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## REVIEW-SYMPOSIUM

# Mechanisms underlying the health benefits of intermittent hypoxia conditioning

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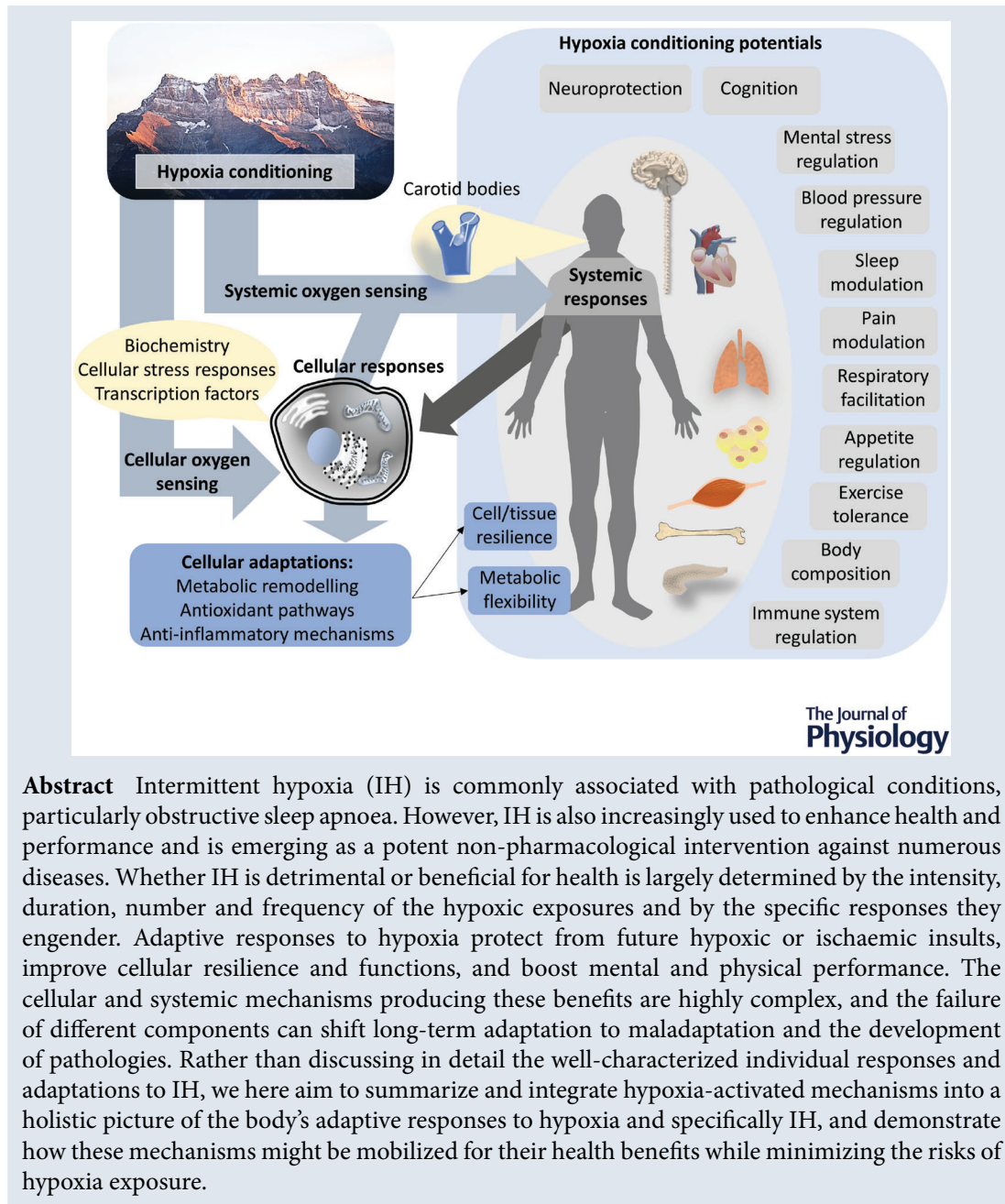
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**Abstract** Intermittent hypoxia (IH) is commonly associated with pathological conditions, particularly obstructive sleep apnoea. However, IH is also increasingly used to enhance health and performance and is emerging as a potent non-pharmacological intervention against numerous diseases. Whether IH is detrimental or beneficial for health is largely determined by the intensity, duration, number and frequency of the hypoxic exposures and by the specific responses they engender. Adaptive responses to hypoxia protect from future hypoxic or ischaemic insults, improve cellular resilience and functions, and boost mental and physical performance. The cellular and systemic mechanisms producing these benefits are highly complex, and the failure of different components can shift long-term adaptation to maladaptation and the development of pathologies. Rather than discussing in detail the well-characterized individual responses and adaptations to IH, we here aim to summarize and integrate hypoxia-activated mechanisms into a holistic picture of the body's adaptive responses to hypoxia and specifically IH, and demonstrate how these mechanisms might be mobilized for their health benefits while minimizing the risks of hypoxia exposure.

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**Abstract figure legend** Hypoxia is a major threat to health, which is why a multitude of cellular and systemic responses and adaptations to hypoxia are mobilized to minimize the risk. Conversely, programmes applying certain intensities, frequencies and durations of moderate, intermittent hypoxia may elicit adaptations that benefit normal function and combat disease. This hypoxia conditioning is the focus of this review.

## Introduction

Maintaining adequate oxygen supply and sensing decreased partial pressure of oxygen ( $P_{O_2}$ ) are crucial for all aerobic species. Severe ambient hypoxia (Fig. 1 and Table 1) can trigger dangerous acute conditions, e.g. high-altitude cerebral oedema, pulmonary oedema and pulmonary hypertension (Luks & Hackett, 2022). Moreover, tissue hypoxia is associated with myriad pathologies (Semenza, 2012) and can drive disease progression, as in cancer (Schito & Semenza, 2016).

Despite the risks of uncontrolled hypoxia, recent discoveries underscore the great potential for calibrated modulation of environmental oxygen availability to augment performance, modulate metabolism and pain, and combat cardiovascular and metabolic disorders, spinal cord injury, neurological and psychiatric disorders, and other diseases. The benefits of controlled hypoxia, termed hypoxia conditioning, have garnered considerable scientific, but also commercial, interest resulting in increasing application of various hypoxia protocols in healthy people and diseased patients. Despite the mounting interest in such approaches, the mechanistic foundations of controlled hypoxia's benefits and potential risks are poorly understood. Cellular and systemic responses to hypoxia include vascular and metabolic remodelling and respiratory and cardiovascular mechanisms to maintain oxygen supply. These physiological responses to hypoxia conditioning ameliorate hypoxic injury and may be harnessed to increase cellular and tissue resilience, health, and performance.

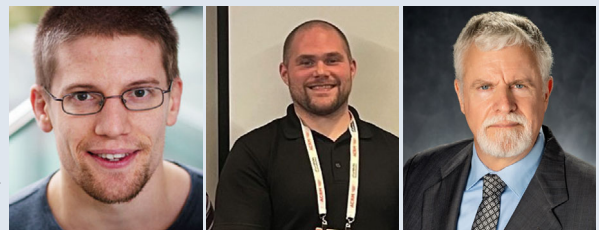
The mechanistic foci of interest vary substantially among hypoxia studies conducted in diverse populations, using myriad methods, protocols, technologies and terminologies (Panza et al., 2023). Consequently,

understanding of the underlying factors is fragmented. Contributing to this problem is an inherent complication of hypoxia research: the divergent outcomes of hypoxia critically depend on the protocol and highly individual responses and vulnerabilities. Crucial aspects of protocols include the hypoxic dose (intensity, duration, frequency, patterns of administration), combining hypoxia with physical activity or pharmacological treatments, the mode and timing of application, the impact of temperature, humidity, barometric pressure and other environmental factors, and individual physiological factors (e.g. sex, age, ethnicity), health history or medications.

Contemporary hypoxic conditioning protocols often consist of repeated, cyclic exposures to moderately reduced fractions of inspired oxygen ( $F_{IO_2}$ ) alternating with normoxia or mild hyperoxia and, thus, represent intermittent hypoxia (IH). These interval hypoxic or hypoxic–hyperoxic exposures (i.e. IHE or IHHE) are applied in multiple weekly sessions over several weeks (Burtscher et al., 2004, 2009; Glazachev et al., 2017). Such protocols are characterized by multiple, typically abrupt transitions from hypoxia to normoxia or hyperoxia. However, sustained hypoxia conditioning protocols also are used.

By integrating the major potential mechanisms yielding beneficial IH outcomes, this review aims to provide a comprehensive view of how hypoxia conditioning may work. Molecular and systemic physiological responses to hypoxia are described and the importance of specific mechanisms for different health benefits is assessed. Due to the mounting recognition of its health benefits, IH is our central topic, but we also will summarize continuous hypoxia benefits that may be relevant for IH. A crucial knowledge gap is the impact of the hypoxic dose on the contributions of different adaptive mechanisms to

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hypoxia benefits. The hypoxic dose determines whether hypoxia triggers beneficial adaptation or maladaptation, as occurs for example in obstructive sleep apnoea (OSA). Importantly, sensitivity to hypoxia differs among organs and physiological functions, rendering some beneficial hypoxia applications ineffective or even dangerous for other systems. Despite the risks of severe hypoxia, here we focus on beneficial outcomes. A central objective of the hypoxia field is the determination of the maladaptive thresholds. While some insights can be gleaned from the existing literature, this aspect requires extensive systematic investigation. In-depth examination of the diverse outcomes of the many published protocols is beyond the scope of this review; instead, we summarize general mechanisms, reference existing reviews on specific parameters or applications, and provide examples.

## Molecular oxygen sensing and mediators of hypoxia responses

Many biochemical and molecular mechanisms contribute to cellular oxygen-sensing and trigger adaptive transcriptional responses (Baik & Jain, 2020; Lee et al., 2020) to maintain essential oxygen-dependent processes, e.g. mitochondrial respiration and fatty acid desaturation. Non-transcriptional cellular responses to hypoxia include altered lipid metabolism, ion channel permeability, altered post-transcriptional modification patterns, e.g. protein phosphorylation (Bartscher, Pepe et al., 2023; Lee et al., 2020; Li et al., 2017), and oxygen-dependent enzymatic reactions, including those catalysed by NADPH oxidase (NOX), nitric oxide (NO) synthases (NOS), haem oxygenases, and  $\alpha$ -ketoglutarate dioxygenases (Lee et al., 2020; Terraneo et al., 2017). Different oxygen-affinities and localizations enable cell

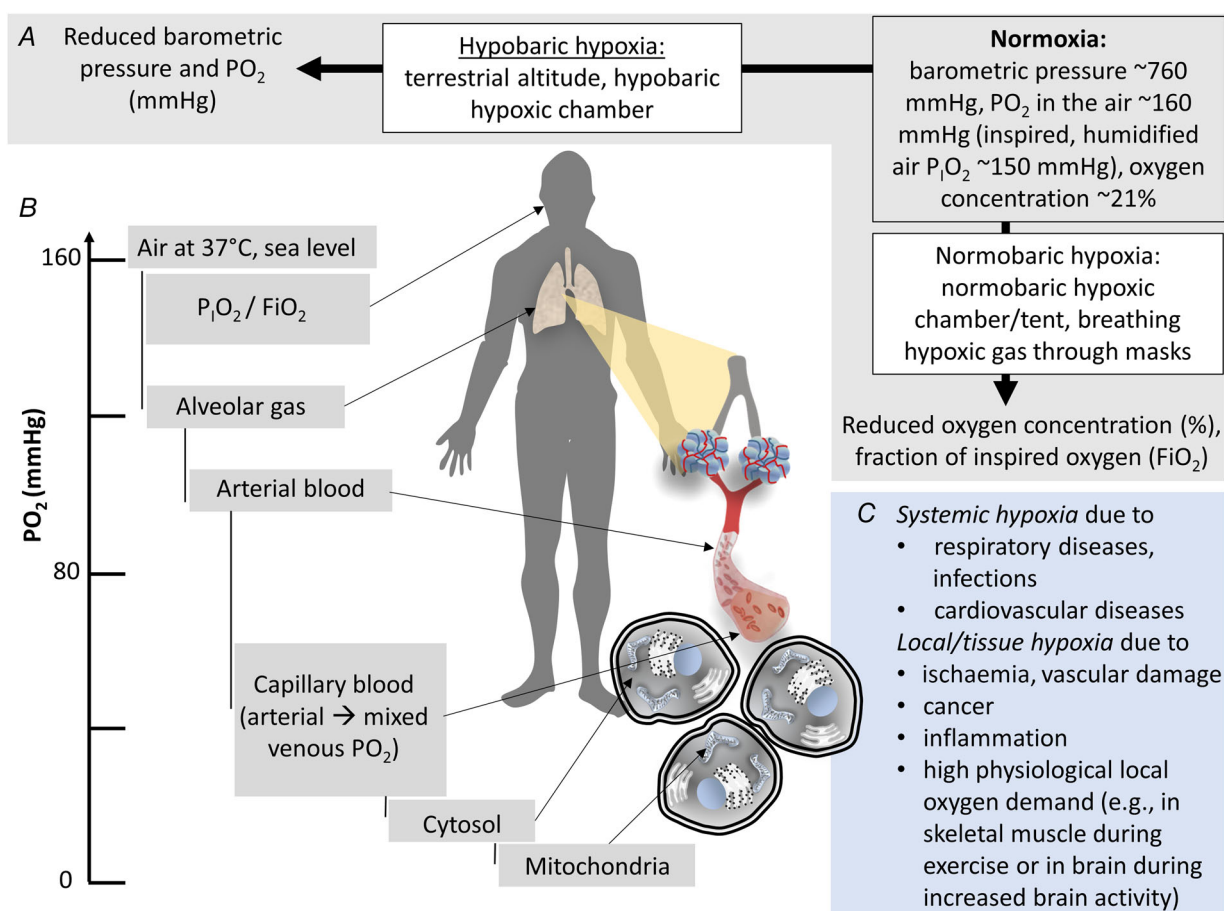


**Figure 1. Normoxia versus hypoxia**

A, ambient types of hypoxia: reduced barometric pressure and associated partial pressure of oxygen ( $P_{O_2}$ ) produces hypobaric hypoxia, while reduction in oxygen concentration – rather than barometric pressure – produces normobaric hypoxia. B,  $P_{O_2}$  gradient from inspired air to mitochondria in peripheral tissues. C, conditions associated with systemic and local hypoxia. Local hypoxia can be elicited, e.g. by exercise and myriad pathological conditions.

**Table 1. Definitions**

|                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hypoxia                                                                                                                      | A condition in which oxygen supply does not match oxygen demand, caused by a low partial pressure of inspired oxygen, low oxygen concentration in the air and/or insufficient oxygenation at the tissue level                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Hypoxaemia                                                                                                                   | A partial pressure of oxygen in the arterial blood below 60 mmHg (8 kPa) or haemoglobin oxygen saturation below 90%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Hyperoxia                                                                                                                    | An abnormally elevated oxygen tension in the blood and tissues, typically produced by breathing gas mixtures with high partial pressures of oxygen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Acute hypoxia                                                                                                                | Initial phase of hypoxia exposure with most pronounced (patho)physiological responses (duration from minutes to days)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Chronic hypoxia                                                                                                              | Prolonged (continuous or intermittent) hypoxia exposure subsequent to the acute phase (days to years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Functional hypoxia                                                                                                           | Physical exercise or extensive motor-cognitive exercise leads to a relative decrease in oxygen supply in skeletal muscle or brain, respectively, compared to the acutely augmented oxygen requirement, resulting in 'functional hypoxia'. Functional hypoxia following physiological challenges may be critical for enduring adaptation required for improved muscle or brain performance                                                                                                                                                                                                                                                              |
| Intermittent hypoxia                                                                                                         | Also termed cyclic or episodic hypoxia. The two major types of intermittent hypoxia exert divergent effects: (1) high-frequency intermittent hypoxia, e.g. obstructive sleep apnoea, elicits mostly maladaptive responses; and (2) low-frequency intermittent hypoxia, e.g. intermittent hypoxia exposure/conditioning, elicits mostly adaptive responses. Other parameters of the hypoxic dose (intensity, duration, exposure patterns) also determine outcomes                                                                                                                                                                                       |
| Continuous hypoxia                                                                                                           | Exposure of an organism to uninterrupted hypoxia, as occurring during high-altitude sojourns                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Intermittent hypoxia conditioning, acute intermittent hypoxia, intermittent hypoxia training                                 | Exposure of an organism to multiple sessions of cycles of moderate hypoxia ( $\dot{V}_{O_2}$ usually 9–15%) breathing alternated with periods of breathing normal air, which elicits primarily adaptive physiological and molecular responses. Also termed IHE (see below), acute intermittent hypoxia (this term is mainly used in studies on the potential of intermittent hypoxia to modulate respiratory plasticity and/or if subjects with spinal cord injury are exposed to intermittent hypoxia) or intermittent hypoxia training (IHT). IHT often refers to a combination of intermittent hypoxia and exercise protocols (however, not always) |
| Intermittent hypoxia exposure/conditioning (IHE/IHC) versus intermittent hypoxia hyperoxic exposure/conditioning (IHHE/IHHC) | These protocols typically consist of repeated 4–8 min exposures to hypoxia, i.e. fractions of inspired oxygen ( $\dot{V}_{O_2}$ = 10–15%, alternating with 2–5 min exposures to normoxia (IHE: $\dot{V}_{O_2}$ = 21%) or hyperoxia (IHHE: $\dot{V}_{O_2}$ = 30–35%), totalling 35–40 min/session applied 3–5 times per week for 3–8 weeks. IHHE has also been termed intermittent hypoxia hyperoxic conditioning (IHHC)                                                                                                                                                                                                                                |

type- and environment-dependent responses.  $\alpha$ -Ketoglutarate dioxygenases regulate RNA abundance, DNA histone demethylation (Batie et al., 2019; Chakraborty et al., 2019) and stability of the oxygen-regulated hypoxia-inducible transcription factors (HIF) (Wang et al., 1995).

**Transcription factors: HIFs, Nrf2 and NF- $\kappa$ B.** Three powerful transcription factors mediate adaptations and/or maladaptations to hypoxic environments. HIF-activated genes primarily augment the blood's oxygen-carrying capacity via erythropoiesis, oxygen delivery to tissues (vascular remodelling) and oxygen-independent ATP production (glucose transport and glycolysis) (Semenza, 2012). Nuclear factor erythroid 2-related factor 2 (Nrf2) regulates antioxidant defences (Bartscher, Mallet

et al., 2022). Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is an integral modulator of inflammatory responses to hypoxia and other stressors (Scholz et al., 2013).

Nrf2, NF- $\kappa$ B, specific protein 1 and various microRNAs/non-coding RNAs contribute to the transcriptional control of HIFs (Taylor & Scholz, 2022). Post-translationally, HIF activity is regulated by oxygen-dependent HIF  $\alpha$ -subunit hydroxylation by the  $\alpha$ -ketoglutarate-dependent dioxygenases prolyl-4-hydroxylases (PHD) and asparagine hydroxylase factor inhibiting HIF (FIH). In normoxia, hydroxylation by PHD, and FIH initiate proteasomal degradation of HIF  $\alpha$ -subunits. Stabilized by hypoxia, HIF  $\alpha$ -subunits heterodimerize with HIF  $\beta$ -subunits to form HIF heterodimers that transcriptionally control an extensive gene programme (Fig. 2).

The three known HIF subtypes have distinct  $\alpha$ -subunits. Overlapping gene regulation by HIF-1 and HIF-2 regulates angiogenesis, lipid metabolism and immunity (Keith et al., 2011; Mole et al., 2009), but distinct temporal and spatial expression, specific co-factors (Lendahl et al., 2009) and DNA binding patterns (Smythies et al., 2019) allow differential functions. For example, HIF-1 specifically regulates the glycolytic switch, while HIF-2 activates vascular remodelling and erythropoiesis (Bartscher, Hohenauer et al., 2023). Although its functions are incompletely understood, HIF-3 seems to regulate HIF-1 and HIF-2 signalling (Lendahl et al., 2009).

HIF activity is cell-type dependent and transient; it declines with time even if hypoxia is maintained, and IH may effect more sustained HIF-activation than continuous hypoxia. HIF-1 $\alpha$  is stabilized in a hypoxic dose-dependent manner (Jiang et al., 1996; Li et al., 2022); moderate reductions in  $P_{O_2}$  stabilize HIF-1 $\alpha$  by inactivating PHD more so than FIH, due to the latter's higher oxygen affinity (Volkova et al., 2022). The ubiquitously expressed HIF-1 primarily mediates acute hypoxia responses and its content in endothelial cells peaks within  $\sim 4$  h of hypoxia (Jaskiewicz et al., 2022). Conversely, HIF-2, which is more restricted to specific cell types, mediates

chronic hypoxia responses, and its endothelial cell content plateaus for several hours after  $\sim 8$  h continuous hypoxia (Holmquist-Mengelbier et al., 2006; Jaskiewicz et al., 2022).

Complementing HIF-induced gene expression, Nrf2 orchestrates expression of antioxidant and anti-inflammatory enzyme genes (Fig. 2) (Bartscher, Mallet, Bartscher et al., 2021). These enzymes synthesize the major intracellular antioxidant glutathione, generate NADPH to maintain antioxidant redox states, catalyse electron transfer to neutralize reactive oxygen species (ROS) and degrade haem to the anti-inflammatory metabolite biliverdin. Cyclic hypoxia–normoxia and hypoxia–hyperoxia activate superoxide formation, primarily by mitochondrial respiratory complexes I and III during hypoxia and NADPH oxidase upon reoxygenation (Bartscher, Mallet et al., 2022). ROS generated from superoxide release Nrf2 from its cytosolic suppressor, kelch-like ECH-associated protein 1 (Keap1), allowing Nrf2 transmigration to the nucleus where it complexes with its coactivator, Maf, and activates its gene programme.

Hypoxia impacts activity of another transcription factor, NF- $\kappa$ B, a potent regulator of genes encoding proteins involved in inflammation, apoptosis and innate

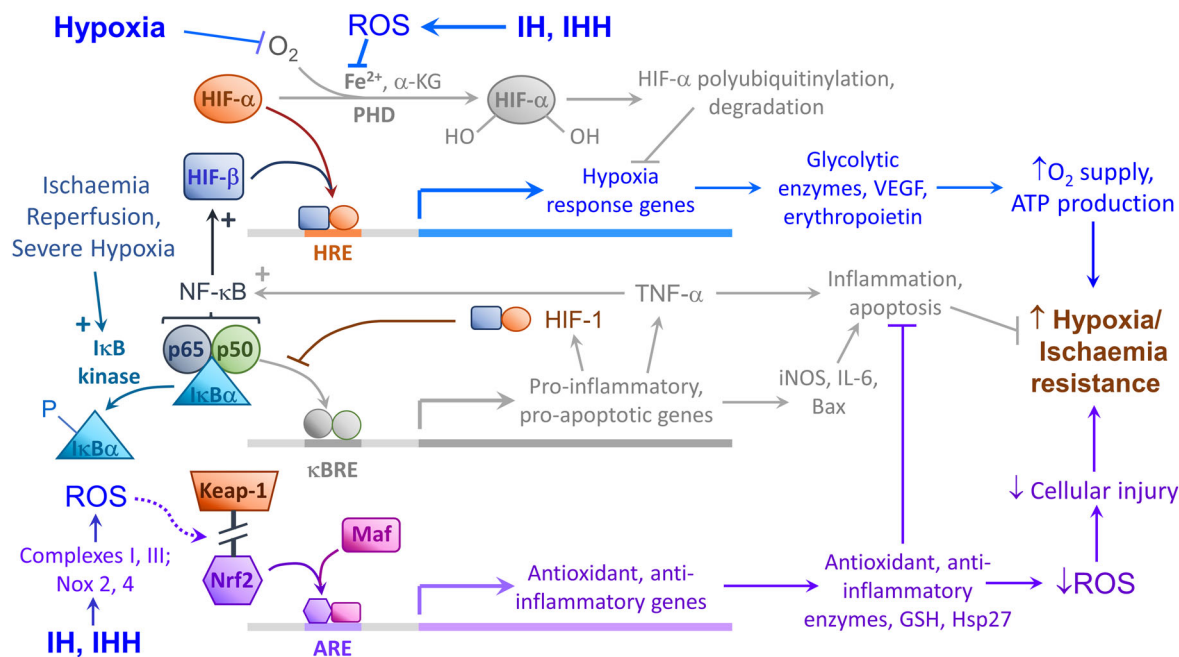


**Figure 2. Transcription factors mediating hypoxia responses that bolster hypoxia/ischaemia resistance**

Hypoxia and reactive oxygen species (ROS)-inducible transcription factors interact with their respective response elements on DNA to activate transcription of genes encoding pro- and anti-inflammatory and antioxidant proteins. Grey lettering and symbols represent mechanisms attenuating the adaptive mechanisms. ARE, antioxidant response element;  $\kappa$ BRE,  $\kappa$ B response element; GSH, glutathione; HIF, hypoxia-inducible factor; HRE, hypoxia response element; Hsp27, heat shock protein 27; IH, intermittent hypoxia; IHH, intermittent hypoxia–hyperoxia; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; Keap-1, kelch-like ECH-associated protein 1;  $\alpha$ -KG,  $\alpha$ -ketoglutarate; NF- $\kappa$ B, nuclear factor- $\kappa$ B; Nox, NAD(P)H oxidase; Nrf2, nuclear factor erythroid 2-related factor 2; PHD, prolyl-4-hydroxylases; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ ; VEGF, vascular endothelial growth factor.

immunity (D'Ignazio & Rocha, 2016). Depending on the extent of hypoxic activation, the NF- $\kappa$ B gene programme either complements or opposes the cytoprotective HIF and Nrf2 gene programmes. Cellular stress activates protein kinases, which phosphorylate NF- $\kappa$ B's repressor subunit, I $\kappa$ B, targeting it for degradation. I $\kappa$ B phosphorylation liberates the transcriptionally active p65–p50 dimer, which translocates to the nucleus where it activates genes encoding inducible NOS, pro-inflammatory cytokines and pro-apoptotic proteins. The complex crosstalk between HIF and NF- $\kappa$ B signalling (D'Ignazio et al., 2016) depends on the intensity and duration of the hypoxic stimulus and can dampen (Amin et al., 2021) or intensify inflammatory responses (Moulin et al., 2020).

Figure 2 depicts the contributions of HIFs, Nrf2 and NF- $\kappa$ B to hypoxia responses. Numerous other transcription factors, e.g. the HIF-1 modulated tumour suppressor p53 (An et al., 1998), and signalling pathways also play important roles in responses and adaptations to hypoxia.

**AMPK and mTOR.** By impairing oxidative ATP-production, hypoxia threatens cellular ATP-dependent processes. AMP-activated protein kinase (AMPK), and mammalian target-of-rapamycin (mTOR) pathways collaborate with HIF to economize cellular ATP expenditure. Among the most ATP-intensive cellular processes are protein synthesis and maintenance of transmembrane electrochemical Na<sup>+</sup> and K<sup>+</sup> gradients by Na<sup>+</sup>/K<sup>+</sup>-ATPases. Hypoxia can activate AMPK independently of AMP/ATP-ratio, AMPK's primary activator, which increases due to cellular ATP supply:demand mismatch (Dengler, 2020). Hypoxic activation of AMPK lowers ATP demand by promoting endocytosis and degradation of Na<sup>+</sup>/K<sup>+</sup>-ATPases (Gusarova et al., 2009) and inhibiting mTOR, eukaryotic initiation factor 2 $\alpha$ , and eukaryotic translation elongation factor 2 to suppress protein synthesis (Liu et al., 2006).

**The unfolded protein and DNA damage responses.** Severe tissue hypoxia can inflict oxidative DNA damage, modify chromatin and suppress oxygen-dependent DNA synthesis (Foskolou et al., 2017; Olcina et al., 2013). DNA damage recognition elicits the DNA damage response, which mobilizes DNA repair orchestrated by phosphoinositide 3-kinase (PI3K)-related kinases (Blackford & Jackson, 2017). The DNA damage response can be associated with transient cell-cycle arrest supporting the repair mechanisms and may increase resilience to future DNA damage. Excessive activation in stressed cells, however, can lead to permanent cell-cycle arrest (senescence) or apoptosis (Blackford & Jackson, 2017).

The endoplasmic reticular (Pueyo et al., 2000) and mitochondrial (Shpilka & Haynes, 2018) unfolded protein responses primarily regulate protein homeostasis and are triggered by various cellular stressors, including hypoxia (Walter & Ron, 2011). These responses are tightly coordinated with DNA damage responses and other signalling pathways including HIF, immune signalling and PI3K/Akt/mTor. Together, these mechanisms orchestrate responses modulating redox state, autophagy, protein homeostasis and metabolic reprogramming (Bolland et al., 2021). Importantly, the HIF, AMPK, mTOR, DNA-damage and unfolded protein responses have different hypoxia activation thresholds, enabling specific, hypoxic dose-dependent responses and adaptation patterns.

### Systemic oxygen sensing

The molecular mechanisms summarized above collaborate with and enable systemic oxygen sensing, leading to direct hypoxia responses. The hypoxic ventilatory response (HVR) in humans and most other mammals increases alveolar ventilation to compensate for reduced inspiratory  $P_{O_2}$  and is initiated by chemoreceptors, particularly the glomus cells of the carotid bodies (Iturriaga et al., 2021; Teppema & Dahan, 2010). When they sense decreased arterial  $P_{O_2}$  and increased lactate concentration (Chang et al., 2015; Torres-Torrelo et al., 2021), the glomus cells activate sensory neurons of the petrosal ganglia. These neurons transmit sensory impulses via the glossopharyngeal nerve to specialized neurons in the nucleus tractus solitarius (Forster & Smith, 2010) to activate the sympathetic nervous system-mediated acute ventilatory chemoreflex response (Iturriaga et al., 2021). Facilitated by pulmonary vasoconstriction, this response increases minute ventilation and the ventilation–perfusion ratio (Kemp et al., 2002; Pamerter & Powell, 2016).

Although the molecular oxygen sensor is still unknown, hypoxia closes oxygen-sensitive potassium channels on carotid and aortic glomus cells, provoking depolarization-induced calcium influx and dopamine neurotransmitter release that activates brainstem neurons (Iturriaga et al., 2021). In mitochondrial complex I subunit Ndufs2 knockout mice, the carotid bodies' oxygen sensitivity was shown to be complex I- and NADH-dehydrogenase dependent (Fernández-Agüera et al., 2015; Jiménez-Gómez et al., 2023). Increased HIF-2 $\alpha$  content and HIF-2-driven expression of the *Cox4i2* gene encoding the atypical carotid body-specific respiratory complex IV subunit Cox4i2 in glomus cells are required for hypoxia sensitivity and HVR in mice (Moreno-Domínguez et al., 2020).

Hypoxia-induced erythropoietin expression in the brain has been shown to regulate the HVR by interacting

with brainstem chemoreceptors and carotid bodies (Soliz et al., 2005, 2009). Whether and how central chemoreceptors directly modulate systemic hypoxia responses in humans remains debated (Funk & Gourine, 2018; Gourine & Funk, 2017; SheikhBahaei, 2020; Teppema, 2018). Classically, central chemoreceptors are exquisitely responsive to fluctuations in pH or the partial pressure of CO<sub>2</sub> ( $P_{\text{CO}_2}$ , the main regulator of alveolar ventilation), not to  $P_{\text{O}_2}$ , and by regulating ventilation they control  $P_{\text{CO}_2}$  in the systemic arterial blood (Guyenet et al., 2019). The main nuclei implicated in chemosensing and respiratory responses are the brainstem pre-Bötzinger complex, retrotrapezius nucleus and raphe magnus nucleus (Goridis & Brunet, 2010). The medullary pre-Bötzinger complex generates the breathing rhythm and regulates respiratory muscle activity patterns, inspiration, blood pressure (BP) and heart rate (Menuet et al., 2020). Retrotrapezoid nucleus neurons innervating the pre-Bötzinger complex (Bochorishvili et al., 2012) control breathing automaticity and are required for active expiration (Guyenet et al., 2019). Serotonergic neurons in the raphe nuclei innervate the retrotrapezoid nucleus to modulate breathing (Mulkey et al., 2007).

### Cellular benefits of mild intermittent hypoxia

**Hormesis and cellular resilience.** Hypoxia conditioning aims to induce adaptations to hypoxic stress that enhance resilience to subsequent stress. Thus, hypoxia conditioning relies on the principle of *hormesis*: a mild but potentially harmful stressor (i.e. hypoxia) can increase the resilience of the target cells/tissues (Esparza-Moltó et al., 2021; Ristow & Schmeisser, 2014), while severe and/or prolonged hypoxia can inflict permanent damage. Hypoxia conditioning ‘trains’ adaptive flexibility in response to stress (Bartscher, Romani et al., 2022).

**Mitochondrial and cellular stress response.** Hypoxia induces numerous mitochondrial responses and adaptations, partially coordinated by HIFs, the mitochondrial biogenesis regulator peroxisome proliferator-activated receptor  $\gamma$  coactivator  $\alpha$  (PGC-1 $\alpha$ ), cellular myelocytomatosis (c-MYC), sirtuin 1 (SIRT1), and AMPK (Ham & Raju, 2017). HIFs also participate in the regulation of the heat shock response in hypoxia by upregulating heat shock factor gene expression, which coordinates the heat shock protein (HSP) activation (Baird et al., 2006) central to ‘cross-adaptation’ and/or ‘cross-tolerance’ to hypoxia and heat exposures (Gibson et al., 2017).

Mitochondria acutely respond to hypoxia by increasing electron transport efficiency to maintain ATP production. The involved mechanisms include a cytochrome *c* oxidase subunit switch (Fukuda et al., 2007) and cytochrome *c* oxidase activity regulation

by hypoxia-inducible gene domain family member 1A (Hayashi et al., 2015). Oxidative phosphorylation slows during prolonged hypoxia, due in part to mitochondrial complex I inhibition (Bartscher, Mallet et al., 2022) that coincides with upregulation of glycolysis and a shift to glucose metabolism. Prolonged continuous hypoxia may decrease mitochondrial mass by reducing mitochondrial biogenesis, increasing mitophagy and altering mitochondrial morphology and dynamics (Bartscher, Hohenauer et al., 2023), effects that have not been well characterized for IH. Hypoxia/reoxygenation through aberrant fusion can produce ‘donut-shaped’ mitochondria (Liu & Hajnoczky, 2011) or megamitochondria (Hao et al., 2023), morphologies potentially contributing to functional recovery or autophagic regulation, respectively.

The remarkable plasticity of mitochondria (oxidative phosphorylation efficiency, substrate utilization flexibility and reliance on alternative metabolic pathways) to hypoxia and other stressors renders them primary candidates to mediate beneficial hypoxia conditioning effects. Improved mitochondrial quality control by upregulated mitophagy and enhanced anti-oxidative mechanisms likely contributes to improved cellular resilience effected by hypoxia conditioning, but empirical evidence regarding the hypoxic doses that elicit these protective effects is scarce, particularly for IH.

**Pro-/antioxidant balance.** Sustained chronic hypoxia produces injurious oxidative stress, with uncoupled mitochondria representing a major ROS source (Smith et al., 2017). An alternative ROS source is the membrane-bound NOX4 isoform, which responds directly to hypoxia (Diebold, Flugel et al., 2010; Kuroda et al., 2014; Radermacher et al., 2013; Terraneo et al., 2017). The increase in pro-oxidant factors does not necessarily translate into overt oxidative damage due to redox signalling adaptation cascades, increasing cellular, and organismal antioxidant power and resilience (Roy et al., 2017; Sazontova & Arkhipenko, 2005). In IH, oxidative stress occurs primarily during reoxygenations and, similar to ischaemia–reperfusion injury, may be at least partly ascribable to xanthine oxidase, which degrades the ATP breakdown product hypoxanthine into xanthine and urate with superoxide anion production proportional to the number of hypoxia–reoxygenation cycles (Nanduri et al., 2013). In contrast to sustained hypoxia, in mild IH circulating oxidative biomarker levels are similar to non-hypoxic levels and oxidative injury is prevented by the activation of antioxidative pathways.

Various antioxidant mechanisms (besides Nrf2) are protective in hypoxia, including the neuroprotective (Yan et al., 2016; Zhao et al., 2012) and cardioprotective (Milano et al., 2013) serine/threonine-specific protein kinase Akt (protein kinase B). Akt, a nexus in several signalling

pathways in myocardium (Sussman et al., 2011) and possibly in most other somatic cells, likely is pivotal to IH-elicited protection in most tissues.

Remarkably, hyperoxia has effects similar to IH: the induction of robust antioxidant defences efficiently counters the increased ROS production (Terraneo et al., 2017). Accordingly, adaptive induction of antioxidant defences may be even more robust in IHHE than in IHE, as was shown in rats (Gonchar & Mankovska, 2012).

**Inflammation and immune system function.** Responses to hypoxia and inflammation are intimately linked. Hypoxia, partially via HIFs, modulates immune cell functions and inflammation (Taylor & Scholz, 2022). HIF-regulating hydroxylases (PHD and FIH) regulate inflammatory signalling via the major proinflammatory cytokine interleukin (IL)-1 $\beta$  and transcription factor NF- $\kappa$ B (Scholz et al., 2013). Conversely, infiltration of oxygen-consuming leukocytes and oxygen-consuming enzyme activation can cause hypoxia and activate HIF in inflammatory environments (Cartwright & Colgan, 2023). HIF-1 $\alpha$  is required for the induction of monocyte trained immunity (Cheng et al., 2014), which provides non-specific or trained immune protection. Oxygen levels are generally critical for immune cell differentiation, activation and recruitment (Eltzschig & Carmeliet, 2011; Zenewicz, 2017), and determine the resolution of inflammation, e.g. in the gastrointestinal tract (Cartwright & Colgan, 2023). Accordingly, IH conditioning mobilized immune cell progenitors and augmented innate immunity in healthy men (Serebrovskaya et al., 2011).

**Cellular proliferation, differentiation, migration and bone health.** Hypoxia is an important regulator of proliferation, differentiation, migration and survival/apoptosis in stem cell and immunological niches, but also in cancer microenvironments (Pulido-Escribano et al., 2022; Simon & Keith, 2008; Taylor & Colgan, 2017). Specifically, HIF-2 $\alpha$  up-regulates the cyclin D1 gene and cellular c-Myc expression, promoting cell cycle progression and proliferation (Gordan et al., 2007). HIFs further regulate cell migration through genes encoding  $\alpha$  and  $\beta$ -1, -3, and -5 integrins and matrix metalloproteinases (Friedl, 2004).

Hypoxia conditioning could potentially modulate proliferation and lifespan of mesenchymal stem cells, suggesting IH applications for stem cell therapies (Lee et al., 2018; Pulido-Escribano et al., 2022). Hypoxia-induced HIF controls angiogenic (e.g. vascular endothelial growth factor) and osteogenic (Dirckx et al., 2018) factors, bone remodelling-related genes, e.g. osteoprotegerin and erythropoietin, and glycolytic enzymes required for osteoblast differentiation (Lee et al., 2017; Semenza, 2001), rendering hypoxia a central regulator of bone formation. Mild IH can elicit

adaptive bone remodelling and mesenchymal stem cell differentiation into osteoblasts (Camacho-Cardenosa et al., 2020; Guner et al., 2013); moreover, in clinical studies IH conditioning inhibited bone resorption biomarkers and stimulated bone formation (Camacho-Cardenosa et al., 2022; Timon et al., 2022).

**Neuroprotection.** With their high oxygen demand and limited antioxidant defences (Sorce & Krause, 2009) neurons are highly vulnerable to ROS (Benderro et al., 2012; Lee et al., 2005). The potential for ischaemic preconditioning to improve the brain's innate capacity to resist and repair ischaemic injury is well recognized (Dirnagl et al., 2009) and IH conditioning may similarly increase the brain's structural and functional resilience (Burtscher, Mallet, Burtscher et al., 2021; Rybnikova et al., 2022). Antioxidant defences bolstered by IH conditioning may minimize neuronal vulnerability to ROS (Burtscher, Mallet, Burtscher et al., 2021). Improved neurogenesis is another potential IH mechanism benefiting the brain, as demonstrated in mice (Li et al., 2023). HIF-1-mediated metabolic reprogramming, such as reduced pyruvate oxidation following induction of the pyruvate dehydrogenase inactivator pyruvate dehydrogenase kinase 1 (Kim et al., 2006; Papandreou et al., 2006), combined with upregulation of glycolytic enzymes (Iyer et al., 1998) may boost neurogenesis.

### Systemic consequences of mild intermittent hypoxia

**Ventilatory response and respiratory facilitation.** Hypoxia sensing by the arterial chemosensors activates the sympathetic nervous system and induces a ventilatory response. IH elicits two primary forms of ventilatory plasticity: progressive augmentation of the HVR during IH and ventilatory long-term facilitation (vLTF) afterward (Puri et al., 2021). vLTF is triggered by activation of serotonergic neurons in the raphe nuclei (Xing et al., 2014) and modifications in the phrenic motor neurons (Nichols & Mitchell, 2021) increasing respiratory motor output and, thereby, minute ventilation (Pamenter & Powell, 2016). Recently it has been shown that vLTF following acute intermittent hypercapnic hypoxia in healthy humans partly depends on the peripheral chemoreflex via tonic carotid body activation (Vermeulen et al., 2020).

Arterial  $P_{CO_2}$ , arousal state (wake vs. sleep) and circadian rhythm modulate HVR and vLTF (Mateika et al., 2018; Puri et al., 2020). Early studies observed changes in HVR, whereas vLTF was absent during wakefulness when  $P_{CO_2}$  was not controlled (Khodadadeh et al., 2006; Mateika et al., 2004; Morelli et al., 2004). When  $P_{CO_2}$  is maintained above baseline, vLTF has been consistently shown in healthy individuals (Gerst et al., 2011; Harris et al., 2006; Lee et al., 2009; Panza, Puri, Lin, & Mateika, 2022; Syed et al., 2013; Tester et al., 2014; Wadhwa et al.,

2008). In contrast, IH with intermittent hypercapnia did not elicit vLTF when administered during sleep (Deacon et al., 2017), underscoring the importance of arousal state and circadian factors.

**Circadian effects and sleep.** Hypoxia responses of cells, tissues and organisms depend on timing relative to the external light–dark cycle and their endogenous circadian rhythms (Manella et al., 2020; Sandbichler et al., 2018). The circadian variations of respiratory responses to IH (Kelly et al., 2020) may contribute to detrimental consequences of hypoxic events in sleep apnoea. Chronic, severe IH during sleep, the central pathophysiological mechanism in sleep apnoea, results in sympathetic over-activation and metabolic and cardiovascular dysfunction. However, some reports suggest moderate forms of sleep apnoea may produce some benefit (Lavie & Lavie, 2009). In elderly adults ( $\geq 65$  years), moderate sleep apnoea (apnoeic index 20–40/h) was associated with a significant survival advantage, in comparison with age-, sex and ethnicity-matched national mortality data (Lavie & Lavie, 2009), exemplifying the importance of the hypoxic dose. When end-tidal  $\text{CO}_2$  was held 3 mmHg above baseline, IH ( $12 \times 2$ -min cycles at  $F_{\text{IO}_2} = 8\%$ , interspersed by 2 min normoxia) allowed a  $\sim 5$  cmH $_2$ O reduction of continuous positive airway pressure (CPAP) without loss of airflow in participants with OSA (El-Chami et al., 2017; Panza, Puri, Lin, Badr et al., 2022). When administered during wakefulness, IH improved upper airway function and increased CPAP adherence in OSA patients (Panza, Puri, Lin, Badr et al., 2022).

The potentially beneficial effects of mild IH may be counterbalanced by increased loop gain and arousal threshold, which can worsen sleep apnoea severity (Alex et al., 2019; Panza et al., 2019). Acute exposures to continuous hypoxia, e.g. at high altitude, can reduce sleep quality (total sleep time, sleep efficiency, deep sleep time) and increase arousals and periodic breathing in healthy individuals (Bloch et al., 2015), potentially by increasing ventilatory responsiveness to  $\text{CO}_2$  (Furian et al., 2022). Pre-existing cardiorespiratory conditions, e.g. chronic obstructive pulmonary disease (COPD), may exacerbate these effects, with nocturnal altitude exposures increasing central sleep apnoea's/hypopneas (Latshang et al., 2019). Further investigations will show if and how (e.g. hypoxic dose) IH might be used to treat sleep apnoea and other disorders; the impact of circadian variation and arousal state on sympathetic responses to hypoxia/hypercapnia are important considerations for IH applications.

**Sympathetic nervous system response and cardiovascular benefits.** Besides the ventilatory responses (see 'Ventilatory response and respiratory facilitation'), sympathetic nervous system activation and/or

parasympathetic inhibition (Meyer et al., 2019) mediate acute cardiovascular adjustments to hypoxia. Although both ventilatory and sympathetic chemoreflexes are induced by the peripheral chemoreceptors, they are triggered at different hypoxia thresholds (Keir et al., 2019; Prasad et al., 2020). The autonomic adjustments include increased heart rate, cardiac output, peripheral resistance and systemic arterial BP (Bartscher, Mallet et al., 2022; Mallet et al., 2021; Parati et al., 2015; Serebrovskaya et al., 2008), collectively supporting oxygen delivery to the brain and active tissues (López-Barneo et al., 2016; Serebrovskaya et al., 2008). Compensatory systemic vasodilatation mediated by hypoxia-induced NO release (Casey et al., 2010) is usually overcome by pressor mechanisms that raise BP during protracted hypoxia exposures (Veglio et al., 1999).

Intermittent hypoxia elicits less sympathetic activation than sustained hypoxia (Chacaroun et al., 2016) and hypoxia conditioning is thought to promote improved cardiovascular responses. Similar to endurance training, hypoxia conditioning may reduce the sympatho-excitatory effects of hypoxia (Miller et al., 2017) by decreasing systolic BP (Chacaroun et al., 2016; Panza, Puri, Lin, Badr et al., 2022) and attenuating vagal withdrawal and  $\beta$ -adrenoreceptor sensitivity (Bartscher et al., 2010). Decreased sympathoexcitation could explain decreased resting heart rates observed in cardiac patients after IH conditioning (Glazachev et al., 2021) and may be associated with the cardioprotection against infarction and arrhythmias reported in IH-conditioned dogs (Mallet et al., 2006; Manukhina et al., 2013). A systematic meta-analysis of studies on patients with cardiovascular diseases demonstrated reductions in resting heart rates (mean difference:  $-5.4$  beat/min), systolic BP (mean difference:  $-13.7$  mmHg) and diastolic BP (mean difference:  $-7.9$  mmHg) in hypertensive patients (Glazachev et al., 2021). These findings were recently confirmed in a small randomized controlled trial in 16 patients receiving CPAP treatment for OSA and hypertension (Panza, Puri, Lin, Badr et al., 2022), where 5 sessions/week of mild IH conditioning for 3 weeks significantly reduced systolic BP by about 10 mmHg (from  $142.9 \pm 8.6$  to  $132.0 \pm 10.7$  mmHg), while CPAP alone did not.

Nitric oxide plays pivotal roles in IH-induced adaptive mechanisms following hypoxia conditioning (Manukhina et al., 2006) and seems to contribute to the BP lowering effects of IH conditioning (Glazachev et al., 2021; Lyamina et al., 2011; Muangritdech et al., 2020). Moreover, IH conditioning-related priming of cellular energy monitors, e.g. adenosine and AMPK, activation of systemic anti-inflammatory signalling and augmentation of antioxidants (Almohanna & Wray, 2018; Bestavashvili et al., 2021) could contribute to the cardiovascular benefits of IH conditioning.

Hypoxia conditioning also protects the vascular endothelium against ischaemia–reperfusion injury; thus, IH ( $3 \times 4$ -min cycles at 11–12%  $F_{O_2}$ ) partially protected brachial artery endothelial function from a subsequent ischaemia–reperfusion insult in young and older adults (Jarrard et al., 2021; Stray-Gundersen et al., 2022). Like ischaemic preconditioning, the small bursts of ROS and NO produced by IH may activate ATP-sensitive potassium channels and upregulate antioxidant defences by suppressing platelet aggregation and leukocyte adherence to the endothelium (Clanton & Klawitter, 2001; Jugdutt, 2002; Ryou et al., 2008). Hypoxia conditioning represents, therefore, a promising strategy to protect the endothelium against ischaemia–reperfusion damage in humans.

Despite the clinical potential of hypoxia conditioning, it is important to emphasize that at higher doses IH may elicit detrimental maladaptations, resulting in increased BP and compromised NO bioavailability (Foster et al., 2009; Iturriaga, 2023; Stuckless et al., 2020).

The sympathetic nervous system and adrenal medulla comprise the sympatho-adrenomedullary axis, a crucial element in the response to mental stress where metabolism and cardiovascular function rapidly adjust to mount the ‘fight or flight’ response (Godoy et al., 2018). Thus, hypoxia also modulates mental stress regulation (see ‘Hypothalamic–pituitary–adrenal axis’ and ‘Mood and stress-related disorders’).

**Blood and circulating factors.** Hypoxia alters the blood composition, with the hypoxic dose importantly determining haematological adaptations (Tobin et al., 2020, 2022). Severe hypoxia may impair platelet function, including adhesion, spreading, aggregation, clot retraction and procoagulant activity, concomitant with aggravation of neutrophil-mediated inflammatory responses (Etulain et al., 2012). Hypoxia-induced erythropoiesis may underlie some performance and health benefits of high-altitude training (Rodriguez et al., 1999), including brain protection mediated, in part, by cerebral erythropoietin expression (Ehrenreich et al., 2022; Schuler et al., 2012).

Exposure to ambient hypoxia also changes blood viscosity and red blood cell behaviour (Raberin et al., 2022). Concomitant hypoxic vasoconstriction in the lungs and vasodilatation in most other vascular beds alters blood distribution throughout the body (Burtscher, Mallet et al., 2022). Among the components of the total blood volume, plasma volume decreases and total haemoglobin (Hb) mass increases in response to hypoxic exposure (Siebenmann et al., 2017). Spleen contractions in response to acute hypoxia contribute to increases of circulating erythrocytes and haemoglobin content (Richardson et al., 2008), possibly protecting

from severe hypoxia (Pernett et al., 2021). Initially, a decrease in total circulating plasma protein produces a reduction in plasma volume (Schlittler et al., 2021; Siebenmann et al., 2017), leading to increased circulating haematocrit and haemoglobin concentration. Subsequently, HIF-2-upregulated erythropoietin accelerates erythroid progenitor maturation and proliferation in the bone marrow (Haase, 2013). Consequently, circulating reticulocytes increase within a few days of hypoxia exposure, ultimately increasing Hb mass and, thereby, oxygen-carrying capacity (Schmidt, 2002). Since Hb mass expansion alone cannot compensate for the initial plasma volume reduction, total blood volume typically declines after intermittent altitude exposure (Siebenmann et al., 2017). Conversely, cardioprotective IH conditioning in dogs (Mallet et al., 2006) and IHHE improving cardio-respiratory fitness in elderly cardiac patients (Dudnik et al., 2018) increased neither haematocrit nor Hb mass; thus, IH exerts cardiac benefits independently of oxygen carrying capacity of the blood. Haematological adaptations may, however, mediate other IH-related benefits, e.g. exercise tolerance (Burtscher et al., 2004).

Besides haematological changes, the release of circulating factors, e.g. cytokines (Serebrovska et al., 2022) or myokines (van Meijel et al., 2023), and their signalling pathways are emerging as mechanisms contributing to IH outcomes, similar to or overlapping with systemic exercise signalling (Burtscher, Millet, Place et al., 2021).

**Nutrient supply, metabolic flexibility, appetite and body composition.** Hypoxia regulates appetite, metabolism and nutrient availability/utilization by altering circulating hormones, including ghrelin and insulin, as described during acute high altitude exposure (Aeberli et al., 2013; Spliethoff et al., 2013) and systematically reviewed for different hypoxia modalities (Matu et al., 2018). Conversely, diet and nutrients also determine adaptations to hypoxia and metabolic alterations (Lee et al., 2020). In sustained, severe hypoxia, reduced protein synthesis following ATP depletion may produce skeletal muscle atrophy (D’Hulst & Deldicque, 2017; Pesta et al., 2023).

Hypoxia-induced metabolic remodelling aims to maintain cellular energy levels by tapping into oxygen-independent alternative pathways, such as glycolysis. Accordingly, exposure to hypoxia acutely lowers serum glucose levels making hypoxia interventions interesting treatment strategies in obesity and metabolic diseases (Kayser & Verges, 2013; Netzer et al., 2015). While IH alone can improve glucose homeostasis in prediabetic patients (Serebrovska et al., 2017), exercising in hypoxia appears particularly suited to reduce metabolic risk factors (Haufe et al., 2008), e.g. by modulating glucose levels or transport (Soo et al., 2023), reducing weight in obese young adults (Kong et al., 2014) or improving

insulin sensitivity in type II diabetics (Mackenzie et al., 2011).

Hypoxia lowers fatty acid oxidation in skeletal muscle, with HIF-1 reducing acetyl-coenzyme A availability – and thereby fatty acid synthesis – by increasing pyruvate dehydrogenase kinase 1 (Taylor & Scholz, 2022). To compensate for decreased fatty acid oxidation, reductive glutaminolysis is upregulated in hypoxia (Metallo et al., 2011), conserving fatty acid for membrane synthesis. In contrast, an increased reliance on fatty acids for oxidative phosphorylation has been demonstrated in brain, kidney and liver of hypoxia-conditioned mice (Midha et al., 2023). In this study, adult mice subjected to chronic continuous hypoxia ( $F_{IO_2}$  = 8% or 12%) consumed less food and lost weight in a hypoxic-dose-dependent manner (Midha et al., 2023). These effects were associated with an acute decrease of plasma ghrelin (after 3 h of hypoxia) and transient increases of leptin (after 24 h) and ghrelin (after 1 week) at 8%  $F_{IO_2}$ . The first 24 h at 8%  $F_{IO_2}$  was further characterized by increased plasma insulin and decreased glucagon, changes promoting cellular glucose uptake in most tissues.

**Hypothalamic–pituitary–adrenal axis.** The hypothalamic–pituitary–adrenal (HPA) axis controls the release of glucocorticoids, including cortisol (de Kloet, 2013). HPA complements the sympatho-adrenomedullary response to mental stress (see ‘Sympathetic nervous system response and cardiovascular benefits’) and contributes to hypoxia adaptations (Bartscher, Niedermeier et al., 2022), while HPA dysregulation is associated with maladaptation and stress-related anxiety and depressive disorders. Hypoxia dose-dependently activates HPA (Bartscher, Niedermeier et al., 2022). Severe, prolonged hypoxia provokes persistent HPA activation with impaired glucocorticoid feedback inhibition, while mild to moderate hypoxia elicits the physiological biphasic glucocorticoid response (Rybnikova, Mironova et al., 2008). Moderate elevation of HPA reactivity to pathogenic psycho-emotional stress (corresponding to ‘mental stress’ in humans) with parallel hippocampal glucocorticoid receptor upregulation represents a key mechanism in the stress-protective effects of hypoxia conditioning and its therapeutic potential to prevent and correct stress-related depressive-like and anxiety pathology, as demonstrated in rats (Rybnikova, Mironova, Pivina, Tulkova, Ordyan, Nalivaeva et al., 2007). Accumulating evidence suggests a robust, context-dependent interaction between glucocorticoids, their receptors and HIFs in hypoxia (Bartscher, Niedermeier et al., 2022; Rybnikova & Nalivaeva, 2021).

**Mood and stress-related disorders.** Mental stress and hypoxic stress induce substantially overlapping

responses (Bartscher, Niedermeier et al., 2022), which are linked to various signalling pathways, e.g. sympatho-adrenomedullary axis-related adrenaline and noradrenaline and HPA-associated glucocorticoids. Hypoxia exposure thereby influences mental stress responses and associated diseases, and severe acute hypoxia can evoke anxiety symptoms including panic attacks as well as symptoms of depression (Bartscher, Niedermeier et al., 2022). Conversely, hypoxia conditioning approaches exerted antidepressant effects (Kushwah et al., 2016; Rybnikova, Mironova, Pivina, Tulkova, Ordyan, Vataeva et al., 2007; Rybnikova, Samoilov et al., 2008) and were effective against post-traumatic stress disorder in animal models (Ding et al., 2019; Manukhina et al., 2018; Manukhina et al., 2020). These hypoxia conditioning benefits have been linked to adaptive improvements in HPA and autonomic responses, better glucocorticoid feedback signalling (Rybnikova & Samoilov, 2015), improved mitochondrial functions (Bartscher, Niedermeier et al., 2022) and reduced inflammation (Gangwar et al., 2019), thereby opposing development of stress-related diseases. Moreover, both stress-related psychiatric disorders and hypoxia exposure are characterized by changes of tryptophan metabolism, and thereby of serotonin production and tryptophan degradation through the kynurenine pathway (Bartscher, Niedermeier et al., 2022). The regulation of tryptophan metabolism by oxygen availability may be an important mechanism and future therapeutic target for psychiatric diseases.

#### **Cerebral blood flow, cognition and dementia prevention.**

Depending on its severity, hypoxia impairs neurological functions (Aboouf et al., 2023) and may cause loss of consciousness and permanent brain injury (Li et al., 2018). Moderately decreased blood oxygen content elicits compensatory increases in cerebral blood flow (Hoiland et al., 2016), while reductions in arterial  $P_{CO_2}$  (Carr et al., 2021) lower cerebral blood flow. Cerebral oxygen delivery thus is influenced by hypoxia-induced hyperventilation and resulting hypocapnia. Improved cerebral blood flow in hypoxia can compensate for reduced cerebral oxygen availability (Hoiland et al., 2016), but severe hypoxia lowers cerebral blood flow (Chen, Qi et al., 2014; Willie et al., 2014) and increases blood–brain barrier permeability (Bailey et al., 2022). ‘Functional hypoxia’ (see Table 1) can occur in the brain as a consequence of motor-cognitive challenges and promotes beneficial cerebral adaptations resulting in increased brain capacities (Butt et al., 2021; Ehrenreich et al., 2023; Wakhloo et al., 2020).

Hypoxia conditioning has been suggested to protect cerebrovascular function and together with its beneficial effects on systemic cardiovascular risk factors may be a

powerful preventive treatment for dementias (Manukhina et al., 2016). Microvascular angiogenesis and improved cerebral microcirculation possibly mediate beneficial effects of hypoxia conditioning, albeit in a narrow therapeutic window; while mild hypoxia ( $F_{IO_2} = 15\text{--}21\%$  for less than 2 h/day) might not be sufficient to stimulate angiogenesis;  $F_{IO_2}$  below 10% or prolonged or high-frequency hypoxia exposures can be detrimental (Guan, Gu et al., 2023; Guan, Liu et al., 2023).

Preclinical studies in rodents laid the groundwork for clinical testing of IHE and IHHE programmes for neurological diseases. In a rat model of Alzheimer's disease produced by injection of toxic amyloid  $\beta$  fragments into the basal magnocellular nuclei, an IH programme attenuated the decline in cerebral blood flow (Mashina et al., 2006), increased systemic NO production and preserved memory function (Manukhina et al., 2008). In transgenic mice modelling Alzheimer's disease, a 21-day IH programme improved memory function and increased cerebrocortical erythropoietin and brain-derived neurotrophic factor (Ryou et al., 2021). In rats abruptly separated from ethanol after 5 weeks on a high-ethanol diet, a 4-week IH programme nearly abolished neuro-behavioral signs of ethanol withdrawal, attenuated ROS formation and mitochondrial permeability transition in cerebrum and cerebellum, and sharply lowered neuronal apoptosis (Ju et al., 2012; Jung et al., 2008).

Recent clinical pilot studies demonstrate neurocognitive benefits of IHE and IHHE programmes in patients in the early stages of cognitive impairment. In elderly adults (64–92 years) with mild–moderate dementia, adding IHHE sessions alternating 10–14%  $F_{IO_2}$  and 30–40%  $F_{IO_2}$  to a multimodal training intervention improved Dementia Detect and Clock Drawing cognitive test scores and functional exercise capacity vs. multimodal training alone (Bayer et al., 2017). In older adults (51–74 years) with mild cognitive impairment, an IHHE programme alternating 12% and 33%  $F_{IO_2}$  improved global cognitive performance on the Montreal Cognitive Assessment Test (Serebrovska et al., 2019). In elderly adults ( $69 \pm 3$  years) with amnesic mild cognitive impairment, an IHE programme alternating 5 min hypoxia (10%  $O_2$ ) and 5 min room air breathing augmented hypoxia-induced cerebral vasodilatation, increased cerebral tissue oxygen saturation and improved mini-mental status examination and digit span scores (Wang et al., 2020). A recent study further suggests that IHHE may specifically upregulate cytokines capable of triggering cellular adaptive reprogramming, leading to therapeutic effects against cognitive dysfunction and neuropathological changes in the progression of Alzheimer's disease (Serebrovska et al., 2022). Importantly, in all these studies the IHE and IHHE protocols were well tolerated by the subjects and produced no adverse events or outcomes.

**Pain and opioids.** Hypoxia modulates pain sensation, with central roles of HIFs, inflammatory pathways and their interplay. HIF-1 $\alpha$  signalling increases synthesis of NOX2 and NOX4 (Diebold, Petry et al., 2010; Yuan et al., 2011), which are involved in the development of neuropathic pain (Kallenborn-Gerhardt et al., 2012). Increased ROS formation due to IH (Lavie, 2005) may also modulate pain sensitivity since ROS are associated with the pronociceptive function of NOX4 and activation of NF- $\kappa$ B target genes, such as those encoding TNF- $\alpha$ , pro-inflammatory interleukins and cyclooxygenase 2 (COX 2) (Lavie, 2005; Zhang & An, 2007), and mediate sensitization of peripheral nociceptors.

In contrast, mild IH may blunt the systemic inflammatory response and pain sensitivity. For example, IH conditioning (four daily 5-min exposures to 10%  $F_{IO_2}$  for 14 days) reduced serum TNF- $\alpha$  and IL-4 levels, while increasing the interferon- $\gamma$  response in adult men (Serebrovska et al., 2011). Mice with HIF-1 $\alpha$ -deficient peripheral primary sensory neurons demonstrated bimodal pain regulation: nociceptive responses to acute cold, heat, inflammatory and ischaemic stimuli were intensified, while chronic neuropathic pain was reduced (Kanngiesser et al., 2014). Similarly, inhibition of HIF-1 $\alpha$  attenuated pain and inflammation in a mouse model of chronic post-ischaemic pain (Hsiao et al., 2016). Acute pain responses in HIF-1 $\alpha$ -deficient neurons were characterized by increased calcium fluxes and reduced electrical activation thresholds (Kanngiesser et al., 2014), suggesting that HIF-1 $\alpha$  signalling keeps acute hypersensitive responses in check but may be involved in chronic pain pathogenesis. Further supporting these divergent effects of HIF-1 $\alpha$  are findings that chronic IH (alternating 90 s exposures to 10% oxygen and normoxia, 8 h/day for several weeks) blunted pain responses in rats (Wu et al., 2015). Concomitantly, cerebrocortical opioid receptor expression was upregulated by hypoxia (Wu et al., 2015), highlighting the crosstalk between opioid receptors and HIFs and its role in pain perception, and furnishing some explanation to the ongoing debate of altered sensitivity to opioid drugs in OSA (Brown et al., 2006; Lam et al., 2016).

The development of tolerance to severe hypoxia by hypoxia conditioning requires the endo-opioid system, as the opioid receptor antagonist naloxone blocks hypoxia conditioning benefits (Burtscher, Maglione et al., 2021). Among the opioid receptors, the  $\delta$ -opioid receptor appears to be the key mediator of hypoxia conditioning. Hypoxia conditioning upregulates both the endo-opioid enkephalin and its preferential receptor, the  $\delta$ -opioid receptor (Gao et al., 2012; Ma et al., 2005), and this regulation likely is mediated by HIF-1 (Schoos et al., 2019). The selective  $\delta$ -opioid receptor antagonist naltrindole abrogated the protective effects of a 20-day IH programme on dog myocardium (Estrada et al.,

2016).  $\delta$ -Opioid receptor signalling also protects from different hypoxic brain injuries and neurological diseases (Bissonnette et al., 2013; Burtcher et al., 2018; Chen, Li et al., 2014; Zhang et al., 2000), probably mediated by  $\delta$ -opioid receptor-dependent improvements of mitochondrial functions (Burtcher et al., 2018) and proteostasis (Burtcher, Syed et al., 2021).

Although mild IH may be a non-pharmacological approach to modulate pain, HIF-1 may also promote chronic pain, and hypoxia can interfere with various pain-related pathways, e.g. those involving the opioid system and NF- $\kappa$ B. Thus, more research is needed to establish IH protocols that strike the balance between effectiveness and safety in specific populations.

**Exercise tolerance, fatigue and motor function.** Whether IH combined with exercise is more effective than normoxic exercise remains unclear (Lizamore & Hamlin, 2017). However, even without concomitant exercise, IHE (Lizamore & Hamlin, 2017) and IHHE (Behrendt et al., 2022) have the capacity to improve metabolic profiles and increase exercise tolerance at submaximal intensity in non-athlete/sedentary populations, although the effects at maximal intensity and in athletes are less clear (Bergeron et al., 2012; Millet et al., 2010). This improvement is likely due to shared adaptive mechanisms of hypoxia and exercise, which mediate improvements in exercise tolerance, fatigue resistance and motor functions when appropriate hypoxic doses and exercise protocols are combined.

Exercising in hypoxic atmospheres increases the reliance on anaerobic ATP production causing metabolic by-products such as blood lactate and hydrogen ions to accumulate (Katayama et al., 2010). Muscles fatigue in hypoxic and acidic environments, so additional motor units must be recruited to maintain mechanical output. Muscle fibre recruitment can be detected using surface electromyography (EMG) (Fernández-Lázaro et al., 2020), which measures the electrical activity produced in active musculature. Surface EMG was increased under hypoxic vs. normoxic conditions both during acute resistance (Scott et al., 2017) and endurance exercise (Amann et al., 2007). It is thought that the early fatigue of type I oxidative fibres due to inadequate oxygen supply necessitates the recruitment of additional high-threshold type II fibres (Manimmanakorn et al., 2013). This shift in fibre recruitment hastens fatigue onset and intensifies perceived exertion during exercise (Amann et al., 2007), ultimately imposing greater mechanical loading and workload on the type II muscle fibres during exercise. The increased workload on these fibres likely results in adaptation and subsequent improvements in muscular performance (Manimmanakorn et al., 2013).

Upregulation of anaerobic ATP production also can increase muscle strength (Manimmanakorn et al., 2013) and jump performance (Coşkun et al., 2022). Hypoxia-induced upregulation of the metabolism-monitoring kinase AMPK activates glucose transport in human skeletal muscle (Krook et al., 2004) and promotes mitochondrial remodelling in skeletal muscle by stimulating PGC-1 $\alpha$  gene expression (Spaulding & Yan, 2022). In addition, HIF-2 contributes to the PGC-1 $\alpha$ -mediated switch towards more oxidative (slow-twitch) muscle fibres (Rasbach et al., 2010). IH may be particularly efficient in eliciting these adaptations, since repeated hypoxic exposures cause HIF-1 down-regulation that may be necessary for long-term exercise adaptations (Lindholm & Rundqvist, 2016). In addition, IH-induced improvements in exercise tolerance have been attributed to other mechanisms already discussed, including increased ventilation and oxygen saturation during exercise, improved microvascular endothelial function, reduced sympathetic activity, increased total haemoglobin concentration, and lung diffusion capacity (Burtcher et al., 2004, 2009; Haider et al., 2009; Shatilo et al., 2008).

IH may improve exercise tolerance in various populations, including healthy older individuals, and those with coronary artery disease, metabolic disease or COPD (Bestavashvili et al., 2021; Burtcher et al., 2004; Dudnik et al., 2018; Glazachev et al., 2017; Haider et al., 2009). However, the outcomes of studies vary, with different effects observed on aerobic and anaerobic exercise tolerance, depending on the specific IH protocol used and the population studied (Burtcher et al., 2010).

Targeting hypoxia responses is gaining attention as a potential treatment strategy for numerous neurological movement disorders including stroke, Parkinson's disease (Burtcher, Syed et al., 2021; Lestón Pinilla et al., 2021) and Huntington's disease (Burtcher, Maglione et al., 2021). The main benefits of hypoxia interventions are thought to be reduced inflammation and enhanced antioxidant capacities, mitochondrial efficiency and neuronal resilience (Burtcher, Mallet, Burtcher et al., 2021). IH is also considered a potential adjuvant to improve ambulation following spinal cord injury (Tan et al., 2020; Trumbower et al., 2012). For instance, walking speed and walking endurance increased by 15% and 36%, respectively, after 5 days of acute IH combined with overground walking training in persons with chronic, partial spinal cord injury (Hayes et al., 2014). The precise mechanisms underlying the improved neuromotor function are yet to be fully elucidated, but brain derived neurotrophic factor-induced facilitation of excitatory synaptic transmission to motoneurons may play a role (Tan et al., 2020).

## Conclusions

Ambient hypoxia elicits complex physiological responses and adaptive mechanisms. In addition to the direct risk of hypoxic injury, maladaptation to hypoxia raises the risks of adverse outcomes and diseases. On the other hand, successful hypoxia adaptations can increase resilience and health, and the potential benefits of hypoxia conditioning approaches have been demonstrated in many domains, with important clinical applications; e.g. BP reduction in hypertensive people (Panza, Puri, Lin, Badr et al., 2022), preservation of cognitive function in older adults (Bayer et al., 2017) or promotion of weight loss in overweight individuals (Serebrovska et al., 2017). Protocols

using mild IH have emerged as particularly promising for these purposes. Whether IH is beneficial or detrimental depends on the hypoxic dose, individual predispositions, physical activity, medications and many other factors which limit comparability of studies and generalization to other conditions or populations. Since hypoxia responses are so diverse, distinct mechanisms and aspects have been emphasized in different research fields, prompting the use of divergent experimental approaches and designs, protocols and primary study outcomes. Together with the unharmonized terminology used to describe hypoxia exposures and protocols (Panza et al., 2023), this diversity impedes study comparisons and the assessment of efficacy and safety.

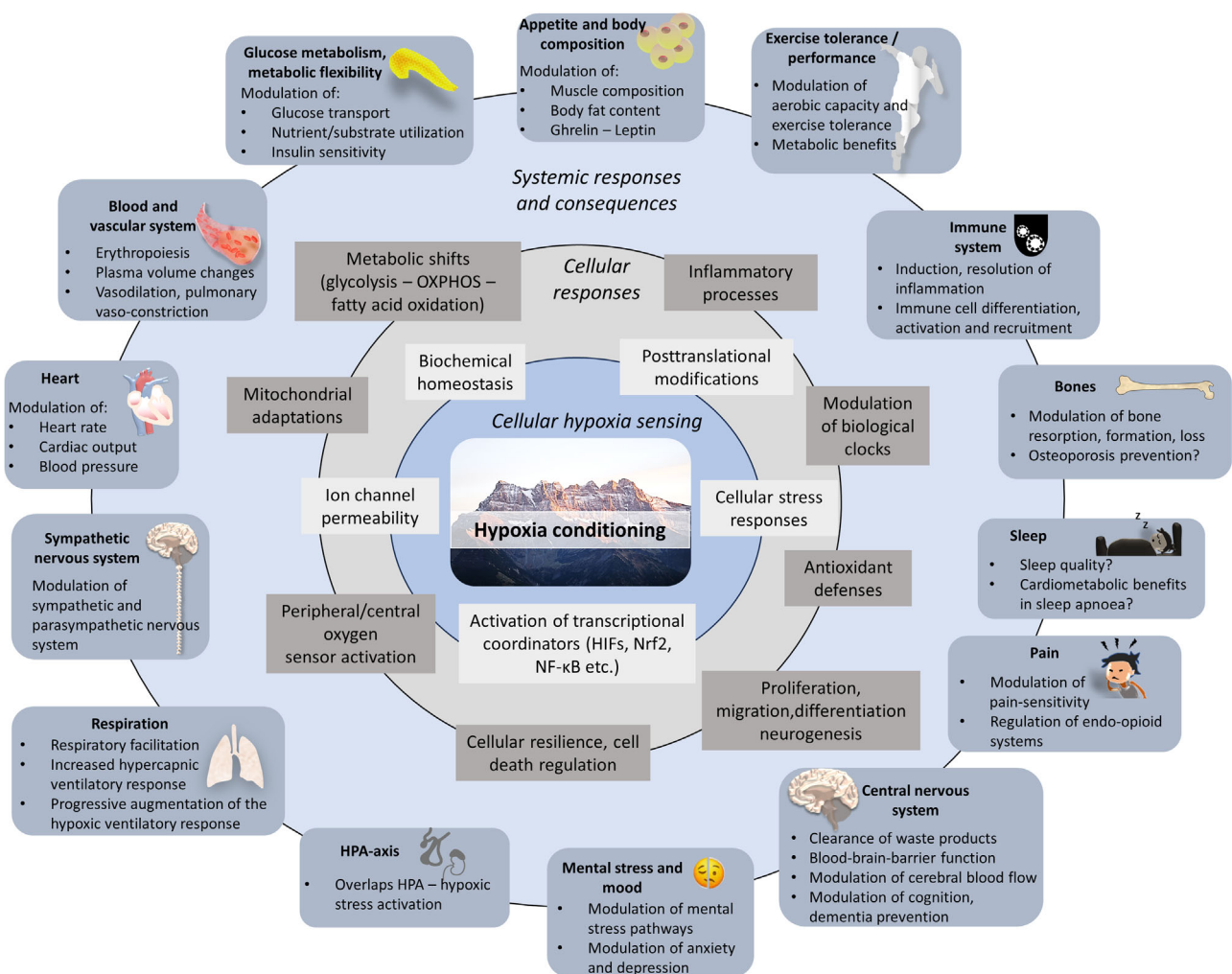


**Figure 3. Potential mechanisms underlying the beneficial effects of hypoxia conditioning, from cellular sensing of hypoxia to responses to hypoxia at the cellular level, to systemic responses to hypoxia**

Hypoxia changes many biochemical and molecular processes in cells and triggers complex systemic responses. While uncontrolled hypoxia may elicit a plethora of adverse health consequences, the control of hypoxia responses by hypoxia conditioning may be exploited to induce hormetic adaptation (see text) to counteract hypoxic injury and pathological developments and instead produce health benefits. HIF, hypoxia-inducible factor; HPA, hypothalamic–pituitary–adrenal gland axis; NF-κB, nuclear factor-κB, Nrf2, nuclear factor erythroid 2-related factor 2.

Much remains to be optimized to fully harness the potential of hypoxia conditioning. It is essential that the different basic and clinical research fields harmonize their understanding and communication of hypoxia conditioning research, differences in adaptation to continuous hypoxia vs. IH be better described, and individually optimal hypoxic doses systematically established. It will be especially important to establish organ/function-specific hypoxic dose thresholds that allow the eliciting of specific benefits, without triggering maladaptation in other organs. For example, a severe IH protocol (90 s cycles of 10% and 21% oxygen for 8 h/day for several weeks; Wu et al., 2015) reduced pain responses in rats, but similar IH protocols elicit maladaptive sympathoexcitation and cardiovascular remodelling in rodents (Navarrete-Opazo & Mitchell, 2014).

We hope that this summary of mechanisms mediating the many benefits of IH (Fig. 3) will spur further progress in the field. Harmonization of terminologies and systematic assessments of studies from different applications, taking into account the different studied conditions and populations, are essential to consolidate the understanding of hypoxia conditioning benefits and risks. In addition, several practical questions related to hypoxia conditioning remain, including: how long do respective benefits persist after concluding hypoxia conditioning? Once the improvements wane, can abbreviated hypoxia conditioning programmes restore them? Do medications or dietary supplements, e.g.  $\beta$ -adrenoceptor antagonists or antioxidants, interfere with hypoxia conditioning outcomes, as shown for cardio- (Mallet et al., 2006) and cerebroprotection (Jung et al., 2008) in animals? Lastly, which conditioning protocols are most effective for different applications in prevention, rehabilitation and performance enhancement (including comparisons of IHE and IHHE)?

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## Additional information

### Competing interests

The authors declare no competing interests.

### Author contributions

J.B. and T.C. were responsible for the concept of the article. J.B. wrote the first draft of the article. All authors contributed to drafting the article or critically revising it for important intellectual content. J.B., G.P. and R.T.M. coordinated the finalization of the draft by integrating the inputs of all authors. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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### Keywords

cardiovascular diseases, cellular stress responses, intermittent hypoxia conditioning, mitochondria, neurological disorders, oxygen sensing

### Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

### Peer Review History