microvascularization augments the glucose transport capacity across the blood brain barrier.

In addition to these mechanisms, the hypoxic brain optimizes its O_2 supply:demand balance by dampening ATP-consuming cellular processes and augmenting glucose uptake for glycolysis. In rats, successful adaptation to prolonged hypobaric hypoxia (LaManna et al., 1992) maintained ATP and phosphocreatine contents and intracellular pH in the brain (Harik et al., 1995; LaManna et al., 1992). Brain glucose uptake and lactate contents increased during hypoxia, indicating increased anaerobic glycolysis (Harik et al., 1995).

Collectively, these adaptations contribute to the neuroprotective capacity of hypoxia conditioning against brain diseases (Stetler et al., 2014). However, direct evidence of hypoxia adaptations in the aging brain is scarce. Table 1 summarizes the few studies directly comparing hypoxia's effects on brain structure and activity in young *vs.* older mice and humans.

In a mouse model of OSA, Rubin et al. (2020) observed higher numbers of GABAergic neurons in the medial prefrontal cortex and hippocampus of older male but not female mice after severe intermittent hypoxia (90 s 5 % O_2 and 90 s 21 % O_2, 8 h/day for 35 days). Fewer parvalbumin-labeled and more somatostatin-labeled GABAergic neurons were noted in the young but not older males modeling OSA. In females, GABAergic neuronal subgroup ratios changed differently depending on age and brain region, but did not change in the overall brain after severe intermittent hypoxia.

Puthon et al. (2017) reported reduced oxygenation of prefrontal cortex in older (65 ± 3 years old) *vs.* younger adults (25 ± 2 years) during incremental cycling tests while the subjects breathed 21 % or 12 % O_2, although the age difference narrowed at 12 % F_IO_2. Conversely, Liu et al. (2020) reported dampened responses to intermittent hypoxia in elderly (age: 71 ± 2 years) *vs.* young adults (24 ± 3 years old); thus, the decreases in arterial and cerebral O_2 saturation and the increases in middle cerebral arterial flow velocity, heart rate and cerebral vascular conductance during hypoxia (F_IO_2 =10 ± 0.2 %) were attenuated in the elderly *vs.* young subjects. The authors suggested that hypoxemia may

have developed more slowly in the older individuals due to their reduced metabolic demand. Concordant with the results of Puthon et al. (2017), cerebral tissue oxygenation was lower ($P < 0.05$) in older (68 ± 1 %) than in young subjects (74 ± 1 %), while pre-hypoxia SaO_2 values in the young and older subjects were comparable. These findings are also in line with an earlier report, in which a blunted cardiac response to hypoxia contrasted with increased ventilation in older people (Richalet and Lhuissier, 2015). The authors of that report concluded that the tolerance to high altitude - and therefore hypoxia – is not impaired in healthy, active older people.

Serebrovskaya et al. (2000) studied the impact of hypoxia on brain dopamine metabolism in older (age: 61 ± 1.4 years) *vs*. younger (23 ± 2 years) men following 3 days at 2200 m. Blood dopamine and DOPA concentrations were higher in the older men at sea level, while at 2200 m, DOPA fell by 22 % in the older men, but increased fourfold in the younger men. Although the hypoxic ventilatory sensitivity was attenuated in the older *vs*. younger men at sea level, sensitivity increased similarly in both groups at the higher altitude. These findings suggest altered dopamine receptor sensitivity and/or reuptake during adaptation to high altitude in older people. It should be noted that blood concentrations might not parallel brain dopamine and DOPA contents. Indeed, dopaminergic cell markers in the substantia nigra decrease appreciably in the elderly (Bannon et al., 1992; Ma et al., 1999).

In summary, both age and hypoxia influence brain oxygenation and activity, and these effects may depend on the hypoxic dose, barometric pressure, and the subjects' physical fitness, exercise regimen and pre-existing conditions. Reduced responses to hypoxia at advanced age could arise from reduced metabolic demand or diminished adaptive capacity. It is possible that attenuated adaptation to hypoxia at advanced age may limit maladaptations produced by exaggerated molecular responses to hypoxia, but at the cost of decreased benefits. These possibilities, and a resultant altered vulnerability of the aging brain to hypoxia, warrant research effort to define pharmacological or behavioral strategies to optimize hypoxia's benefits while minimizing its detriments. Sex differences in brain adaptations to hypoxia in the elderly merit attention as well, especially because young men and women demonstrated fundamentally distinct physiological responses to hypoxia (Horiuchi et al., 2019).

4.2. Higher vulnerability to hypoxia in the aging brain?

Hypoxia exposures during mountain climbing (Fayed et al., 2006), air travel (Lim et al., 2012; McGuire et al., 2013, 2014, 2016) and diving (Connolly and Lee, 2015) have been associated with brain lesions and white matter abnormalities. Hypoxic conditions, potentially in combination with other factors such as temperature changes, can damage DNA (Møller et al., 2001) and cause AMS, high-altitude pulmonary and cerebral edema (Hackett and Roach, 2001) and other forms of brain damage (Wilson et al., 2009).

Severe hypoxia harms the brain by triggering neuroinflammation, oxidative stress, microglial activation and neurodegeneration. In mice, Sapin et al. (2015) reported increasing density and morphological alterations of microglia and increased inflammatory markers in the dorsal hippocampus after severe chronic, but not acute, intermittent normobaric hypoxia (60 s cycles alternating 5 and 21 % O_2, 8 h/day for 6 or 24 weeks). In a chronic, intermittent, normobaric hypoxia rat model of OSA (3 min 12 % O_2 and 3 min 21 % O_2, 8 h/day for 7 days), markers of oxidative stress and inflammation accumulated both systemically and in specific brain regions, including the substantia nigra, entorhinal cortex and hippocampus, considered to be primarily associated with early stages of age-related neurodegeneration (Snyder et al., 2017). Hypoxia-induced oxidative stress in rat brain is age-dependent, with newborns more vulnerable than adults (Koudelová and Mourek, 1992; Mourek et al., 2005; Schreiber and Trojan, 1993). Damage to biomolecules by ROS impairs cellular homeostasis and is both cause and consequence of organelle stress contributing to cellular injury. For instance, endoplasmic reticulum stress was implicated in brain damage following CIH in juvenile rats (Cai et al., 2014).

Neural growth factors also may influence the outcome of hypoxic insults. Xie et al. (2010) demonstrated that reduced contents of brain-derived neurotrophic factor (BDNF) contributed to CIH's impairment of long-term potentiation in a murine OSA model, while BDNF microinjection averted CIH-induced deficits. Serum BDNF concentrations correlated with cognitive function in healthy elderly (Gunstad et al., 2008). MicroRNAs (miRNAs) are another class of molecules dysregulated by CIH and associated with cognitive dysfunction. Gao et al. (2017) reported marked increases in miR-26b and decreases in miR-207 in hippocampus, in association with memory and learning deficits and activation of pro-apoptotic caspase-3 in rats subjected to alternating 5% and 21 % O_2, 30 cycles/h, 8/d for 1–4 weeks. Barhwal et al. (2020) recently reported demyelination of hippocampal neurons in 3-month--old rats exposed to 7620 m simulated altitude for 14 days. Longer hypoxia exposures, however, were associated with remyelination that depended on the activity of carbonic anhydrase.

Besides the age-related decreases in HIF signaling and differences in hypoxia's effects on brain function, other observations suggest an altered, sometimes attenuated or delayed, capacity to adapt to hypoxia in older humans (Kronenberg and Drage, 1973; Peterson et al., 1981; Serebrovskaya et al., 2000). Vestergaard et al. (2020) recently demonstrated impaired cerebral blood flow reactivity and reduced cerebral O_2 consumption in older *vs*. younger subjects while breathing 10 % O_2. The authors hypothesized (Vestergaard et al., 2020) that decreased resilience to hypoxia may be a core aspect of brain aging. Accordingly, hypoxia has also been suggested to be an important factor in the etiology of neurodegenerative diseases (Peers et al., 2009). Despite the reduced adaptive capacity of older adults, their tolerance of moderate hypoxia is usually maintained and the consequent adaptations might potentially be harnessed therapeutically (Serebrovskaya et al., 2008). Improving resilience to hypoxia may thus antagonize brain aging and neurodegenerative processes.

Table 2 summarizes evidence in rodents regarding the interaction of age and hypoxia on the risk of brain damage and potential reductions in brain adaptation to hypoxia. Jorba et al. (2017) investigated brain tissue stiffening, a hallmark of neurodegenerative diseases like Alzheimer's disease, using atomic force microscopy in a mouse model of OSA. They found no differences in cerebrocortical or hippocampal stiffness in 2- *vs*. 18 month-old mice, or with CIH modeling OSA. Biswal et al. (2016) compared the effects of sustained, severe hypobaric hypoxia (simulated altitude 7600 m) in 3- *vs*. 24-month old rats. One week of hypoxia provoked hippocampal accumulation of lipofuscin and the pro-aging protein S100A9, while tau, SNAP25, APOE and Sod2 contents fell. The hypoxia effects on these proteins resembled those of aging. S100A9 accumulation and SNAP25, Sod2, tau and APOE depletion in young hypoxia-challenged and aging rats were associated with impaired learning and spatial memory retrieval. Moreover, hippocampal neurons showed hypoxia- and aging-associated disruption of mitochondrial cristae. These alterations were aggravated by extending the hypoxia program to 2−3 weeks. These findings suggest CIH may accelerate brain aging (*cf*. Section 3).

Benderro and LaManna (Benderro and LaManna, 2011) reported delayed molecular adaptations to hypoxia in the brains of aged mice. Bickler et al. (2010) subjected organotypic hippocampal slices from 7 to 10 day old and 2-year-old rats to 1−10 min O_2-free pretreatment, and then 10 min O_2 -glucose deprivation (OGD) to model ischemia. Hypoxia-conditioning neuroprotection against OGD was lost, and hypoxia-adaptive gene expression fell sharply in slices from the older adult *vs*. neonatal rats. Bickler et al. proposed that altered intracellular Ca^{2+} homeostasis may inhibit hypoxia-activated signaling cascades evoking neuroprotective adaptations. However, it should be noted that the organotypic slice cultures from the two age groups were prepared differently. Moreover, the *in-vitro* approach may not fully recapitulate the complex processes producing systemic and cerebrovascular

adaptations to hypoxia.

Rapino et al. (2005) reported that severe intermittent hypoxia can induce cytoplasmic HIF-1α accumulation that is associated with more pronounced cell death in cerebral cortex of 24- *vs.* 3-month old rats. Gozal et al. (2003) also reported greater intermittent hypoxia-induced brain damage in older adult rats. Finally, Benzi et al. (1994a, 1994b) demonstrated both moderate and severe intermittent hypoxia inactivated synaptosomal Na^+, K^+ ATPase, high-affinity Ca^{2+} ATPase and Ca^{2+}, Mg^{2+} ATPase in both 3- and 24-month old rats.

In summary, age appears to be an important modulator of responses to hypoxia in rodents. As the feasibility of studying brain damage in combination with hypoxia is very limited in humans, only rodent studies were identified regarding the aging brain's adaptability to stress. The possibility that aged brain is more vulnerable to severe hypoxia should be considered with caution, since human data is lacking, *in vitro* models are beset by technical limitations, and the influence of the hypoxic dose is not yet well defined. Reports of the effects of on human brain summarized in the next subsection predominantly concern cognitive function.

4.3. Modulation of cognition by hypoxia in aging individuals

Although the detrimental effects of severe hypobaric hypoxia on cognitive function in adult humans are well documented (Asmaro et al., 2013; Bonnon et al., 1995; de Aquino Lemos et al., 2012; Griva et al., 2017; Nation et al., 2017), the underlying mechanisms and specific conditions in which hypoxia enhances cognition are not yet well defined. Case studies indicate that acute hypoxia exposure can evoke global amnesia in rare cases (Litch and Bishop, 2000). Subtler memory impairment at higher elevations may be ascribable to reduced deep sleep-dependent memory formation (Tesler et al., 2015). The development of cognitive symptoms and mood impairments in hypoxia, however, varies considerably among individuals. Adequate physical and mental preparation, in particular acclimatization, seem capable of mitigating cognitive impairment at high altitude (Harris et al., 2009; Karinen and Tuomisto, 2017; Merz et al., 2013).

The following epidemiological studies examined the relationships between human subjects' altitude of residence and their cognitive function. These reports should be interpreted cautiously due to the many confounders, including socio-economic status and access to healthcare, which may have contributed to the divergent outcomes. Hota et al. (2012) identified a form of mild cognitive impairment (MCI) in acclimatized lowlanders living at high altitude that could be distinguished from MCI presaging Alzheimer's disease. Also, in a study of Ecuadorans ascending to 4860 m, those already residing above 3000 m developed cognitive impairments more severe than did lowlanders ascending to the same altitude (Davis et al., 2015). Verbal and spatial working memory were impaired in young adult (20–24 years old) male and female residents of Lhasa, Tibet (3650 m) as compared to low altitude Andean high altitude *vs.* Andean low altitude residents and reported subtle impairments in speed, but not accuracy, of cognitive operations in the high altitude residents. This altitude effect was similar among different age groups. In contrast, Richardson et al. (2011) reported no adverse effects of chronic hypoxia in adolescents who resided from birth at 3700 m in Bolivia, and instead found evidence of successful neurophysiological adaptations. Thielke et al. (2015) demonstrated a negative correlation of Alzheimer's disease mortality with altitude of residence in California counties up to 1800 m mean elevation. Certain high altitude populations may have also special protection against dementia, for example a tribal population in the North Indian state Himachal Pradesh (Raina et al., 2016).

Apart from these observational reports, interventional research has advanced our mechanistic understanding of hypoxia's effects on brain pathologies. However, much of this knowledge was obtained in animal models, and its relevance to human brain is unclear. For example, in adult rats, acclimatization for 24 h at a simulated altitude of 4572 m, followed by 3 days exposure to an altitude equivalent to 7620 m, caused anxious behavior and memory deficits that were associated with dendrite deterioration, decreased BDNF content and reduced levels of markers for functional synapses (Kumari et al., 2020).

Hypoxia impacts the brain *in utero*. Prenatal hypoxia may adversely influence neuropathology and cognition in the APPSwe/PS1A246E mouse model of Alzheimer's disease (Zhang et al., 2013b). The potential relationship of prenatal hypoxia (Nalivaeva et al., 2018) and of intermittent hypoxia in human infants and children (Poets, 2020) with adverse neurological and cognitive outcomes were reviewed recently. Reduced O_2 concentration may, however, be highly beneficial to prevent neurological deficits in mitochondrial diseases, as shown in a mouse model of Leigh syndrome (Ferrari et al., 2017; Jain et al., 2019, 2016).

In OSA patients (Andrade et al., 2018; Daulatzai, 2012, 2013; Leng et al., 2017; Liguori et al., 2017), hypoxia-reoxygenation (Liu and Le, 2014) and associated oxidative stress have been implicated in cognitive deterioration and Alzheimer's disease pathogenesis. A longitudinal study demonstrating an association of OSA with MCI and dementia in older women linked apnea/hypopnea and hypoxemia, but not sleep duration or fragmentation, to the development of cognitive impairment (Yaffe et al., 2011). These findings corroborate the partial reversal by CPAP of cognitive dysfunction in OSA patients (Ferini-Strambi et al., 2003).

Experimental models of OSA replicate its cardinal feature, CIH (Navarrete-Opazo and Mitchell, 2014), which can cause cognitive dysfunction. Mechanistically, several molecular pathways have been found dysregulated in rodent CIH models with cognitive defects. In 4 week-old mice, 60 s cycles of 6–8 % and 19–21 % O_2, 8 h/day for 4 weeks produced spatial learning and memory impairments that were prevented by an Alzheimer's disease drug, the *N*-methyl-D-aspartate receptor antagonist memantine (Wang et al., 2015). In hippocampus, CIH elevated intracellular Ca^{2+} concentration, activated caspases, and inactivated Ras-extracellular-signal regulated kinase and CREB. Yagishita et al. (2017) used gene-ontology based microarray analyses to interrogate the impacts of CIH (2 min 5 % O_2 + 2 min 21 % O_2, 8 h/day for 5 or 28 days) *vs.* aging (10 week-old *vs.* 12 month-old mice) on kinase signaling cascades in the hippocampus. Hippocampi of both the young CIH-exposed and the older mice showed increased tau phosphorylation *via* the mammalian target of rapamycin-p70 S6 kinase signaling pathway, and depletion of postsynaptic proteins. Both aging and CIH-challenged younger mice displayed hyperactivity in the Y-maze test, a behavioral hallmark of genetically modified mice modeling Alzheimer's disease (Roberson et al., 2007).

Well calibrated, moderate IHC protocols, on the other hand, have been shown to improve numerous brain functions and offer potential treatment strategies for a number of neuropathologies, including Alzheimer's disease (Manukhina et al., 2010, 2016). Table 3 summarizes 5 recent studies evaluating the cognitive benefits of hypoxia conditioning in older adults. Schega et al. reported favorable effects of hypoxia conditioning combined with full body strength and endurance training on cognitive performance in sedentary (Schega et al., 2013) and physically active (Schega et al., 2016) older people. Bayer et al. (2017) identified increased exercise tolerance and cognitive benefits in geriatric patients when combining multimodal rehabilitation programs with IHHC. Serebrovska et al. (2019b) also demonstrated cognitive benefits of IHHC, and extended these findings by reporting several effects of IHHC on circulating biomarkers, *e.g.* amyloid β contents in platelets. Recently Wang et al. (2020a) reported that their IHC intervention improved cognitive functions in elderly, while reducing resting arterial pressures and increasing cerebral oxygenation.

Studies in rodents provide some insights on IHC's neuroprotective mechanisms. For example, hypoxia conditioning – at least during development – seems to enhance metabolic capacity after hypoxia-induced insults (Vannucci et al., 1998). Zhan et al. (2013) showed that hypoxia conditioning reduced activation of the MEK/ERK signaling pathway following ischemia in adult rat brain. The intensities of ROS,

NO and HIF signaling, and of inflammation, following hypoxic stimuli are among the most likely determinants of whether IHC augments or impairs cognition.

In summary, well calibrated hypoxia conditioning protocols (IHC, IHHC) show potential to ameliorate cognitive decline. Hypoxic conditioning can directly benefit the brain, *e.g.* by improving brain cell resilience, but also indirectly through a reduction of risk factors (for example cardiovascular deterioration) of Alzheimer's disease and other dementias. Combining intermittent hypoxia with other interventions, *e.g.* physical activity, to target those modifiable risk factors (Rabin et al., 2019), may be particularly effective. Given the promising outcomes of recent IHC studies on mild cognitive impairment, and considering the protective effects of IHC on the brain, such interventions may be valuable treatment strategies against age-related neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease. The next section discusses in detail the mechanistic links between these neurodegenerative diseases and adaptations to hypoxia.

5. Hypoxia, neuroprotection and neurodegeneration

Hypoxia conditioning offers a promising strategy to treat diseases of the central nervous system (Baillieul et al., 2017; Verges et al., 2015). IHC elicits neuroprotection against cerebral ischemia (Dirnagl et al., 2009); thus, IHC (8 % FIO_2, 4 h/day for 2 weeks) improved ischemic tolerance in a mouse stroke model (Stowe et al., 2011). While severe hypoxia induces anxiety-like behavior in rats (Kumari et al., 2020), moderate IHC may ameliorate psychological stress and depression (Navarrete-Opazo and Mitchell, 2014), in part by eliciting hippocampal neurogenesis (Zhu et al., 2010). Accordingly, there is mounting interest in IHC intervention for anxiety-related neuropathologies, *e.g.* post-traumatic stress disorder (Ding et al., 2019; Manukhina et al., 2018, 2020). Reports of enhanced cognition in hypoxia-conditioned older people (Bayer et al., 2017; Schega et al., 2013, 2016; Serebrovska et al., 2019b; Wang et al., 2020a) support the application of IHC to treat neurodegenerative diseases.

The loss of specific cell populations in the central nervous system characterizes neurodegenerative diseases. With the exception of some familial forms of neurodegeneration (*e.g.* Huntington`s disease, and 5–10 % of Alzheimer's and Parkinson's disease patients), age is the main risk factor for neurodegenerative diseases (Hou et al., 2019; Reeve et al., 2014). As humanity ages, the burden of these debilitating disorders continues to mount. Despite massive investments in drug development, no treatments have yet been found to modify the course of the most common neurodegenerative diseases, Alzheimer's disease and Parkinson's disease. While efficient palliative treatment possibilities for Parkinson's disease symptoms are available (Jankovic and Tan, 2020), they are largely lacking for Alzheimer's disease (Joe and Ringman, 2019; Long and Holtzman, 2019). Ongoing development of approaches to address the unmet need for disease course-altering treatments, however, sustains hope for better treatment options in the future (Ewen et al., 2021; Jankovic and Tan, 2020), and IHC is one such approach.

Training under hypoxia has already proven to be beneficial (and distinct from normoxic training) in terms of mood, fitness and metabolism in multiple sclerosis patients (Mähler et al., 2018). Hypoxia conditioning approaches yielded promising results in patients with MCI (Table 3) and may be beneficial in Huntington's disease (Burtscher et al., 2021). Here, we emphasize the potential of hypoxia conditioning to treat Alzheimer's disease, the most common form of dementia, and Parkinson's disease, the most common neurodegenerative motor disorder. Hypoxia and related molecular signaling pathways are intricately involved in the pathogeneses of both.

5.1. Shared mechanisms in hypoxia, aging and neurodegenerative diseases?

Neurodegeneration and aging are strongly linked to the mechanisms of cellular, brain and systemic responses to hypoxia. The major pathogenetic mechanisms of neurodegeneration, including neuroinflammation (Ransohoff, 2016), oxidative stress and mitochondrial dysfunction (Beal, 2005; Lin and Beal, 2006) have been implicated in "normal" aging, too. Indeed, inflammation ("inflammaging" paradigm of aging) (Franceschi et al., 2000, 2017), oxidative stress (free radical theory of aging) (Harman, 1956) and mitochondrial dysfunction (Alexeyev, 2009; Kauppila et al., 2017; Trifunovic and Larsson, 2008) all increase with aging and are ranked among aging's central promotors.

Hypoxia can either provoke or suppress oxidative stress, mitochondrial dysfunction (Hwang and Lee, 2011) and inflammation (Eltzschig and Carmeliet, 2011) and the HIF pathway is crucially involved, suggesting hypoxia conditioning could potentially modulate brain aging (Mallet et al., 2020). Because the cellular mechanisms of aging, neurodegeneration and hypoxia conditioning overlap, targeting oxidative stress, mitochondrial dysfunction and neuroinflammation by IHC could afford efficacious treatments for neurodegenerative diseases.

5.2. Nrf2 in neurodegenerative diseases

Activity of the Nrf2 system declines with age and in rodent models of Alzheimer's disease, Parkinson's disease and vascular dementia (Wang et al., 2020b; Yang and Zhang, 2020). Activation of Nrf2, both pharmacologically (El-Ghaiesh et al., 2020; Joseph et al., 2020; Lin et al., 2020; Sun et al., 2020) and by administering constituents of medicinal plants (Ahmad et al., 2020; Choi et al., 2018; Liu et al., 2019; Ruíz-Salinas et al., 2020) proved to be neuroprotective in rodent models of Alzheimer's and Parkinson's diseases. The neuroprotection conferred by Nrf2 stems from its primary function as coordinator of the endogenous antioxidant response (Brandes and Gray, 2020), and also may be mediated by Nrf2's favorable effects on protein homeostasis, as has been reported in primary rat neuronal models of Parkinson's disease associated toxicity (Skibinski et al., 2017). Other neuroprotective mechanisms of Nrf2 include the modulation of anti-inflammatory responses and of mitochondrial functions, as recently summarized by Brandes and Gray (Brandes and Gray, 2020). Although the therapeutic potential for Nrf2 modulation has been demonstrated in various animal models of neurodegenerative diseases (Brandes and Gray, 2020), the interplay of IHC/IHHC with Nrf2 in Alzheimer's or Parkinson's disease patients or in related animal models has not yet been investigated, but merits research effort.

5.3. HIF: mediator and suppressor of neurodegenerative diseases

Because HIF signaling is implicated in the pathogeneses of neurodegenerative diseases, pharmacological modulation of HIF has been proposed as a strategy to prevent or arrest neurodegeneration (Correia et al., 2013; Correia and Moreira, 2010). Indeed, stabilization of HIF-1α in *Caenorhabditis elegans* by ablation of the prolyl hydroxylase egl-9 or the VHL tumor suppressor ortholog vhl-1 reduced proteotoxicity from amyloid β (Alzheimer's disease) and polyQ (Huntington's disease) overexpression, and also extended lifespan (Mehta et al., 2009). Decreased HIF-1 activity is prominently implicated in Alzheimer`s disease, as reviewed by Ashok et al. (2017), and HIF-1α polymorphisms recently were linked to differential risk of developing Parkinson's disease (Qin et al., 2019). Accordingly, pharmacological modulation of HIF has shown promise in several Parkinson's disease models. Activation of glycolysis by terazosin in rats, mice and flies (Cai et al., 2019) or HIF-1 activation by agmatine in SH-SY5Y neuronal cells (Ferlazzo et al., 2019), lactoferrin in rats (Zakharova et al., 2018) and mice (Xu et al., 2019), deferoxamine in mice (Guo et al., 2016), and prolyl hydroxylase inhibitors in SH-SY5Y cells and mice (Li et al., 2018) have proven beneficial in models of Parkinson`s disease, underscoring the potential efficacy of hypoxia-based therapies.

5.4. Proteotoxicity and hypoxia

A common phenomenon among diverse neurodegenerative diseases is the occurrence of proteinaceous intra- or extracellular inclusions (Soto and Pritzkow, 2018). While α-synuclein enriched aggregates characterize synucleinopathies, including Parkinson's disease, multiple systems atrophy and dementia with Lewy bodies (Galvin et al., 2001), the proteins aggregating in Alzheimer's disease are amyloid β (Masters et al., 1985) and hyperphosphorylated tau (Grundke-Iqbal et al., 1986).

Yet other amyloidogenic proteins (*e.g.* TDP43, SOD1, huntingtin) form aggregates in other neurodegenerative diseases. It is increasingly clear that the different amyloids also are involved in pathologies of neurodegenerative diseases not originally associated with them, and cross-seeding effects of aggregations might play important roles in neuropathology (Lim, 2019). In addition to neurodegenerative diseases, the proteotoxicity of protein aggregates has been implicated in "normal" brain aging, too (Cohen and Dillin, 2008). Of particular interest in the present context is the role of hypoxia in promoting or opposing proteotoxicity. In the following subsections such interactions are discussed in the settings of Alzheimer's and Parkinson's diseases.

5.4.1. Proteinopathy and hypoxia in Alzheimer's disease

The most common form of dementia, Alzheimer's disease, is characterized by intracellular deposition of neurofibrillary tangles (Kidd, 1963) mainly composed of hyperphosphorylated tau protein (Grundke-Iqbal et al., 1986; Kidd, 1963; Grundke-Iqbal et al., 1986) and extracellular deposition of amyloid β containing plaques (Masters et al., 1985). The amyloid cascade hypothesis (Hardy and Higgins, 1992; Hardy, 2017) is the leading model of Alzheimer's disease pathogenesis. It posits that early amyloid β is the main driver of pathological processes leading to the development of other pathological hallmarks including neurofibrillary tangles, vascular damage and ultimately neuronal death and the attendant cognitive decline. We here focus on the role of hypoxia, especially in late-onset sporadic Alzheimer's disease. Recent reviews elaborate new developments in Alzheimer's disease related to protein pathology (van der Kant et al., 2020; Walsh and Selkoe, 2020; Wang et al., 2017), oxidative stress and glucose metabolism (Butterfield and Halliwell, 2019) and the emergent role of the non-neuronal cells in Alzheimer's disease etiopathogenesis (Arranz and De Strooper, 2019).

Observations of Alzheimer's disease-related pathology in OSA patients and rodent OSA models suggest an intriguing link between hypoxia and Alzheimer's disease proteopathy. However, although OSA is associated with elevated amyloid β concentrations in serum (Bu et al., 2015) and cerebrospinal fluid (Sharma et al., 2018), the association of amyloid β with OSA in animal models is equivocal. Ng and colleagues (Ng et al., 2010) reported hippocampal amyloid β accumulation in 2 month-old rats exposed to CIH (60 s 5 ± 0.5 % O_2 and 60 s 21 % O_2, 8 h/day for 3–7 days). CIH (10 min cycles between 5 % and 21 % O_2, 8 h/day for 4 weeks) increased cerebrocortical content of amyloid β-42, the more neurotoxic of the amyloid β isoforms (Fernandez et al., 2014), in 6-month-old mice of another transgenic strain modeling Alzheimer's disease (Shiota et al., 2013). In contrast, 10−11-month old transgenic APP/PS1 mice modeling Alzheimer's disease did not exhibit increased cerebrocortical amyloid β content or plaque loads after CIH (2 min 10 % O_2 and 2 min normoxia, 10 h/day for 4 weeks) (Macheda et al., 2019). Although manifold methodological differences preclude direct comparisons, these reports suggest that only in young healthy animals, chronic intermittent hypoxia modeling OSA elicits amyloid β accumulation. This early amyloid build-up may predispose to the eventual pathogenesis of Alzheimer's disease (Sharma et al., 2018). Mechanistically, hypoxia decreased content of the major amyloid β-degrading enzyme neprilysin in human neuroblastoma cells (Fisk et al., 2007), possibly by activating caspases 3, 8 and 9 to degrade the amyloid precursor peptide's intracellular domain fragment, an activator of neprilysin expression (Kerridge et al., 2015). In rats (Raz et al., 2019), and in wild-type (Yagishita et al., 2017) and Alzheimer's disease model mice (Gao et al., 2013), hypoxia elicited tau hyperphosphorylation, which is required for the formation of neurofibrillary tangles.

Further evidence of hypoxia's integral role in Alzheimer's disease pathology comes from studies showing the role of other Alzheimer's disease related proteins in adaptations to hypoxia. For example, the Alzheimer's disease-related presenilin2 isoform PS2V was shown to impair unfolded protein responses following hypoxia (Moussavi Nik et al., 2015) and the strongest genetic risk factor of late-onset Alzheimer's disease, apolipoprotein E4, is associated with heightened vulnerability to intermittent hypoxia modeling OSA (Kaushal et al., 2012).

Clinical evidence also substantiates potential associations of Alzheimer's disease and hypoxia. For example, tau concentrations in CSF and blood increased after cardiac arrest (Randall et al., 2013). In elderly hypertensive patients with acutely decreased blood pressure, the reduced brain O_2 availability correlated with elevated phosphorylated tau and memory decline (Glodzik et al., 2014). Hypoxia also elicits robust upregulation of amyloid precursor protein (Salminen et al., 2017) and amyloid β (Peers et al., 2009) *in vitro*, although this effect might be less pronounced *in-vivo* (Serrano-Pozo et al., 2017).

On the other hand, IHC protocols increased cognitive capacities of even healthy rodents (Navarrete-Opazo and Mitchell, 2014), improved cerebrovascular function in Alzheimer's disease (Manukhina et al., 2008), and limited microvascular rarefaction, another Alzheimer's disease hallmark (Goryacheva et al., 2011). IHC also reduced neurodegeneration in a rat model of Alzheimer's disease (Manukhina et al., 2010), in which a neurotoxic amyloid β fragment, amyloid β (25–35) was injected into the basal magnocellular nucleus after exposure to 4000 m simulated altitude, 4 h/day for 14 days. In this model, IHC afforded cerebrovascular benefits *via* NO-regulation, ultimately halting neurodegeneration and cognitive decline. These cerebrovascular benefits included VEGF-mediated angiogenesis which ameliorated microvascular rarefaction, increased eNOS activity, and augmented NO storage in *S*-nitrosothiols and dinitrosyl iron complexes (Manukhina et al., 2016). Recently, IHC (4 h/day of 5000 m simulated altitude for 15 consecutive days) was shown to attenuate cognitive deficits and anxiety in 9 month-old APP/PS1 mice while reducing amyloid β and pro-apoptotic protein contents in cerebral cortex and hippocampus and augmenting hippocampal neurogenesis and BDNF content (Meng et al., 2020).

Collectively, these studies exemplify the striking divergence of severe *vs*. moderate hypoxia in Alzheimer's disease pathology. While severe hypoxia may trigger or promote sporadic Alzheimer's disease pathogenesis and progression, the controlled IHC-induction of neuroprotective adaptations could potentially render the brain more resistant to Alzheimer's disease pathology.

5.4.2. Proteinopathy and hypoxia in Parkinson's disease

Although deficits in alveolar ventilation sufficient to produce hypoxemia have been implicated in Parkinson's disease pathogenesis (Pokusa et al., 2020; Vijayan et al., 2020), the mechanistic relationship between hypoxia and Parkinson's disease remains under-investigated. In particular, the relationship between hypoxia and the Parkinson's disease-related protein α-synuclein merits attention. The association of Parkinson's disease with several mutations and multiplications of the α-synuclein gene, *SNCA*, as reviewed by Lashuel et al. (2013), showed misfolded and aggregated α-synuclein to be pivotal to Parkinson's disease pathogenesis. The finding that aggregated α-synuclein is a major component of Lewy bodies and Lewy neurites, the proteopathic hallmarks of Parkinson's disease, confirmed α-synuclein aggregation as a central pathogenic event (Spillantini et al., 1997).

Circulating α-synuclein is elevated in OSA patients (Sun et al., 2019) and also initially during intermittent hypoxia in mouse brain (Yu et al., 2004). Repeated moderate hypoxic exposures, however, blunt the increase in cerebrocortical α-synuclein (Yu et al., 2004). Molecular modulation of the hypoxia response by targeting the δ-opioid receptor

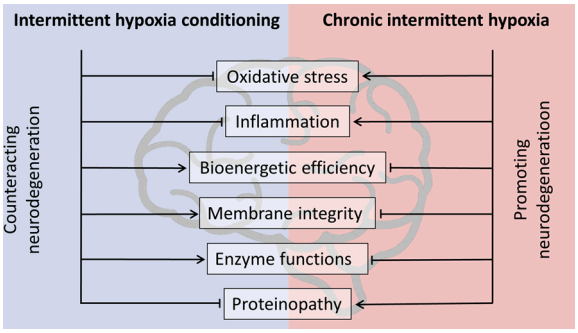

Fig. 2. *Beneficial vs. adverse effects of intermittent hypoxia.* Intermittent hypoxia conditioning (IHC) and chronic intermittent hypoxia (CIH) protocols can elicit opposite effects on cellular injury mechanisms. While the severe hypoxic episodes of CIH may promote neurodegenerative processes, well-calibrated IHC has the capacity to increase the resistance to hypoxic insults and is neuroprotective.

blunted α-synuclein upregulation induced by severe hypoxia or by the parkinsonism causing agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), in HEK293 T cells (Chen et al., 2014). Upregulation of α-synuclein phosphorylation at Serine 129, a marker of α-synuclein aggregation, was detected in experimental stroke models, and suppression of α-synuclein phosphorylation improved outcomes following ischemic stroke (Kim et al., 2016b). In cellular models of hypoxia, activation of δ-opioid receptors, which has been implicated in hypoxia-induced cytoprotection, mitigated α-synuclein accumulation and oligomerization (Chen et al., 2019). Hypoxia modulation of Parkinson's disease pathology provides the rationale for focused investigation of hypoxia conditioning as a treatment strategy for this devastating disease (Burtscher et al., 2021a).

6. Conclusions and outlook

Severe hypoxia harms the brain by compromising the brain parenchyma's O_2 supply essential for oxidative phosphorylation and other O_2-consuming molecular processes. Severe environmental hypoxia or pathological conditions such as OSA likely accelerate brain aging and neurodegeneration. On the other hand, the brain is an extraordinarily plastic organ in which hypoxic stress initiates hormetic adaptations involving numerous molecular mediators including HIFs and Nrf2, and myriad metabolic and enzymatic alterations, ultimately enhancing O_2 supply, bioenergetics and cellular survival to preserve tissue integrity (Fig. 2). Preclinical and clinical evidence clearly demonstrates that repeated moderate hypoxic bouts, *i.e.* IHC, can preserve or enhance brain functions. Mounting evidence shows that molecular adaptations to hypoxia, *e.g.* HIF pathway components, are neuroprotective and potential targets for pharmacological interventions. Moreover, a major advantage of hypoxia conditioning is that it can both interrupt pathological processes and also preserve metabolic activity and healthy cellular environments, and thereby impede age- or neurological disease-related brain maladaptations.

The intimate association of protein misfolding and unfolded protein responses with hypoxia conditioning mechanisms (Mao and Crowder, 2010) raises the possibility that amyloidogenic proteins central to neurodegeneration may be upregulated in response to severe or chronic hypoxic/ischemic insults. We speculate that the increase of amyloidogenic protein contents in the brain following hypoxia could stem from cellular defense mechanisms against hypoxic stress. The hypoxic insults may elicit the pathologic protein aggregation patterns that characterize neurodegenerative diseases. While protein aggregation pathologies are widely considered to be central drivers of neurodegenerative disease pathogeneses, convincing evidence in human patients that they are not mere epiphenomena of underlying causal neurodegenerative processes (*e.g.* hypoxia), or (failed) compensatory mechanisms to protect from insults including severe hypoxia, is still lacking (Espay et al., 2019). The capacity of hypoxia conditioning to increase the cellular resilience to hypoxic, ischemic and possibly proteotoxic stress, suggests that related approaches could conceivably be harnessed to prevent the development of hypoxic/ischemic insults and amyloid pathology. Hypoxia conditioning therefore is a promising potential treatment for neurological disorders, particularly neurodegenerative diseases.

Traditionally, "hypoxia" is an emotive term in the clinic, associated mainly with negative consequences of systemic hypoxemia and local tissue hypoxia. This review presented the mounting preclinical and clinical evidence that mild – intermittent – hypoxia (*i.e.,* IHC) potentially could be applied as a therapeutic modality for diseases related to brain aging, despite the acute vulnerability of the brain –particularly the aging brain – to severe hypoxia. Systematic investigations to elucidate detailed mechanistic adaptations, including IHC's impact on proteins related to neurological diseases, are essential to develop and implement IHC as an efficient, well-accepted treatment strategy for neurodegenerative diseases.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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