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Review Article

Hypoxia. Impact of Hypoxia on Various Organ Systems. The Role of Hypoxia in aging

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Abstract

The absolute dependence of the mammalian brain on oxygen for ATP production makes it highly vulnerable to hypoxia, whether at high altitude or in the clinical setting of anemia or pulmonary disease. Hypoxia is critical to the pathogenesis of numerous neurological disorders, including Alzheimer's, Parkinson's, and other age-related neurodegenerative diseases. Conversely, decreased oxygen in the environment, such as staying or living at high altitudes, may have favorable effects on aging and mortality. Moreover, controlled exposure to hypoxia may represent a treatment strategy for age-related neurological disorders. This review discusses the evidence for beneficial and deleterious effects of hypoxia on the aging brain and the molecular mechanisms that mediate these multidirectional effects.

Keywords: hypoxia; organ systems; aging

Introduction

The absolute dependence of the mammalian brain on oxygen for ATP production makes it highly vulnerable to hypoxia, whether at high altitude or in the clinical setting of anemia or pulmonary disease. Hypoxia is critical to the pathogenesis of numerous neurological disorders, including Alzheimer's, Parkinson's, and other age-related neurodegenerative diseases. Conversely, decreased oxygen in the environment, such as staying or living at high altitudes, may have favorable effects on aging and mortality. Moreover, controlled exposure to hypoxia may represent a treatment strategy for age-related neurological disorders. This review discusses the evidence for beneficial and deleterious effects of hypoxia on the aging brain and the molecular mechanisms that mediate these multidirectional effects. It draws on an extensive literature search on the effects of hypoxia/altitude on brain aging and a detailed analysis of all identified studies directly comparing brain responses to hypoxia in young and elderly humans or rodents. Special attention is given to the risks and benefits of hypoxia exposure in the elderly, as well as potential therapeutic applications of hypoxia in neurodegenerative diseases. The beneficial or detrimental effects of hypoxia on the brain are a matter of dose. The adverse neurological effects 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 an altitude of 8839 m in an open balloon, close to the altitude of Mount Everest (Glaisher, 1862). Barely surviving, the balloonists described severe neurological symptoms, including appendicular and later trunk paralysis, blindness, initially preserved cognition, and subsequent loss of consciousness (Glaisher, 1862). However, a few weeks of acclimatization (West, 1988) can allow people to climb Everest without supplemental oxygen (O2), as demonstrated by Reinhold Messner and Peter Habeler in 1978. Without acclimatization, staying at much lower altitudes can cause life-threatening conditions due to brain and/or pulmonary edema (Hackett and Roach, 2001), mood disorders (Nelson, 1982), mild cognitive impairments affecting e.g. learning (Pagani et al., 1998) or verbal memory (Pelamatti et al., 2003; Nelson, 1982; Wilson et al., 2009). Even neurological symptoms resembling neurodegenerative diseases associated with aging, such as parkinsonism (Hur, 2015; Park and Yang, 2013; Swaminath et al., 2006), have been observed after climbing to high altitudes. At high altitudes, the reduced partial pressure of O2 attenuates O2 supply to the brain. The resulting hypoxia is a major determinant of the effects of high altitude on the brain. Although low-pressure environments alone may modulate these symptoms slightly (Millet and Debevec, 2020), hypoxia associated with rapid altitude gain is the primary cause (West and Richalet, 2013). Molecular O2 is essential for oxidative metabolism and is therefore vital for aerobic organisms. However, O2 dependence for aerobic metabolism is also associated with the production of potentially harmful reactive O2 molecules from which organisms must protect themselves (Bunn and Poyton, 1996). The balancing act of avoiding both O2 deficiency and O2 toxicity has been compared to Ulysses' perilous voyage between Scylla

and Charybdis (Bunn and Poyton, 1996). As the most O2-dependent organ (Kann and Kovács, 2007), the brain consumes 20% of resting O2 consumption in humans (Silver and Erecińska, 1998), making it extremely vulnerable to hypoxia. Systemic hypoxia occurs in numerous pathologic conditions, including infections, inflammation, lung disease, cancer, stroke, and ischemic heart disease. Severe, episodic, or persistent hypoxia is also caused by decreased O2 consumption, 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 with O2 replacement strategies, such as continuous positive airway pressure (CPAP), emphasizes the key role of hypoxia in the pathogenesis of these disorders. On the contrary, brief and repeated exposure to mild to moderate hypoxia triggers cellular and physiological adaptation, the phenomenon of intermittent hypoxic conditioning (IHC), making organisms more resistant to subsequent hypoxic or ischemic strokes (Mayfield et al., 1994). The cardio- and neuroprotective effects of IHC (immunohistochemistry) (Manukhina et al., 2016) were first demonstrated on rat brain by Dahl and Balfour (1964). IHC is potentially useful in many pathological conditions (Aleshin et al., 1997; Burtscher et al., 1999; Tkatchouk et al., 1994; Zhuang and Zhou, 1999) and has been shown to be effective in 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 from many neuropathologic conditions. Several factors determine the ultimate risks and benefits of hypoxic conditioning. These factors include the parameters of the hypoxia regimen: the use of normobaric (i.e., reduced fraction of inhaled O2 (FIO2) at near sea level barometric pressure) versus hypobaric (FIO2 = 20.93% at reduced O2 partial pressure 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 the "dose" of hypoxia). A subject's hypoxia tolerance, physiological capacity, physical fitness, genetic makeup, and nutritional status (Richalet and Lhuissier, 2015), as well as meteorological variables at high altitude such as wind and temperature (Burtscher et al., 2018), also influence hypoxia conditioning outcomes. Intermittent hypoxia is typically applied in hypoxia-normoxia (Neubauer, 2001) or hypoxia-hyperoxia alternation cycles (Bayer et al., 2017). Depending on the dose of hypoxia, intermittent hypoxia either induces beneficial adaptations (i.e., IHC) or simulates lung disease (e.g., chronic intermittent hypoxia (CIH) modeling. Anoxia, a lack of oxygen, or hypoxia, a state of low oxygen concentration can interrupt developmental sequences and cause a range of molecular, cellular, and neural changes and injury. Hypoxia plays normal physiological roles during vertebrate embryo development, including promoting the utilization of anaerobic metabolism, controlling vascular network formation, supporting heart and bone development, and stimulating neural crest cell migration (Dunwoodie, 2009). However, non-physiologic hypoxia disrupts embryonic development and can lead to death.

Adaptations to hypoxia

Hypoxia poses serious challenges to the human body, depending on the dose applied, and can trigger the onset and/or contribute to the progression of neurological diseases. The potentially increased vulnerability to hypoxia during aging is of particular relevance to age-related neurodegenerative diseases. The body addresses hypoxia through various adaptations relevant to aging and neurodegenerative diseases. Several detailed 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). Adaptations to hypoxia are largely mediated by reactive oxygen species (ROS), leading to improved oxygen supply and bioenergetics by regulating hypoxia-responsive elements [1]. Hypoxia conditioning can have beneficial effects on inflammation, oxidative stress, mitochondrial function and cell survival [2]. Inflammation [3], oxidative stress [4] and mitochondrial dysfunction [5] increase with age and are considered as major contributors to aging.

Although HIFs (hypoxia-inducible factors) are important regulators of beneficial adaptation to hypoxia, they may also contribute to maladaptation, aging, and the pathogenesis of numerous cardiovascular and cardiorespiratory diseases [6]. Recently, the involvement of HIF signaling in hypertension, atherosclerosis, aortic aneurysm, pulmonary arterial hypertension and heart failure has been reviewed [7]. Accordingly, modulators of HIF signaling have potential for pharmacological intervention strategies in cardiovascular diseases [7,8].

Molecular responses to hypoxia and hypoxic conditioning

For the purposes of this review, it is important to distinguish hypoxic conditioning from the related phenomena of hypoxic pre- and postconditioning. All three interventions use moderate, non-damaging 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 delivered by separate sessions of continuous or intermittent hypoxia administered before (preconditioning) or shortly after (postconditioning) an acute ischemic-hypoxic stroke, such as ischemic stroke or myocardial infarction. The more commonly used term "hypoxic conditioning" includes hypoxic pre- and post-conditioning and describes hypoxia exposure programs that are typically administered repeatedly and intermittently, but, unlike pre- and post-conditioning, also often over days or weeks. Hypoxia conditioning does not necessarily refer to a specific ischemichypoxic stroke and can be performed, for example, during prodromal phases of chronic neurological conditions such as late neurodegenerative diseases, which usually do not have such identifiable, targeted and acute strokes. As indicated above, the quality and dose of the hypoxic stimulus, as well as environment, species, age, health status, autonomic activity, and other factors combine to determine the efficacy of molecular adaptations. Hypoxia conditioning modulates gene and protein expression in the brain in 2 distinct phases (Rybnikova and Samoilov, 2015). First, tolerance induction, in which immediate early genes and molecular mechanisms for protein synthesis and posttranslational regulation are mobilized, develops within minutes to hours after hypoxia. Later expression of tolerance, involving additional gene expression and protein synthesis, confers long-term neuronal resistance to subsequent insults.Hypoxic conditioning, especially IHC, has a number of beneficial effects on the brain and has been shown to be effective in numerous experimental brain pathologies (Manukhina et al., 2016), but aging modulates these benefits. Decreased HIF signaling may be central to age-related neurodegenerative disorders (Correia et al., 2013; Correia and Moreira, 2010). The lack of systematic studies on the reciprocal interaction of hypoxia and aging on the brain prompted a literature search to identify reports that shed light on the potential risks and benefits of hypoxic preconditioning in agerelated neurological diseases. Hypoxia-induced hypoxemia, sympathetic vasoconstrictor activation, pulmonary hypertension, and arrhythmias are potential health risks, especially for vulnerable populations and the elderly [61]. In addition, hypoxia-induced oxidative and DNA damage [62] and altitude sickness are hazards of altitude/hypoxia exposure. Severe cellular hypoxia can also lead to cellular dysfunction and cell death, mechanisms central to the pathogenesis of cardiovascular diseases such as atherosclerosis, pulmonary arterial hypertension or heart failure [63].

On the other hand, especially the cardioprotective effects of intermittent hypoxic conditioning [64, 65] may contribute to its potential to improve aerobic capacity and exercise tolerance and to ameliorate a number of pathologies [66-72].

Different aspects of the effects of hypoxia

Systemic hypoxia occurs due to low partial pressure of oxygen (PO2) in ambient air and hence inhaled oxygen (PiO2). Mammalian organisms can adapt to hypoxic exposure with widely varying tolerance, even among humans [10]. Depending on the dose of hypoxia [41, 42, 44], hypoxia can have deleterious or beneficial effects.

In humans, systemic effects of hypoxia usually occur during stays at high altitude. Conditions of hypobaric hypoxia at high altitudes can lead to various forms of mountain sickness [4, 45-47].

On the other hand, living or training at high altitude or artificial hypoxia is commonly used to improve the performance of athletes [48,49]. Intermittent exposure to hypoxia is also used to increase human tolerance to high altitude

[50,49,51-54] and may even have therapeutic value for numerous diseases [55,52,56]. The answer to the question of how hypoxia can induce these extremely divergent effects is simple and complex at the same time; it is a matter of dose [41, 42, 44]. The dose of hypoxia exposure consists of several factors, including the severity of hypoxia, the duration and the number or frequency of exposures. In addition, the resulting cumulative duration of hypoxia and additional parameters such as arterial carbon dioxide levels have a crucial influence on the dose [42]. In addition, the mode of hypoxia administration (e.g., normobaric or hypobaric [57]), individual adaptability [58], the level of physical activity performed and diet [59], and cross-effects with other environmental factors such as temperature [60] influence the outcome of hypoxia exposure. This is particularly relevant when adaptation to hypoxia is studied at high altitude.

Acute hypoxia versus prolonged and chronic hypoxia

Acute exposure to hypoxia causes chemoreceptor-mediated activation of the sympathetic nervous system resulting in increased heart rate (HR), cardiac output, peripheral resistance, and systemic blood pressure. In addition, it induces changes in the pulmonary system with increased ventilation when blood oxygen levels fall, as determined by the carotid body, and pulmonary vasoconstriction, which initially serves to optimize the matching of ventilation and perfusion during focal hypoxia to facilitate gas exchange in the lungs. Responses to hypoxia ideally result in a reduction in oxygen-dependent processes, improved oxygen supply, and protection against hypoxia-related cellular and tissue damage. Currently, there is no consensus on when the acute phase of hypoxia responses ends because the time frame of respiratory, cardiovascular, and hematologic responses differs. Here we categorize exposure to hypoxia for less than 24 hours as “acute” and exposure that lasts longer (several days or weeks) as “prolonged”. Prolonged exposure over several days or weeks will result in sustained hematological and vascular adaptations including increased red blood cell and hemoglobin counts, as well as increased vascularization and increased tolerance to mountain sickness. However, it also results in decreased stroke volume as well as increased heart rate, pulmonary artery pressure, and systemic arterial pressure. “Chronic” hypoxia usually refers to prolonged exposure, such as that which occurs in populations living at high altitudes.

Regulation of gene expression in response to hypoxia

Adaptive responses to hypoxia at the cellular level are initiated by signaling molecules, primarily reactive O2 species, i.e. ROS (reactive oxygen species) (Sies and Jones, 2020) and transcription factors such as hypoxia-inducible factors (HIFs), central regulators of O2 homeostasis (Semenza, 1999), and nuclear erythroid 2-related factor 2 (Nrf2) (Leonard et al., 2006).

Hypoxia-inducible factor (HIF)

At normoxic O2 concentrations and in the presence of α-ketoglutarate and divalent iron, HIF α-subunits are hydroxylated by prolyl hydroxylases (members of the αketoglutarate dioxygenase superfamily) on prolyl residues in the O2-dependent degradation domain of the α-subunit. Van Hippel-Lindau (VHL) proteins interact with hydroxylated α-subunits to promote their polyubiquitination, which directs their degradation by 26 s proteasomes (Kaelin and Ratcliffe, 2008; Lee et al., 2020; Lendahl et al., 2009). Also, under normoxic conditions, a factor that inhibits HIF-1 suppresses HIF transactivation by hydroxylation of an asparagyl residue in the transactivation domain of the α-subunit.

Low O2 conditions stabilize HIF α-subunits, which dimerize with their β-subunit counterparts, after which HIF heterodimers bind hypoxia-responsive elements (HREs) in the promoters of HIF-regulated genes. This HIF-regulated gene expression initiates molecular remodeling to reduce cellular O2 demand by increasing glycolytic capacity and attenuating hypoxia-induced cell death

(Almohanna and Wray, 2018). Erythropoiesis, angiogenesis, and changes related to energy metabolism are among the most studied HRE-mediated adaptations (see what it is) Hypoxemia-induced erythropoiesis, well studied in rodents (MooreGillon and Cameron, 1985) and humans (Knaupp et al., 1992), is mainly regulated by activation of HIF-1 erythropoietin gene expression in kidney and liver (Haase, 2013). In the brain parenchyma, erythropoietin has a neuroprotective function as an anti-inflammatory factor and activator of the transcription factor Nrf2 and its antioxidant and anti-inflammatory gene program.As discussed earlier, under hypoxia conditions, HIF1α is a master regulator of the response to oxygen levels through control of gene expression. Gene expression profile studies in in vivo and in vitro models have shown that the activated HIF1α pathway stimulates the expression of a number of genes that contribute to angiogenesis, energy metabolism and cell survival (Kenneth and Rocha, 2008; Shukla et al., 2018). Transcriptional targets of HIF1α, including erythropoietin, glucose transporters, glycolytic enzymes and vascular endothelial growth factor, either enhance oxygen delivery to tissues or facilitate metabolic adaptation to hypoxia (Semenza, 1999;

Majmundar et al., 2010).

Recently, the in vivo effects of hypoxia on RNA expression changes were analyzed in relation to the development of connectivity in the CNS. Comparing normoxia with hypoxia, Milash et al. (2016) reported that hypoxia caused transcriptional desynchronization, both in terms of timing and expression levels, of genes required for connectivity development. These genes (1270 in total) were identified based on their inclusion in Gene Ontology (GO) terms “axon guidance” or “synapse”, and their functions ranged from transcription factors to cell surface receptors. Interestingly, hypoxia had the most profound effect on the expression of a subset of genes, suggesting that targeting only these subsets may be a therapeutic pathway. However, the authors did not determine why only a subset of CNS connectivity genes were most affected and what the unifying features of these genes were.The HIF system activates adaptive responses that resist aging, but HIF itself can be suppressed with age (Katschinski, 2006). HIF-1 has been identified as a potent. a modulator of senescence in C. elegans (Leiser and Kaeberlein, 2010), the effect is mediated by acyl-coenzyme A binding proteins (Shamalnasab et al., 2017) and is temperature (Leiser et al., 2011) and oxidative stress (Hwang and Lee, 2011) dependent. Moreover, Kim et al. (Kim et al., 2003) demonstrated impaired binding of HIF-1 to HREs in aged diploid human fibroblasts. Decreased HIF-1 function has also been demonstrated in aging mice (Frenkel-Denkberg et al., 1999). Consistent with these results, the cardioprotective effects of hypoxic conditioning were less pronounced in old rats compared to young rats (Honma et al., 2002).

Taken together, these results demonstrate an inverse relationship between HIF activity and age, which portends a decline in the capacity of the HIF system in the elderly. Disruption of the molecular mechanism of adaptation to hypoxia may increase the vulnerability of the elderly to severe hypoxia and/or ischemia.

Protein aggregation in hypoxia

Amyloidosis is a hallmark of neurodegenerative diseases in which different amyloidogenic species cause various neuropathic diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), prion diseases including Creutzfeldt-Jakob disease, Levy's corpuscle disease, amyotrophic lateral sclerosis (ALS), etc. Protein aggregates often correlate with diseases, e.g., AD is characterized by tau protein and β-amyloid aggregates, PD by alpha-synuclein, and BC by hantingtin (Htt) protein aggregates. In contrast, protein aggregates are not

only pathogenic but also exert a protective effect on stressed striatal neurons. According to Leitman et al, the process of aggregate formation is protective, isolating and segregating problematic proteins. Arrasate et al found that inclusion formation (IB) reduced intracellular levels of diffuse hantingtin protein (Htt) and prolonged survival, suggesting that IB formation protects neurons by reducing levels of toxic diffuse forms of Htt. Similar findings on the neuroprotective role of aggregated protein were observed in a mouse model of spinocerebellar ataxia in which polyglutamine forms of ataxin-1 protein are expressed. Proteins must be folded into their stable three-dimensional structure to be functional. However, due to folding errors, mutations, DPM, proteostasis network failure, pathological conditions and unfavorable conditions such as elevated temperature, extreme pH, high pressure and agitation, proteins unfold/incorrectly fold and aggregate. Aberrant protein aggregation remains a common feature of neurodegenerative diseases, where improper assembly of Aβ1-42 has been linked to Alzheimer's disease. A relative increase in Aβ1-42 levels promotes Aβ aggregation into toxic species. However, aggregation-mediated Aβ1-42 toxicity was reduced in Caenorhabiditis elegans when senescence was delayed by a reduction in the insulin/insulin-like insulin growth factor 1 (IIS) signaling pathway. Thus, modulation of the IIS pathway may be a promising approach for developing therapies for Alzheimer's disease. Importantly, in C. elegans nematodes, flies, mice, and humans, the IIS pathway regulates stress tolerance, aging, and determines lifespan.

Using the C. elegans model of aging, Kaufman et al. found mitochondrial protein aggregation and impaired mitochondrial protein homeostasis as a hallmark of hypoxia, while mitochondrial dysfunction and reduced protein turnover are associated with aging. Recently, Adav et al. assessed the quantitative profile of brain mitochondrial proteins in Alzheimer's disease (AD) using both isobaric tags for relative and absolute quantification (iTRAQ) and a tagless quantitative method and found altered mitochondrial proteins. These authors found destabilization of the junction between the membrane and matrix arm of mitochondria in AD. Kaufman and Crowder estimated that the increase in detergent-soluble proteins, which are thought to be improperly coiled and aggregated, was a consequence of hypoxic conditions. Thus, protein aggregation is a common feature of aging, hypoxia and neurodegenerative diseases. During hypoxia and aging, the proteostasis pathway is impaired due to protein aggregation. The proteins of these aggregates have been found to be associated with neurodegenerative diseases, indicating that protein aggregation is an integral part of aging and neurodegenerative diseases and the effects of hypoxia. Not only protein

aggregation but also protein or peptide preparations (i.e., small peptides with 7, 6, 5, and 4 residues) are of major concern. Protein preparations use domain swapping to avoid aggregation, but replacing the aggregation prone segment from an amyloidogenic protein with a non-amyloidogenic homolog triggers amyloid formation. Thus, a short aggregation-prone region of the protein/peptide sequence and structural specificity can cause protein aggregation. However, the exact cause of protein aggregation and the mechanistic link between protein and tissue degeneration are not yet fully understood.

Abnormal protein folding and aggregation can cause cellular dysfunction, cell death and organelle failure, which are the major pathologic findings in the postischemic brain, where impaired autophagy was thought to be the main cause of abnormal proteostasis and protein aggregation. The most prominent structural motif of a functional protein in its native conformation is the alpha helix. The betalayer conformation also exists in many functional native proteins, but the transition from the alpha-helix to the beta-layer is a major feature of amyloid and protein aggregation. Under physiologic flow conditions, shear flow causes protein aggregation and amyloid formation. Loosely packed proteins in the unfolded state expose their hydrophobic core, which can interact with the cellular environment and undergo self-aggregation, while partially folded proteins act as precursors in the protein aggregation process. In investigating the underlying cause of protein aggregation, physicochemical analysis revealed that these aggregates vary in size, their proteomic composition and cellular location. Age- and oxidative stressinduced protein aggregates had a compact conformation, and protein carbonylation was the cause of compact aggregation. Based on solubility, the aggregates were classified into soluble and insoluble, where the soluble form can be more easily unfolded, while insoluble aggregates accumulate and impair cellular function. Profiling the proteomic composition of soluble and insoluble human brain tissue aggregates revealed proteins such as S100A9, ferritin, hemoglobin subunits, S100-A8, S100-B, collagens, mitochondrial creatine kinase (U-type), β-tubulin, and laminin exclusively in compact aggregates, and most importantly, they were deamidated. Site-specific deamidation revealed the deamidation of more than one residue of S100A9, which may introduce a negative charge that alters Ca++ binding capacity and enhances the ability of the protein to form pathological aggregates in the brain. Using a variety of aging models including C. elegans, mouse bone marrow and spleen cells, DPM has been found to be a cause of protein aggregation. In conclusion, recent literature suggests that ROS produced during hypoxia and aging increase non-enzymatic DPM such as carbonylation, oxidation, glycation, deamidation, citrullination, and lipoxidation. These protein modifications alter protein charge and hydrophobicity, cause protein misfolding and aggregation, and their deposition in brain tissue may be a key sign of degenerative diseases and aging. Despite abundant evidence for aggregate formation and their effects, the exact mechanism(s) of protein aggregation and/or nuclear triggering remains unclear.

Contribution of hypoxic injury to human neurodevelopmental disorders and abnormal development of the central nervous system

Hypoxic injury is a clinical mechanism that is distinct from anoxia or hypoxiaischemia, although there is a continuum of effects and pathophysiology. Preterm infants are the population at greatest risk for chronic hypoxic injury and subsequent adverse neurocognitive and neuropsychiatric outcomes (Horwood et al., 1998; Johnson and Marlow, 2011). Preterm infants can experience up to 600 hypoxic episodes per week, each lasting at least 10 seconds or longer (Martin et al., 2011a). The cause(s) of this chronic hypoxia are not well understood. Abnormal autonomic regulation, especially of the cardiopulmonary system, may be the likely primary cause, but etiologies may also include placental insufficiency, lung disease, pulmonary hypertension, or congenital heart disease. The opposite condition, hyperoxia, in which oxygen concentrations are increased by medical interventions, such as those often administered to premature infants, also disrupts normal brain development (Deuber and Terhaar, 2011; Reich et al., 2016). Hypoxic exposure in preterm infants occurs from approximately 12 weeks post conception (PCA) to term delivery (40 weeks PCA) (Martin et al., 2011a, 2012). This developmental window coincides with the time of preterm birth from 24 to 36 weeks PCA and includes the time when axons and synaptic connections are formed in the human CNS (ten Donkelaar et al., 2004; Ren et al., 2006; Kostović and Jovanov-Milosević, 2006; Molyneaux et al., 2007; Stiles and Jernigan, 2010; Vasung et al., 2010; Semple et al., 2013). Alterations in synapse development and function have been recognized as an important component of NDDs caused by prematurity and hypoxia (Gilman et al., 2011). Exposure to hypoxia is associated with worse outcomes in preterm infants. In the long term, up to 35% of preterm infants will develop an NDD such as attention deficit disorder, autism, cerebral palsy, motor impairment, depression, epilepsy, or mental retardation (Bass et al., 2004; Barrett et al., 2007; Laursen et al., 2007; Saigal and Doyle, 2008; Williams et al., 2010; Salmaso et al., 2014). Ironically, although survival rates for preterm infants have improved significantly and the total number of former preterm infants (an infant or child born preterm but now older) has increased over the past decade (Mathews et al., 2011), neurodevelopmental outcomes have not improved and therapeutic strategies are lacking (Fanaroff et al., 2007; Hintz et al., 2011). This has led to an increase in the number of children with NDD.

Modulation of cognitive function by hypoxia in aging humans

Although the deleterious effects of severe hypobaric hypoxia on cognitive function in older adults 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 under which hypoxia enhances cognitive function are not yet fully defined. Case studies suggest that acute exposure to hypoxia can cause global amnesia in rare cases (Litch and Bishop, 2000). More subtle memory impairments at high altitudes may be associated with reduced formation of deep sleep-dependent memory (Tesler et al., 2015). However, the development of cognitive symptoms and mood disorders in hypoxia varies considerably between individuals. Hota et al (2012) identified a form of mild cognitive impairment (MCI) in acclimatized lowlanders living at high altitude that can be distinguished from MCI that portends Alzheimer's disease. Furthermore, in a study of Ecuadorians who climbed to an altitude of 4860 m, those who already lived above 3000 m developed more severe cognitive impairment than lowlanders who climbed to the same altitude (Davis et al., 2015). Verbal and spatial working memory were impaired in young adult (20-24 years old) men and women living in Lhasa, Tibet (3650 m) compared to Andean residents (see in which. Countries these cities are located and correct for country) living at low altitude, and minor impairments in speed but not accuracy of cognitive operations were reported in high altitude residents. This effect of altitude was similar among different age groups. In contrast, Richardson et al. (2011) reported no adverse effects of chronic hypoxia in adolescents living from birth at 3700 m in Bolivia and instead found evidence of successful neurophysiological adaptation. Tilke et al. (2015) demonstrated a negative correlation of Alzheimer's disease mortality with altitude of residence in California counties up to an average elevation of 1800 m. Some high-altitude populations may also have particular protection against dementia, such as a tribal population in the North Indian state of Himachal Pradesh (Raina et al., 2016).

In addition to these observational reports, intervention studies have advanced our mechanistic understanding of the effects of hypoxia on brain pathologies. However, much of this knowledge has been gained in animal models, and its relevance to the human brain is unclear. For example, in adult rats, acclimatization for 24 h at a simulated altitude of 4572 m followed by a 3-day exposure to an altitude equivalent to 7620 m induced anxious behavior and memory deficits that were associated with dendritic deterioration, decreased BDNF content, and reduced levels of markers of functional synapses (Kumari et al., 2020).

The effect of hypoxia on the brain in the womb

Hypoxia affects the brain in the womb. Prenatal hypoxia can adversely affect neuropathology and cognitive function in the APPSwe/PS1A246E mouse model of Alzheimer's disease (Zhang et al., 2013b). The potential association of prenatal hypoxia (Nalivaeva et al., 2018) and intermittent hypoxia in infants and children (Poets, 2020) with adverse neurological and cognitive outcomes has recently been reviewed. However, reducing O2 concentrations may be highly beneficial in preventing neurological deficits in mitochondrial diseases, as shown in a mouse model of Ley syndrome (Ferrari et al., 2017; Jain et al., 2019, 2016). In patients with OAS (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 the association of OAS 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 results support the partial elimination of cognitive dysfunction with CPAP in patients with OSA (Ferini-Strambi et al., 2003). Experimental models of OSA reproduce its cardinal feature, CIH (Navarrete-Opazo and Mitchell, 2014), which can cause cognitive dysfunction. Mechanistically, several molecular pathways have been found to be dysregulated in rodent models of CIH with cognitive defects. In 4-week-old mice, 60-second cycles of 6-8% and 19-21% O2, 8 h/day for 4 weeks caused impairments in spatial learning and memory that were prevented by the Alzheimer's disease drug, the N-methyl-d-aspartate receptor antagonist memantine (Wang et al., 2015). In the hippocampus, CIH increased intracellular Ca2+ concentration, activated caspases, and inactivated Rasintracellular signal-regulated kinase and CREB. Yagishita et al. (2017) used gene ontology-based microarray analysis to examine the effects of CIH (2 min 5% O2 + 2 min 21% O2, 8 h/day for 5 or 28 days) versus aging (mice aged 10 weeks versus 12 months) on kinase signaling cascades in the hippocampus. Hippocampi of both young CIH-exposed and aged mice showed increased phosphorylation of tau through the target of the mammalian rapamycin-p70 S6 kinase kinase signaling pathway and depletion of postsynaptic proteins. Both aging and young mice exposed to CIH showed hyperactivity in the Y-maze test, a behavioral hallmark of genetically modified mice modeling Alzheimer's disease (Roberson et al., 2007). On the other hand, well-calibrated moderate IHC protocols have been shown to improve multiple brain functions and offer potential treatment strategies for a number of neuropathologies, including Alzheimer's disease (Manukhina et al., 2010, 2016). Shega et al. reported favorable effects of hypoxic conditioning combined with whole-body strength and endurance training on cognitive performance in sedentary (Shega et al., 2013) and physically active (Shega et al., 2016) older adults. Bayer et al. (2017) found increased exercise tolerance and cognitive benefits in geriatric patients when combining multimodal rehabilitation programs with IHHC. Serebrovskaya et al. (2019b) also demonstrated cognitive benefits of IHHC and extended these findings by reporting several effects of IHHC on circulating biomarkers, such as: Amyloid β content in platelets. Recently, Wang et al. (2020a) reported that their IHC intervention improved cognitive function in older adults while reducing resting blood pressure and increasing cerebral oxygenation.

Effects of intermittent hypoxia-normoxia or hypoxia-hyperoxia on the aging cardiovascular system

Protocols with a single session of intermittent hypoxia should be distinguished from the others. Responses may differ significantly after a single session of intermittent hypoxic exposure than after an entire protocol consisting of multiple sessions. Only two studies have examined the effect during and/or after a single intermittent hypoxia session in the elderly in relation to cardiovascular outcomes [20, 21]. Liu et al. (2020) reported that the cerebrovascular response to hypoxia decreased with age [20]. These results support previous findings showing decreased cerebrovascular reactivity to hypoxia in elderly compared to young adults during 5-min isocapnic hypoxic exposure [19]. Regarding blood pressure, no reduction was observed in elderly people with prehypertension after just one session of intermittent hypoxia [21]. However, in healthy elderly subjects, intermittent hypoxia reduced systolic blood pressure and diastolic blood pressure during the first and last attack (5 attacks in total) of the first session [20]. This suggests that during acute exposure (5 min), hypoxia-induced peripheral vasodilation [22] is more pronounced than sympathetic-mediated vasoconstriction induced by hypoxia [23]. Carbon dioxide appears to play a determinant role in acute blood pressure responses to hypoxia, as poikilocapnic hypoxia caused peripheral vasodilation and a decrease in blood pressure [20, 22], whereas hypercapnic hypoxia significantly increased blood pressure [24] and isocapnic hypoxia caused either an increase [24] or no change in blood pressure [19]. Hypercapnia increased blood pressure equally in young and elderly subjects, whereas hyperventilation-induced hypocapnia decreased blood pressure but to a lesser extent in elderly subjects [25]. Consequently, poikilocapnic hypoxia, rather than hypercapnic hypoxia, may be more appropriate for acute blood pressure reduction. This may affect the therapeutic efficacy of devices such as hypoxic tents or air recirculation systems. Overall, this emphasizes the importance of considering other stressors related to the modality of hypoxic exposure (e.g., chronic intermittent hypoxia in a patient with obstructive sleep apnea is associated with hypercapnia and acidosis, whereas intermittent hypoxic conditioning is associated with hypocapnia and alkalosis [26]). Intermittent hypoxic conditioning (i.e., 3 to 5 sessions per week),

including IHHC protocols, has recently been investigated as an innovative therapeutic strategy for several dysfunctions, especially of the vascular system. Thus, most studies using these interventions have focused on hematologic and/or blood pressure changes. Ten studies have examined blood pressure changes after intermittent hypoxic conditioning in older adults [34, 36, 39, 40, 130-133]. Six of them reported blood pressure reductions after intermittent interventions in elderly healthy subjects or patients with coronary heart disease, previous myocardial infarction, or metabolic syndrome [27, 31, 32]. Four other studies reported either a trend toward lower blood pressure in healthy subjects or patients or no change [29, 30]. Dudnik et al. (2018) reported a significant decrease in diastolic blood pressure but not systolic blood pressure ($p = 0.07$) in ambulatory patients with cardiac disease after 15 sessions of IHHC. After a prolonged period of intermittent hypoxia (24 weeks), Timon et al. (2022) simply observed a trend toward lower systolic blood pressure and diastolic blood pressure ($P = 0.068$ and $P = 0.057$, respectively) [28]. This discrepancy may be explained by the 45-min exposure to hypoxia ($FiO2 = 16\%$) for a continuous period rather than the recommended intermittent regimen. Another study using long periods of intermittent hypoxia (25 min) combined with exercise failed to improve blood pressure after 18 sessions [30]. Indeed, hypoxic cycles of 2 to 10 min duration have been previously proposed to reduce blood pressure for greater safety and efficacy in the elderly [9]. Moreover, a study investigating the effects of IHHC in very elderly participants (mean age 81 ± 8 years) reported improved exercise endurance in the absence of blood pressure changes [29]. This may be due to insufficient vascular reserve in very elderly individuals or patients (e.g., diabetic) to benefit from hypoxic stimuli. Indeed, an attenuation of the hyperemic vasodilatory response due to blunted NO signaling during hypoxia with aging has been reported [34]. The underlying mechanisms putatively regulating blood pressure are mainly related to NO availability due to increased endothelial NO synthase [137], erythrocyte NO synthase [30] and sympatholysis [138]. In addition, evidence of decreased arterial stiffness and reduced mild inflammation [28] after IHHC may contribute to improved vascular function and blood pressure. Hematologic and hemorheologic changes are also hypothesized to be associated with changes in blood pressure after and during exposure to hypoxia. Increased blood viscosity, which is highly dependent on hematocrit (Hct) and red blood cell (RBC) behavior [37], leads to increased wall shear stress, which increases NO [38]. Increases in erythrocyte count, Hct and hemoglobin (Hb) concentration were reported after only five days of intermittent hypoxia conditioning, while continuous exposure (same total hypoxic exposure time of 350-360 min) caused no change [39]. This is supported by other studies; for example, Burtscher et al. reported an increase in erythrocyte count and Hb without changes in Hct, and Glazachev et al. [39] demonstrated a higher relative reticulocyte count after IHHC compared to a control intervention, suggesting stimulated erythropoiesis. However, one study reported no change after 10 sessions of isocapnic intermittent hypoxia [27]. Further studies and comparable protocols, methods and controls will be crucial to fully characterize hematological and hemorheological changes after intermittent hypoxia.

Sympatholysis is another major mechanism potentially responsible for hypoxiainduced changes in blood pressure. This is supported by changes in heart rate variability. The mean-squared serial difference reflecting vagal outflow increased after 4 weeks of intermittent hypoxic training (+71.6 ± 52.5%), while changes 4 and 8 weeks after the intervention are less evident [31].

Despite conflicting results on efficacy, partly due to differences in study populations and protocol settings, well-calibrated interventions of intermittent hypoxic training are generally considered safe in older adults [39]. An effective strategy to lower blood pressure in the elderly (but not too old [29]) is the repeated application of short hypoxic cycles (2-10 min, $FiO2 \geq 10\%$) over several weeks.

Exposure to hypoxia may have beneficial effects on longevity and mortality from cardiovascular disease

Cellular and nematode lifespan can be extended under conditions of chronic hypoxia.

Interestingly, the HIF system appears to be reduced during aging in human fibroblasts [9] and in mice, suggesting a potential causal relationship between HIF signaling and aging also in mammals [10].

In humans, epidemiologic studies provide some indications for a possible modulation of aging by hypoxia. Living at high altitude has different effects on mortality and a number of diseases such as cardiovascular disease. Importantly, residents of moderate and high altitudes are not only exposed to constant hypoxic conditions, but are also exposed to a complex set of other physical and lifestyle factors. These potentially modulate cardiovascular function and aging and include ultraviolet radiation and other climatic parameters, living conditions and physical activity, access to goods and health care, etc. [11, 12].

Although clear causal relationships have yet to be established, a growing body of evidence reports reduced mortality from cardiovascular disease in people living at moderate altitudes. For example, it has been reported that mortality from arteriosclerotic heart disease becomes lower with increasing residential altitude in New Mexico (from 914 to over 2135 m) for men (but not for women) [13]. Ezzati and colleagues [14] reported a decrease in mortality from cardiovascular disease (coronary heart disease) in US counties located at higher altitudes, while mortality from chronic obstructive pulmonary disease increased [14, 15]. Stroke-related mortality decreased at altitudes with the strongest epidemiologic effects between 2000 and 3500 m [16]. (This put in part with cardiovascular disease.) The decrease in all-cause mortality among residents of moderate altitudes (up to about 2000 m) was primarily due to lower cardiovascular mortality in the alpine countries of

Switzerland and Austria [17, 18].

Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome is a growing health problem affecting nearly one billion people worldwide; it is an independent risk factor for cardiovascular disease associated with obesity, insulin resistance, hypertension, arrhythmias, stroke, coronary heart disease, and heart failure. The concomitant cardiovascular and metabolic diseases associated with obstructive sleep apnea are a major challenge to the prognosis and complexity of comprehensive treatment of obstructive sleep apnea. Continuous positive airway pressure, the first-line therapy for the treatment of obstructive sleep apnea, is highly effective in improving symptoms and quality of life but has limited impact on comorbidities. Deciphering the molecular pathways involved in the metabolic and cardiovascular consequences of obstructive sleep apnea is a priority for the development of new pharmacologic targets in combination with or as an alternative to continuous positive airway pressure. Intermittent hypoxia, a characteristic feature of obstructive sleep apnea, is a key intermediate mechanism underlying metabolic and cardiovascular complications. Experimental setups have been established to expose cells, rodents and healthy humans to intermittent hypoxia, to analyze the molecular mechanisms of the comorbidities associated with obstructive sleep apnea. The main objective of this review is to summarize the molecular pathways, cellular and tissue interactions that contribute to the cardiometabolic consequences of intermittent hypoxia. Sympathetic activation, mild inflammation, oxidative stress and endoplasmic reticulum stress are induced by intermittent hypoxia and play a role in cardiometabolic dysfunction. The key role of hypoxiainducible transcription factor-1 and the underappreciated and less described importance of hypoxia-inducible transcription factor-1 will be discussed in detail Mitochondrial functional changes under conditions of intermittent

hypoxia.Mechanisms involved in the deleterious effects of obstructive sleep apnea (OSA). Intermittent hypoxia (IH) leads to sympathetic nervous system hyperactivity, inflammation, oxidative stress and endoplasmic reticulum stress. Hypoxiainducible factor-1 (HIF-1) appears to play an important role in the consequences of OSS and AI. Mitochondrial integrity may also be an interesting target to explain OSS-related pathologies. Adapted from [73]. COAS is now generally recognized as an independent risk factor for cardiovascular and metabolic diseases, but is largely underestimated in patients from these risk groups [74]. COAS is independently associated with the prevalence and incidence of hypertension, stroke, coronary heart disease, heart failure, and atrial fibrillation [74], [75]. COAS is also associated with metabolic disorders such as obesity, insulin resistance, type 2 diabetes, nonalcoholic fatty liver disease, and metabolic syndrome [74]. Deciphering the mechanisms involved in the cardiometabolic consequences associated with OSA is a major challenge for the field. OSA is characterized by the occurrence of recurrent complete or incomplete pharyngeal collapses during sleep, causing intermittent hypoxia and sleep fragmentation [74]. The mechanisms underlying pharyngeal collapses are complex and multifactorial. Several factors influence upper airway stability. Apnea and hypopnea occur in the context of anatomic reduction in upper airway caliber as a result of obesity or anomalies of the maxillofacial or pharyngeal soft tissues. Decreased pharyngeal dilator activity at the onset of sleep causes apneas and hypopneas that end in micro-awakenings, allowing muscle activity to recover and reopen the upper airway. Other factors such as pharyngeal neuropathy, impaired protection of upper airway reflexes, or rostral fluid shift from the legs to the neck during sleep are powerful contributors to pharyngeal collapse [74]. Diagnosis of sleep apnea requires in vitro or outpatient sleep studies (polysomnography) to assess sleep and cardiorespiratory variables. When evaluating respiratory events in polysomnographic analysis, apnea is defined as a >90% decrease in airflow for at least 10 seconds. Obstructive hypopnea is characterized by a decrease in airflow of at least 30% associated with a decrease in arterial blood oxygen saturation of at least 3% and/or microexcitation. Polysomnography is the gold standard for recording respiratory events during sleep and allows calculation of the apnea-hypopnea index (AHI), defined by the number of apneas and hypopneas per hour of sleep. Only half of patients with OAS are symptomatic, and a significant percentage of subjects are referred and treated to limit their cardiometabolic risk. OAS is a heterogeneous condition and phenotypic subgroups have been recognized that differ significantly in age, gender, symptoms, obesity, comorbidities, and environmental risk factors [76].

Human data

Although limited, there is some evidence for changes in CNS connectivity in humans who live and/or were born at high altitude, which inherently imposes chronic exposure to hypoxia. Changes in electroencephalogram (EEG) patterns in Bolivian children born at high altitude indicate changes in neural function and/or circuitry (Richardson et al., 2011). Children born and living at higher altitudes were more likely to have NDD (Wehby, 2013). Interestingly, altered brain connectivity patterns have been observed even in individuals who move to higher altitudes at a young age, suggesting potential changes in synaptic connectivity (Chen et al., 2017). These limited studies are suggestive, but larger epidemiological and imaging studies are needed to assess hypoxia-induced changes in CNS connectivity and the presence of NDD. In addition, although genetic and evolutionary changes associated with physiological and hematological responses to high altitude and hypoxia have been extensively studied (reviewed in Azad et al., 2017), essentially no comparable information is available regarding genetic or evolutionary adaptations of the developing CNS to high altitude and hypoxia. Another source of information on hypoxia and the potential for changes in human CNS connectivity comes from studies of preterm birth in humans. MRI studies of former preterm infants who were exposed to chronic hypoxia show changes in MRI indices, including changes in functional MRI activation patterns (fMRI), indicating altered connectivity and reduced fractional anisotropy of white matter tracts, suggesting reduced axonal tract connectivity (Gozzo et al., 2009; Mullen et al., 2011; Salmaso et al., 2014). Development of the corpus callosum and other axonal pathways of the cerebral hemispheres is impaired in preterm infants (Glass et al., 2008; Mullen et al., 2011; de Kieviet et al., 2012; Hasegawa et al., 2011; Thompson et al., 2007; van Pul et al., 2012). The incidence of RAS is three times higher in preterm infants (Lampi et al., 2012), and the prevalence of RAS approaches 25% in extremely preterm infants, i.e. those born at less than 27 weeks PCA (Limperopoulos et al., 2008). Preterm infants who develop RAS may not have noticeable brain developmental abnormalities, but may have fMRI changes demonstrating abnormal synchronization of neural activity consistent with changes in brain connectivity (Dinstein et al., 2011).

Hypoxia and aging

Aging is characterized by progressive functional decline (Kauppila et al., 2017), which can be modified by altering O2 availability. Despite the important role of O2 in oxidative metabolism, moderately reduced O2 concentrations may benefit aging organisms. Hypoxic environments are associated with unusually long lifespans in some mammals, including the naked mammal (Kim et al., 2011) and bowhead whale (Keane et al., 2015). Moderate reduction in mitochondrial respiration, i.e., reduced O2 utilization, also prolongs the viability of cultured cells (Packer and Fuehr, 1977) and the lifespan of Caenorabditis elegans (Feng et al., 2001; Kayser et al., 2004; Lee et al., 2003; Mehta et al., 2009). 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 from patients with obstructive sleep apnea syndrome (Kim et al., 2016a).

Hypoxic respiratory response in aging

In addition to the HIF system, aging alters O2 perception and respiratory responses to hypoxia. Aging is associated with decreased respiratory capacity due to changes in peripheral and central chemoreceptor function (Teppema and Dahan, 2010) and decreased ventilatory pump performance due to decreased respiratory muscle strength and chest wall pliability (Janssens, 2005). The carotid corpuscles of old rats were found to have reduced mitochondrial content and fewer O2sensitive glomus cells (Pokorski et al., 2004). Also in rats, aging has been associated with increased catecholamine content in carotid corpuscles but reduced hypoxia-induced catecholamine release (Conde et al., 2006). Moreover, hypoxia-induced increase in HIF-1α and expression of HIF gene products, VEGF and iNOS, decreased with age (Di Giulio et al., 2003, 2005). In aging individuals, the ratio of connective tissue to neurons in the carotid corpuscles increases (Sarrat-Torres et al., 2020), and supporting cells and infiltrating lymphocytes replace chemosensory glomus cells (Hurst et al., 1985). Central chemoreceptors may partially compensate for the deterioration of carotid glomerular cells (Pokorski et al., 2004) because the hypoxic respiratory response in older adults, although impaired compared to young adults (Liu et al., 2020), is not severely impaired (Teppema and Dahan, 2010).

CONCLUSION: Hypoxia remains one of the significant problems in the field of medicine and physiology, affecting many aspects of human health. A review of the literature and current research has established that hypoxia can have various forms and causes, high altitude, pathologies of the respiratory and cardiovascular systems, and many external factors. An important aspect of hypoxia is its multifactorial nature. Different types of hypoxias - hypoxic, hypemic, ischemic and tissue hypoxia - can occur depending on the specifics of the underlying disease and the patient's condition. Each of these forms requires an individualized approach in both diagnosis and treatment. Research has shown that symptoms of hypoxia can range from mild malaise to serious disorders of vital organs. Prevention and treatment of hypoxic conditions should be based on a comprehensive approach, which includes both the identification and elimination of the underlying cause and the use of therapeutic interventions. In addition, given the relevance of the topic, it should be noted that further research is needed to better understand the

pathophysiologic mechanisms of hypoxia, as well as to develop new methods of diagnosis and treatment. In conclusion, it is important to emphasize the awareness of hypoxia as a complex pathological condition that requires an integrated and interdisciplinary approach from both medical sciences and practical medicine, which will improve the quality of life of patients and reduce the negative consequences of hypoxic conditions.

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