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The interplay of hypoxic and mental stress: Implications for anxiety and depressive disorders

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ABSTRACT

Adequate oxygen supply is essential for the human brain to meet its high energy demands. Therefore, elaborate molecular and systemic mechanism are in place to enable adaptation to low oxygen availability. Anxiety and depressive disorders are characterized by alterations in brain oxygen metabolism and of its components, such as mitochondria or hypoxia inducible factor (HIF)-pathways. Conversely, sensitivity and tolerance to hypoxia may depend on parameters of mental stress and the severity of anxiety and depressive disorders. Here we discuss relevant mechanisms of adaptations to hypoxia, as well as their involvement in mental stress and the etiopathogenesis of anxiety and depressive disorders. We suggest that mechanisms of adaptations to hypoxia (including metabolic responses, inflammation, and the activation of chemosensitive brain regions) modulate and are modulated by stress-related pathways and associated psychiatric diseases. While severe chronic hypoxia or dysfunctional hypoxia adaptations can contribute to the pathogenesis of anxiety and depressive disorders, harnessing controlled responses to hypoxia to increase cellular and psychological resilience emerges as a novel treatment strategy for these diseases.

1. Introduction: the fear of suffocation

The fear of suffocation is rooted deeply in the human mind. While fundamental for survival, it can become a debilitating symptom of anxiety and depressive disorders, including panic disorders. Accordingly, the suffocation false alarm theory by DF Klein (Klein, 1993) postulates that spontaneous panic attacks may generally be a result of the (inappropriate) activation of "an evolved physiologic suffocation alarm system".

Respiratory symptoms like shortness of breath and a feeling of suffocation are common symptoms of anxiety disorders, which furthermore are frequent comorbidities of respiratory diseases (Maurer et al., 2008). Conversely, mood changes and panic attacks due to low oxygen supply, such as at high altitude, are also well-recognized (Bahrke and Shukitt-Hale, 1993). Humans dispose of elaborate systems to detect dysregulations of oxygen supply, both on the cellular and on the systemic level. It is not surprising that the involved pathways overlap substantially with molecular and systemic mechanisms related to anxiety and depressive disorders, as well as to chronic stress, a major risk factor to develop these disorders. Hereafter, the term anxiety and depressive disorders will be used to collectively describe depressive disorders, anxiety or fear-related disorders (including Generalized anxiety disorder, 6B00), and disorders specifically associated with stress (including Post traumatic stress disorder, 6B40) following the International classification of diseases (ICD-11) (WHO, 2018). These disorders are among the most important contributors to the global burden of disease within the group of "Mental, behavioral or neurodevelopmental disorders" of the ICD-11 (WHO, 2018; Whiteford et al., 2013).

Emerging evidence indicates that the modulation of hypoxia adaptations may be a novel, non-pharmacological and safe therapeutic strategy for related diseases. Many intervention approaches have already been shown to have great potential for athletic performance

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enhancement and prevention of a number of pathological conditions and thus are ripe to be explored in the context of anxiety and depressive disorders.

The aim of the present article is to summarize the complex interplay between hypoxia, mental stress, anxiety and depressive disorders. To this end, epidemiological evidence for a role of hypoxia in the pathogenesis of these diseases will be discussed. Physiological and anatomical overlaps of sensing and adaptations to hypoxia with anxiety and depressive disorders are presented with a special focus on central mechanisms of stress responses as well as the sympathetic nervous system and HPA (hypothalamic–pituitary–adrenal)-axis. In addition, an overview on the current knowledge on the reciprocal relationship of mental stress, anxiety states and traits as well as depression-linked conditions on oxygen physiology and in particular on responses to hypoxia will be provided. Finally, we highlight how systemic and molecular mechanisms of hypoxia adaptation may provide protection for anxiety and depressive disorders.

Key questions

→Are physiological responses to hypoxia linked with mechanisms related to chronic mental stress, anxiety and depressive disorders?

→Can the modulation of hypoxia adaptations be harnessed as treatment strategies for these disorders?

2. Chronic stress, anxiety, and depressive disorders

Given the presence of multiple stressors in our lives, both an efficient coping of the human organism with these stressors and effective recovery from stress is important to avoid negative consequences, an ability termed resilience. Stress is often referred to as allostatic load, defined as the "wear-and-tear on the body and brain promoting ill health, involving not only the consequences of stressful experiences themselves, but also the alterations in lifestyle that result from a state of chronic stress" (McEwen and Gianaros, 2010). Physiological stress regulation (or achievement of allostasis) is complex and involves a variety of systems (McEwen, 1998).

While acute responses are desirable to protect and to best prepare the human body to deal with the stressor (McEwen, 1998), it is the chronic exposure to stress and insufficient recovery from stressors that play an important role in the development of anxiety and depressive disorders (de Kloet et al., 2005). If experienced over a longer period of time without sufficient recovery, the term chronic stress is used (Radley et al., 2015). Chronic stress is an important factor in the pathogenesis of many mental, behavioral and neurodevelopmental disorders, including anxiety and depressive disorders (de Kloet et al., 2016; McGonagle and Kessler, 1990; Sandi and Richter-Levin, 2009). Similar to stress responses, anxiety is a life-sustaining physiological reaction in order to cope adequately with difficult and/or dangerous situations. It increases alertness, caution and mental and physical concentration. Anxiety is also the primary symptom of disorders such as generalized anxiety, panic disorders or specific phobias and can occur in post-traumatic stress disorders (PTSD) or depressive disorders. High anxiety traits are also risk factors for the development of depression (Sandi and Richter-Levin, 2009). In the following, we firstly aim to describe relevant physiological pathways and secondly aim to connect these pathways to findings on dysregulations in people with anxiety and depressive disorders.

2.1. Neural pathways and the sympatho-adrenomedulary axis

Stressors, such as pain or hypoxia, are detected by specific sensors that induce a stress response. The sympatho-adrenomedulary (SAM) axis mediates fast but often short term effects (Godoy et al., 2018). SAM-effects are mediated by catecholamines, with epinephrine and norepinephrine (secreted from the adrenal medulla and sympathetic nerves) activating sympathetic signaling pathways that amongst others modulate the function of blood vessels, glands, visceral organs and smooth muscles and leads to increased heart rate, dilated pupils, and elevated blood pressure (Tank and Lee Wong, 2015). This enhances alertness and the metabolic and cardiovascular changes prepare the organisms for exercise or "fight or flight" situations (Godoy et al., 2018). In addition, noradrenergic brain regions, in particular the locus coeruleus, are important players in acute stress regulation, also due to their regulation of the hypothalamic-pituitary-adrenal (HPA) axis (Godoy et al., 2018). The chronic activation of the locus coeruleus is also involved in pathological consequences of stress, as discussed below. The complex interplay of the central stress response regulation has been reviewed by Godoy and colleagues (Godoy et al., 2018) and also involves in particular the nucleus of the solitary tract, pre-frontal cortex (prelimbic area) and limbic structures, including the amygdala and hippocampus.

2.2. The hypothalamic-pituitary-adrenal (HPA) axis, glucocorticoids, and cortisol

The HPA axis is initiated by the paraventricular nucleus of the hypothalamus. Compared to the SAM axis, effects along the HPA axis take longer to appear (minutes), but also last for a longer duration (Sapolsky et al., 2000). Stressors induce the release of oxytocin, vasopressin, and corticotropin-releasing factor (CRF). The latter stimulates the anterior pituitary to produce adrenocorticotropic hormone (ACTH) (Vale et al., 1981), which – delivered by the blood stream to the adrenal gland – leads to the release of glucocorticoids, the most prominent being cortisol (corticosterone in rodents) (De Kloet, 2013). Cortisol enables the organism to deal more efficiently with stressful situations (e.g., by increasing glucose concentration in the blood), but at the same time exerts a negative feedback loop effect on both the hypothalamus and pituitary to avoid over-production of corticotropin-releasing and adrenocorticotropic hormone. Glucocorticoid and mineralocorticoid receptors are parts of the negative feedback loops (de Kloet et al., 2005).

The regulation mechanisms of the HPA and SAM axes synergistically enhance dealing with acute stress and are well balanced in health (Godoy et al., 2018). Chronic stress, however, can disrupt this balance and thereby can contribute to the pathogenesis of anxiety and depressive disorders.

2.3. Stress regulation in the context of anxiety and depressive disorder development

Dysfunctional stress regulation in the context of anxiety and depressive disorder development is best understood for the HPA axis. Various disturbances of the HPA axis were reported in people with anxiety and depressive disorders, including increased levels of CRF and ACTH (Holsboer, 2003), increased levels of cortisol (Vreeburg et al., 2009) and other glucocorticoids (Spijker and van Rossum, 2012), increased size of adrenal glands (Rubin et al., 1995), as well as increased activity of the pituitary, specifically associated with depressive disorders (Pariante and Lightman, 2008). Chronic mental stress leads to impaired control of glucocorticoid secretion by the HPA axis and may result in elevated cortisol levels. High cortisol levels are also characteristic for depression (Carroll et al., 1976) and they have been reported to be resistant to the normal negative feedback regulation of glucocorticoids by the HPA axis (Carroll et al., 1968). Glucocorticoid resistance further modulates the immune system and can induce a proinflammatory state (Perrin et al., 2019; Silverman and Sternberg, 2012).

Increased glucocorticoid levels may be neurotoxic, in particular in brain regions importantly linked to anxiety and depressive disorders, such as the hippocampus (Sapolsky, 1996). Accordingly, reduced hippocampal volume was reported in people with prolonged depressive disorders (Sapolsky, 1996). In rats, glucocorticoids were shown to decrease neuronal excitability and brain-derived neurotrophic factor (BDNF) levels (Schaaf et al., 1998). Lower expression of BDNF is also a hallmark of depressive disorders (Dwivedi, 2009).

Notably, beside a hyperactivation of the HPA axis and increased glucocorticoid levels, a *reduced* glucocorticoid production caused by adrenal fatigue can be observed in various disorders, e.g., post-traumatic stress disorder, atypical/seasonal depression, or chronic fatigue syndrome (Agorastos and Chrousos, 2021).

With regard to SAM, there is evidence that chronic stress may lead to an enhanced expression of noradrenaline (Ulrich-Lai and Herman, 2009). Findings in animal models suggest a connection with anxiety disorders and the dysregulation of the locus coeruleus due to chronic stress (Morris et al., 2020). Chronic stress might be associated with an increased reactivity of the locus coeruleus at the occurrence of subsequent stressors. This effect has been linked to pathological anxiety-like behaviors in rodents (Morris et al., 2020). Persistent activity of the locus coeruleus is discussed in the pathophysiology of posttraumatic stress disorder (Southwick et al., 1999). Effects of chronic stress also include an up-regulation of the amygdala baseline activity in rats (Kavushansky and Richter-Levin, 2006). The amygdala is an important structure in the emotional and motivational drivers of human behavior and likely involved in the etiopathogenesis of anxiety disorders (Janak and Tye, 2015).

In the following section, we summarize how hypoxic stress is sensed and how the organism deals with it.

Key points
→ Acute mental stress responses can increase management of stressful situations, while chronic mental stress can be detrimental
→ The catecholamine-mediated sympatho-adrenomedulary (SAM) axis mediates fast but often short term mental stress responses
→ The hypothalamic-pituitary-adrenal (HPA) axis mediates longer-lasting mental stress responses via the release of glucocorticoids, including cortisol
→ Chronic mental stress interferes with the coordination of SAM and HPA axes and is associated with anxiety and depressive disorders

3. Oxygen sensors and adaptations/maladaptations to hypoxia

A variety of pathological conditions can cause regional hypoxia (including stroke or cancer) or impaired oxygen supply to tissues (e.g. respiratory diseases). Here, we focus on environmental hypoxia, as it occurs for example in high altitudes, where the reduced barometric pressure leads to reduced inspired oxygen-levels (hypobaric hypoxia). In laboratory environments, hypoxia can be simulated in various ways, besides the artificial reduction of the barometric pressure, also by reducing the concentration of oxygen using normobaric hypoxic chambers or tents or modulating inspired oxygen concentrations through face masks (both approaches resulting in normobaric hypoxia).

3.1. Molecular oxygen sensing, hypoxia adaptations and metabolic consequences

Oxygen-levels are sensed by a number of molecular mechanisms in the cell triggering physiological responses during hypoxia in order to increase either oxygen supply or reduce oxygen demand. Biochemical reactions requiring oxygen will be initially affected, in particular the reactions catalyzed by NADPH oxidase, nitric oxide synthases (NOS) and heme oxygenase (Terraneo and Samaja, 2017). In addition, lower oxygen availability reduces oxidative phosphorylation at mitochondria (Burtscher et al., 2022). All these effects result in the formation of reactive oxygen species (ROS), important signaling molecules for hypoxia adaptations. They are also involved in the induction of another line of responses to hypoxia that is mediated by powerful transcription factors, most notably hypoxia inducible factors (HIFs), nuclear factor erythroid 2-related factor 2 (NRF2) and NF-κB. Their involvement in human hypoxia adaptations has recently been reviewed (Burtscher et al., 2022; Pham et al., 2021). Here, a short summary on the effects of HIFs is provided, with particular emphasis on aspects that play central roles also in chronic stress, anxiety and depressive disorders.

α-subunits of HIFs are the ubiquitous HIF-1α and tissue-specific HIF-2α and HIF-3α (Pan et al., 2007). In normoxia, the oxygen-dependent enzymatic modification by prolyl hydroxylases (PHDs) and subsequent polyubiquitination by the von Hippel-Lindau (VHL) protein effectuate the continuous degradation of these HIF α-subunits. In hypoxia, the α-subunits stabilize, heterodimerize with β-subunits and activate hypoxia response elements (HRE) to orchestrate a plethora of adaptations to reduced oxygen levels, including the regulation of proteins mediating oxygen supply to tissues and antioxidant defense (Ratcliffe et al., 1998).

HIFs are also involved in metabolic remodeling, that includes the upregulation of glycolytic pathways, leading to decreased oxygen utilization by oxidative phosphorylation and increased glycolysis and associated lactate production (Burtscher and Millet, 2021). Hypoxia is further associated with inflammation and this interaction is bidirectional: inflammation activates HIF pathways – even in the absence of hypoxia - (McGettrick and O'Neill, 2020) but HIFs also modulate inflammatory signaling (Pham et al., 2021). Accordingly, severe hypoxia has been demonstrated to upregulate markers for neuroinflammation, such as microglial inflammatory gene expression in rats (Smith et al., 2013).

Taken together, the metabolic remodeling following hypoxia leads to cross-modulation of hypoxia-adaptations and inflammatory processes that are protective against acute hypoxic stress. But these effects can also result in maladaptations and neuroinflammation, which are integral in the pathogenesis of many neuropsychiatric diseases, including anxiety and depressive disorders.

3.2. Systemic adaptations to hypoxia

Peripheral chemoreceptors (mainly the carotid bodies) are in charge for monitoring arterial blood oxygenation (PO_2) levels. They initiate a hypoxic ventilatory response (HVR) that increases ventilation and sympathetic activity, for example leading to increased heart rate (Marshall, 1998a).

While hyperventilation improves oxygenation, it also results in hypocapnia (i.e., reduced arterial pressure of CO_2). CO_2 is an intracellularly generated metabolic byproduct, which is conveyed by the blood circulation to the lungs and exhaled to the ambient air. Increasing CO_2 levels stimulate the respiratory drive, decrease blood pH and the affinity of hemoglobin. The arterial partial pressure of CO_2 ($PaCO_2$) is maintained at a very narrow range. Various chemosensory feedback mechanisms ensure the maintenance of homeostasis despite changing environmental conditions (e.g., hypoxia, hypercapnia). Respiratory chemosensitivity represents an important ability of the brain to detect changes in CO_2 and to initiate regulatory processes (e.g., via changes in the breathing activity) (Huckstepp and Dale, 2011). Reflex chemostimulation by CO_2 causes dyspnea (shortness of breath). Only small elevations in the $PaCO_2$ provoke large increases in breathing (hypercapnic ventilatory response), e.g., 1 mmHg increase in the $PaCO_2$ results in a 20–30% increase in ventilation. Central chemoreceptors are particularly important for this response (Nattie, 1999; Wilson and Teppema, 2016), but recent research suggests that tonic carotid activity also impinges on the centrally mediated hypercapnic ventilatory response (Forster and Smith, 2010). Carotid body chemosensing activates the nucleus tractus solitaries (NTS) and/or through NTS projections to the parafacial respiratory group (pFRG)/ retrotrapezoid nucleus (RTN) (Forster and Smith, 2010). CO_2 levels above or below the narrow physiological range, resulting in hyper- or hypocapnia, may represent "normal" conditions in hypoxia/at high altitude or during exercise, but may become hazardous to the health in conditions like chronic obstructive pulmonary disease, asthma, cystic fibrosis, obesity hypoventilation or congenital central hypoventilation syndrome (Cummins et al., 2020).

The systemic adaptations to hypoxia have been reviewed in greater detail elsewhere (Burtscher et al., 2022). A summary of the most important other physiological responses and the expected time frames at

altitudes of about 4000 m are depicted in Fig. 1. These responses include alterations in blood oxygen saturation, cognitive and physical performance, cardiac output, heart rate, blood pressure and hematocrit. The emphasis in the following sections is on the activation of systemic stress responses following hypoxia exposure due to their relevance for anxiety and depressive disorders.

3.3. The sympathetic nervous system in acute hypoxia

Acute hypoxemia (low blood oxygen) increases sympathetic nervous activity mediated by stimulation of arterial chemoreceptors, primarily those of the carotid bodies. Hypoxia causes glomus cells to depolarize, provoking the release of neurotransmitters (e.g., acetylcholine, ATP, serotonin) and inducing afferent impulses to the medulla by the carotid sinus nerve (Marshall, 1998b; Schultz et al., 2007). Sympathetic responses to chemoreflex activation are closely associated with elevated phrenic nerve activity and pulmonary ventilation (in order to counteract hypoxemia) (Taylor et al., 1999). Central respiratory areas (see below) interact with pre-sympathetic neurons in the medulla, thereby modulating sympathetic effects on the cardiovascular system (Taylor et al., 1999). Sympathetic nerve activity changes during the respiratory cycle, peaking during early expiration, and is more pronounced with higher breathing rates and diminished during slow breathing and with increasing tidal volumes (Narkiewicz et al., 2006). In humans, activation of the arterial chemoreceptors increases cardiac sympathetic activity (with elevation of heart rate, contractility and cardiac output) and the sympathetic vasoconstrictor outflow to skeletal muscle, renal and splanchnic beds (Marshall, 1994). However, sympathetic vasoconstriction is counteracted by hypoxia-induced nitric oxide release, causing vasodilation in most vascular beds (except in the lung) (Kulandavelu et al., 2015), thus complicating the prediction of individual systemic blood pressure responses to acute hypoxia. Moreover, sympathetic and parasympathetic responses to the cardiovascular system occur concomitantly, that may help to limit sympathetic vasoconstriction of coronary and cerebral vessels (Marshall, 1994; Schultz et al., 2007). Whereas cardiovascular functions are primarily mediated by norepinephrine, metabolic effects like hyperglycemia, hyperlactatemia, hyperlipemia, and increased oxygen consumption are mediated by epinephrine (Bravo, 1989). Hypoxia-induced sympathoadrenal activation is associated with increased glycogenolysis and glycolysis, and increased blood lactate levels during any given level of submaximal exercise (Kayser, 1996). With acclimatization, a tighter metabolic control may result in lowering of exercising lactate levels (Green et al., 1992).

3.4. The HPA axis in hypoxia exposure

In response to hypoxic stress also the HPA axis gets rapidly activated and contributes to hypoxia adaptations. The HPA axis is important already in fetal adaptations to low oxygen levels. Hypoxia can occur in the developing fetus during gestation, especially during periods of placental insufficiency, high altitude exposure or when the mother is smoking. Studies with pregnant ewes that were kept at an altitude of 3820 m to induce long-term hypoxic conditions in the fetuses (maternal arterial PO_2 of approximately 60 Torr) showed elevated plasma ACTH concentrations in fetal blood and increased CRF receptor 1 expression in the fetal pituitary gland when compared with fetal samples from ewes kept at an altitude of 300 m (maternal arterial PO_2 of approximately 100 Torr) (Myers et al., 2005). Interestingly, these markers of increased HPA axis activity were accompanied by increased vasopressin

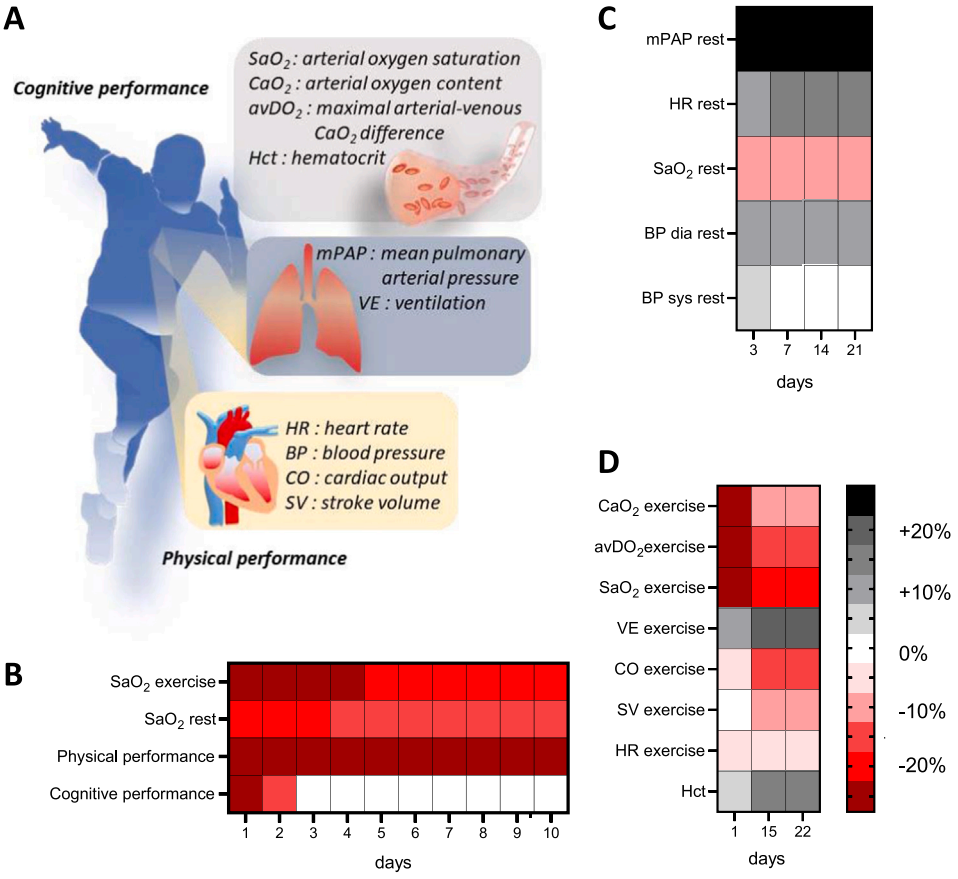

Fig. 1. High altitude responses. Selected parameters of physiological changes at high altitude (A) and timelines of these changes (in percent to low altitude baselines of the respective studies) at high altitude exposures (B-D). Data from the referenced sources were re-drawn at the indicated altitudes: (B) 4300 m (Muza et al., 2010), (C) 4111 m (Gaur et al., 2020), (D) 4300 m (Horstman et al., 1980).

expression in the hypothalamic paraventricular nucleus, whereas CRF expression was statistically similar in the hypothalamus of hypoxic and normoxic fetuses (Myers et al., 2016). Vasopressin is a known secretagogue of ACTH in sheep (Liu et al., 1994) and, during chronic stress, in rats (Aguilera and Rabadan-Diehl, 2000; Aguilera et al., 2008). It could therefore be an important neuropeptide in the control of cortisol or corticosterone release during hypoxia alongside CRF. Whether this applies to humans is not known, although elevated vasopressin levels in blood of people exposed to high altitude have been observed (Loeppky et al., 2005). These high vasopressin levels have been linked to direct effects of vasopressin on respiration through its actions in brainstem nuclei that control breathing (Proczka et al., 2021), and altered water retention during hypoxia (Loeppky et al., 2005).

Studies in rats have further confirmed the activation of the HPA axis during hypoxia. Severe chronic intermittent hypoxia (8 h per day of continuous hypoxia, FiO2 = 10% for 7 days) has been demonstrated to sensitize HPA axis and noradrenergic stress reactivity in rats (Ma et al., 2008). In this study hypoxia activated brain regions (as indicated by increased protein levels of the immediate early gene Fos) related to HPA axis regulation (paraventricular nucleus, bed nucleus of the stria terminalis, amygdala and noradrenergic neurons in the locus coeruleus) similar to immobilization stress (Ma et al., 2008). Another study in rats ascribed decreased cognitive function during chronic hypoxia (induced by simulated altitude of 7620 m for seven days) to a surge of corticosterone release as the corticosterone inhibitor metyrapone improved their memory impairments (Baitharu et al., 2012).

One of the interesting effects of the enhanced cortisol signaling that is mediated through its glucocorticoid receptor (GR) is an increase of HIF-1α levels, as demonstrated in vitro in HeLa cells (Kodama et al., 2003), and in vivo in genetically modified zebrafish larvae (Marchi et al., 2020; Vettori et al., 2017). The enhanced GR signaling does not seem to directly upregulate HIF-1α but rather inhibit VHL, leading to HIF-1α stabilization (Marchi et al., 2020). Conversely, HIF-1α modulates GR signaling although the underlying mechanisms are not fully elucidated. In cultures of HeLa cells, human proximal tubular epithelial cells and mouse pituitary AtT-20 cells, HIF-1α upregulated GR expression (Kodama et al., 2003; Leonard et al., 2005). Such stimulatory effects were not found in transgenic zebrafish larvae with constitutively high HIF-1α levels. Rather, it seems that in these fish HIF-1α reduces cortisol levels and GR signaling (Marchi et al., 2020), suggesting that HIF-1α inhibits HPA axis activity and GR signaling intracellularly. This result has been recapitulated in transgenic mouse lines. Mice deficient in HIF-1α in adrenal cortical cells showed enhanced levels of enzymes involved in corticosterone production and blood corticosterone levels. When HIF-1α was overexpressed, corticosterone synthesis was impaired and circulating corticosterone levels were correspondingly low (Watts et al., 2021). It should be noted, however, that the zebrafish and mouse transgenic animal models have not yet been studied in hypoxic conditions.

A recent study in mice, however, has revealed interactions between HIF-1α and GR signaling in vivo during hypoxia. Hypoxia increased the expression of HIF-1α and HIF-2α, which in turn activated the HPA axis: enhanced transcription of HIF-controlled genes in the hypothalamus that are also expressed during stress (Vanderhaeghen et al., 2022). Corticosterone/GR signaling appears to modulate a different set of genes in normoxia as compared to hypoxic conditions, in which lipolysis and ketogenesis are notably promoted (Vanderhaeghen et al., 2022). The reprogramming of GR-signaling towards transcription of hypoxia target genes requires a remodeling of gene transcription regulation. This has indeed been found in HeLa and HEK cells, in which hypoxia resulted in upregulated microRNAs 103 and 107. Both repressed the zinc-finger transcription factor KLF-4 that otherwise binds to the GR responsive element in the promoter region of normoxic target genes. The reduced binding of KLF-4 and other co-modulators of GR-mediated transcription therefore could prevent the transcription of these genes, but not of hypoxia target genes such as HIF-1α (Yang et al., 2020).

In summary, recent studies on the HPA activation under hypoxic conditions demonstrate intimate interactions between corticosterone / cortisol and GR signaling on the one hand, and HIF-signaling on the other hand. Together, these pathways bring about metabolic and gene expression changes that are necessary to adapt to low ambient oxygen levels but are also involved in stress regulation (Fig. 2). Dysregulation of this interplay therefore may be involved in the pathogenesis of stress-related pathologies, such as anxiety and depressive disorders.

Both the HPA and the SAM axes are involved in the development of acute mountain sickness (AMS), a maladaptive adaptation to hypoxia. Therefore, the connection between stress regulation and AMS development will be discussed in more detail.

3.5. The vulnerability to acute mountain sickness and its potential connection to stress and anxiety

The influence of hypoxic environments on mood (Bahrke and Shukitt-Hale, 1993; Shukitt-Hale et al., 1998) and – conversely – the impact of stress, mood, anxiety and depression-related characteristics on the tolerance to hypoxic stress are still poorly understood. Here, we will focus on a common condition associated with exposure to hypoxia that has recently been controversially discussed in the context of stress (Berger et al., 2020; Estoppey et al., 2019; Gatterer et al., 2019, 2020) and anxiety, namely AMS.

AMS frequently affects non-acclimatized persons exposed to altitudes of more than 2500 m (Roach et al., 2018) and includes symptoms such as headache, nausea, anorexia, gastrointestinal distress, generalized malaise and lassitude (Swenson, 2015). While AMS is not usually associated with severe health consequences, in some cases potentially fatal high altitude pulmonary or cerebral edema can ensue (Hackett and Roach, 2001). The precise etiology of AMS remains to be elucidated but it appears to be a consequence of cerebral hypoxia and resulting compensatory mechanisms. Genetic predisposition, impaired cerebrovascular coupling, changes in cerebral blood flow, increased intracranial pressure, altered redox status and/or disruption of the blood brain barrier all play roles in the development of AMS (Bailey et al., 2009; Gatterer et al., 2019; Lawley et al., 2016; Swenson, 2015). There are, however, also associations of AMS with anxiety- and stress-related parameters, including HPA axis modulation (Boos et al., 2018b; Missoum et al., 1992; Taylor et al., 2008).

As discussed, chronic stress can disrupt HPA and SAM axes balance and thereby contributes to the pathogenesis of anxiety and depressive disorders. Conversely, the HPA and SAM balance may also be involved in the tolerance to hypoxic stress. An important component of the HPA axis that is regulated by hypoxia is corticosterone, as demonstrated in rat studies (Hwang et al., 2017; Zoccal et al., 2007). We recently found an association of pre-ascent cortisol levels with AMS (Gatterer et al., 2019), as well as divergent cortisol awakening responses between persons with and without AMS (Estoppey et al., 2019). It was suggested that - for unknown reasons - AMS-sensitive persons show a stronger stress response to altitude exposure, secreting higher levels of CRF, which leads to greater ACTH release and in turn to higher cortisol levels. Besides, research suggests that CRF and the CRF receptor 1 may be involved in AMS and high altitude cerebral edema (HACE), by activation of aquaporin-4 (AQP4) in cortical astrocytes (Chen et al., 2014).

In addition to the involvement of the HPA axis, sympathetic responses to hypoxia also appear to be implicated in AMS susceptibility (Loeppky et al., 2003; Spliethoff et al., 2013). Sympatho-excitation due to stress and feelings of anxiety was supposed to exert effects on AMS development. In fact, some studies suggest significant associations of trait and state anxiety with AMS (Bian et al., 2016; Boos et al., 2018a; Missoum et al., 1992) whereas others do not (Niedermeier et al., 2017). In addition, it has been shown that, particularly in AMS-sensitive individuals and those prone to mental stress, exposure to hypoxia increases sympathetic tone, leading for example to fluid retention, which has been associated with the development of AMS (Gatterer et al., 2013;

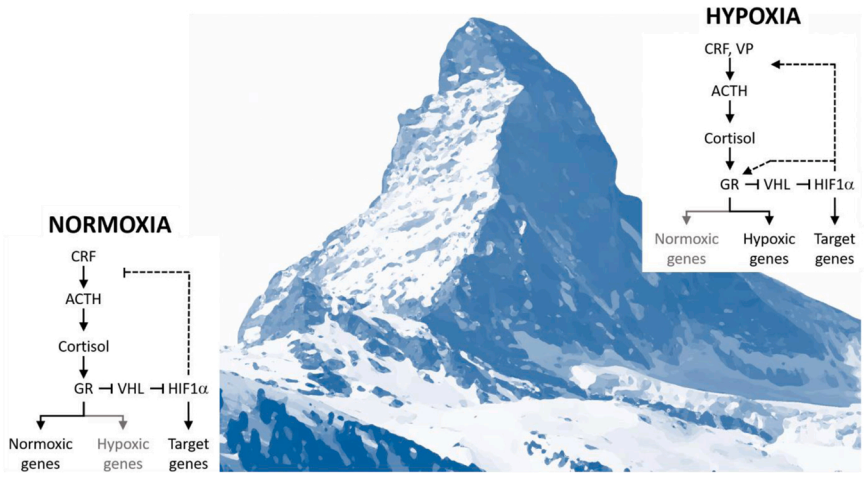

Fig. 2. Differential functioning of the HPA axis during normoxia and hypoxia. During normoxia, CRF from the hypothalamus is in most cases the primary secretagogue of pituitary ACTH. Cortisol released from the adrenals binds to glucocorticoid receptors (GR), leading to the activation of normoxic genes and the stabilization of HIF-1α through inhibition of its degrading protein, the Von Hippel-Lindau protein (VHL). HIF-1α is thought to provide negative feedback to the HPA axis (dashed line), as evidenced by low blood cortisol levels in animal models overexpressing HIF-1α. Under hypoxic conditions, hypothalamic vasopressin (VP) contributes to the stimulation of ACTH release, the GR switches from normoxic to hypoxic gene targets, and HIF-1α provides positive feedback to the HPA axis (dashed line), as inferred from increased expression of genes that are both HIF-responsive and stress-sensitive. HIF-1α may also promote the expression of GR to enhance responses of cells and tissues to glucocorticoid signaling during hypoxia. See text for references.

Loeppky et al., 2003). The discussed effects of vasopressin levels in hypoxia and their effects on respiration (Proczka et al., 2021) water retention (Loeppky et al., 2005) and the HPA axis are further indications for the intimate link between hypoxic and mental stress responses. Interestingly, the most popular drug used to prevent AMS is acetazolamide, which modulates water fluxes on the systemic and cellular level (Swenson, 2015). As a carbonic anhydrase inhibitor, it produces mild diuresis, metabolic alkalosis, increased ventilation and thereby improves arterial oxygen content. But also, acetazolamide's inhibitory action on aquaporin channels and the resulting reduction of water flux into the brain may be favorable for AMS. Additionally, acetazolamide reduces inflammation and oxidative stress and upregulates heat shock proteins (Swenson, 2015).

The first line drug to treat mountain illnesses is the synthetic glucocorticoid dexamethasone, one of the most efficient drugs to treat AMS (Johnson et al., 1984; Tang et al., 2014). Glucocorticoid administration (e.g., dexamethasone), provokes an increase in blood glucose concentration due to its stimulation of hepatic gluconeogenesis and the inhibition of glucose uptake by peripheral tissues. Glucocorticoids are highly effective drugs eliciting anti-inflammatory and immunosuppressant effects, but especially with chronic administration they cause serious side effects, including hypertension, steroid diabetes, osteoporosis and muscle atrophy, adrenal gland depression and immunosuppression (Bordag et al., 2015). Dexamethasone has also been long known for its preventive effects on symptoms of AMS (Rock et al., 1987), and its administration may protect against increases in vascular endothelial and blood-brain barrier permeability, suppresses inflammatory cytokines and reactive oxygen species production, and causes sympatholysis (Swenson, 2016). It furthermore reduces cortisol levels in healthy humans possibly by decreasing CRF secretion through negative feedback (Joyce et al., 2018). Based on this effect, it has also been argued that AMS may be associated with decreased cortisol levels (Panesar, 2004), which is probably not the case. As mental stress has been suggested to stimulate the sympathetic nervous system through dexamethasone-insensitive pathways (Seematter et al., 2002), beneficial physiological hypoxia adaptations likely involve other pathways than those associated with dexamethasone effects as well.

3.6. The influence of stress and anxiety on adaptations to hypoxia

A paucity of data is available on whether mental stress and anxiety affect adaptations to hypoxia that include maintaining oxygen and energy supply to tissues. Acute altitude adaptations are characterized by hyperventilation, hemoconcentration and initiation of erythropoiesis to increase total oxygen carrying capacity (Burtscher et al., 2018) (Fig. 1). Furthermore, adjustments of metabolic pathways aimed to maintain adequate ATP levels take place (Burtscher et al., 2018; Hochachka, 1986). The question arises whether stress and anxiety may affect these responses and thus adaptations.

Chronic stress and feelings of anxiety are clearly linked to the disruption of the HPA and SAM axes balance. Adding a further stressor (i.e., hypoxia) to an already unbalanced body, may negatively influence adaptations to hypoxia, by for instance exacerbating noradrenalin and cortisol levels as well as inflammation. Furthermore, it seems reasonable to speculate that the bidirectional link between glucocorticoids and HIF-signaling may interfere with HIF-regulated altitude adaptations (e.g., ventilatory acclimatization (Moya et al., 2020), metabolic adaptations (Seagroves et al., 2001), etc.). It could also be assumed that mood changes during high altitude exposure may interfere with recovery/adaptation of cerebral functions at altitude by negatively affecting various cognitive capacities (Bolmont et al., 2000).

A better understanding of the associations between stress, anxiety and depression on adaptations to hypoxia may open up new avenues not only for the risk assessment of hypoxia (e.g. high altitude) exposure but possibly also for the development of new treatment strategies for anxiety and depressive disorders (see chapter 6).

Key points
- → On the molecular level, the transcription factors hypoxia inducible factors (HIFs) and nuclear factor erythroid 2-related factor 2 (NRF2) are important coordinators of the hypoxic response
- → Systemically, hypoxia induces respiratory and cardiovascular responses that are regulated by peripheral and central chemoreceptors
- → Both the sympatho-adrenomedulary axis and the hypothalamic-pituitary-adrenal axis are activated by hypoxia and intricately tangled with hypoxia responses
- → It is thus not surprising that mental stress and anxiety appear to modulate the susceptibility to high altitude sicknesses
- → How mental stress and anxiety concretely interfere with hypoxia adaptations is largely unexplored

4. Epidemiological associations of hypoxia with stress, anxiety and depressive disorders

Acute exposure to hypoxia exerts pronounced mental effects. This has been shown in real altitude (hypobaric hypoxia) as well as in normobaric hypoxia settings. For example, Nelson reported changes in paranoia, obsessive-compulsiveness, depressive symptoms and hostility at altitudes of > 5000 m (Nelson, 1982). Shukitt and Banderet observed transiently reduced friendliness but increased happiness at an altitude of 4300 m (Shukitt and Banderet, 1988). More pronounced emotional and mental changes with increasing altitude suggest a hypoxia-dose dependent effect (Shukitt-Hale et al., 1998). Normobaric hypoxia simulating an altitude of 4500 m for 24 h increased depressive mood, anger and fatigue as well (de Aquino Lemos et al., 2012). On the other

hand, well prepared and motivated mountaineers during the ascend of Mount Everest did not experience reduced mood or increased anxiety or psychological inflexibility (Karinen and Tuomisto, 2017). The authors of another study showed that in particular a monotonous environment and reduced social interactions, increased depressive feelings in well-acclimatized young adult lowlanders that were exposed to high altitude (4500–4800 m) for 8 months (Das et al., 2018). There is also increasing evidence from rodent models that severe hypoxia can cause anxiety-like behavior, for example repeated exposure of severe hypoxia (15 min in an air-tight cage) cause anxiety- and depressive like behavior in mice (Olugbemide et al., 2021). In rats, severe hypobaric hypoxia (up to a simulated altitude of 7620 m) induced anxiety-like symptoms and fear extinction deficits (Kumari et al., 2020).

In general, high inter-individual differences and a strong effect of acclimatization seem to characterize emotional and mental effects following hypoxia exposure. The next sections are dedicated to epidemiological evidence of long-term hypoxia exposure, such as for altitude residents, on anxiety and depressive disorders.

4.1. Hypoxia and anxiety disorders

The increased risks of anxiety in people with respiratory diseases and the association of spirometry results with anxiety symptoms (Spitzer et al., 2011) suggest a link between anxiety and hypoxia. An increased prevalence of different anxiety syndromes such as generalized anxiety disorder (adjusted odds ratio (AOR): 11.0); panic disorder (AOR: 7.1) and specific phobia (AOR: 3.7) has indeed been reported for chronic obstructive pulmonary disease (COPD) patients compared to non-COPD participants (Ohayon, 2014). These reports are confirmed by a systematic review on anxiety and COPD (Willgoss and Yohannes, 2013). The occurrence of anxiety may also be higher in respiratory diseases than in other pathological (e.g. chronic orthopedic) conditions (Vögele and von Leupoldt, 2008).

Furthermore, symptoms of anxiety can be caused by hypobaric hypoxia and have been reported to increase in severity and frequency with increasing altitude (Table 1). Most studies on symptoms of anxiety at high altitude have been performed in individuals who were previously healthy, and in several studies, anxiety scores remain below a cutoff indicating clinical relevance. However, some studies report the appearance of clinically relevant symptom severity in a subset of participants (Shah et al., 2020). Reports on de novo or relapses of anxiety disorders, especially panic attacks, following visits to high altitude clinics further indicate an increased incidence at higher altitude (Fagenholz et al., 2007; Sracic et al., 2014), although this association may be underestimated. High altitude exposure can induce somatic symptoms triggered by hypoxia, such as breathlessness, palpitations, dizziness, headache, and insomnia, which are similar to those reported in panic attacks or severe anxiety, often rendering the distinction difficult (Roth et al., 2002).

4.2. Hypoxia, depressive disorders and suicide

Hypoxia may also be involved in the etiology of depressive disorders. Thus, short- or long-term exposure to hypoxia has been associated to increased probabilities of depression and elevated suicide rates, although this remains debated.

Depression and suicide rates are intimately linked (Möller, 2003) and have both been associated with living at altitude; this has been reported for depression (DelMastro et al., 2011; Gamboa et al., 2011; Wang et al., 2019; Zaeh et al., 2016) and suicide (Alameda-Palacios et al., 2015; Betz et al., 2011; Bezerra Filho et al., 2012; Brenner et al., 2011; Haws et al., 2009; Kim et al., 2011). Already moderate altitudes of about 600 – 900 m may affect both depression and suicide rates (Brenner et al., 2011; Kious et al., 2019; Sabic et al., 2019). For suicide, Haws and colleagues (Haws et al., 2009) observed increased rates in US counties at higher altitude with altitude remaining an independent risk factor after

Table 1
Association of altitude with anxiety symptoms in humans.

Investigated population	Standardized instruments	Main results	Reference
2939 civil servants (~50% female) high (1500–3500 m) or very high (>3500 m) altitude long term residence; individuals with severe mental illness excluded	GAD-7	- for every 100 m increase in altitude, anxiety severity increased by 0.042 points ($p < 0.001$) - significantly higher GAD-7 scores at very high compared to high altitude	(Wang et al., 2021)
40 healthy adults, 10 females, the study included apnea training, ascent to an altitude of 5100 m over 14 days	GAD-7	- mean GAD-7 scores within normal range. Day 14 (5100 m): 28/40 subjects no significant anxiety, 8/40 mild anxiety; 4/40 moderate anxiety - significant effect of altitude on GAD-7 scores	(Shah et al., 2020)
668 healthy males, measurements at sea level and 3700 m (after 24, 72, and 168 h)	SAS	- individual SAS scores increased significantly within 24 h at 3700 m – decrease to above baseline levels at 72 and 168 h. Mean SAS scores within normal limits	(Bian et al., 2019)
426 young males without somatic diseases, ascend from low altitude to 3600 m over 40 days (data collection after acclimatization), before ascending to 4400 m (data collection at arrival)	SAS	- at 3600 m 49/426 and at 4400 m 51/329 were diagnosed with anxiety according to SAS	(Dong et al., 2013)
850 subjects ascended by plane from 500 m to 3700 m over a period of 2 h, data collection within 24 h after arrival at 3700 m	SAS	- significant increase in mean SAS ratings from 500 m to 3700 m: from mean (IQR) 21 (3) to 24 (6), means still within normal range	(Bian et al., 2013)
80 healthy adults, 67.5% men, measurements at baseline (848 m) and at 9 consecutive altitude levels during a progressive trek to 5140 m	STAI Y-1 STAI Y-2	- STAI Y-1 scores fell from 848 m to 3619 m - significant increase to above baseline scores at $\geq$ 4072 m - significant main effect for sex (higher STAI Y-1 scores in women) and altitude - baseline STAI Y-2 scores independently predicted future severe AMS and STAI Y-1 scores at high altitude	(Boos et al., 2018a)
3731 medical students (51% male) at low (<900 m) or high (>900 m) altitude	GAD-7	- moving from low to high altitude significantly increased GAD-7 total score (OR = 1.40, 95% CI = 1.0040–1.95), no association with residence at altitude per se	(Kious et al., 2019)

(continued on next page)

Table 1 (*continued*)

Investigated population	Standardized instruments	Main results	Reference
44 participants (57% male) with no uncontrolled medical condition (2 prior diagnosis of anxiety, 3 depression) 19-day expedition to 5372 m	Adapted and shortend STAI Y-1	- anxiety symptoms significantly increased with altitude - 42/43 (98%) experienced anxiety symptoms at some point during the expedition - the peak incidence of anxiety was 33/43 at 4670 m (day 2) - the average length of illness was 11.3 (9.6–13.0) days.	(Oliver et al., 2012)
129 military volunteers (gender not specified) without previous psychiatric diagnosis, working at 4572 − 5486 m	HADS	- HADS Anxiety mean 7.93 + SD 5.1 27/129 21% Mild anxiety 27/129 21% Moderate anxiety 6/129 5% Severe anxiety	(Ahmad and Hussain, 2017)
Nationwide cross-sectional study representative sample of Nepalese adults aged 18–65 years (N = 2100), selected by multistage random cluster	HADS	- age- and gender-adjusted point prevalences of HADS-A: 16.1%, and HADS-cAD (combined anxiety depression) 5.9% - in a multivariate model: HADS-A no association with altitude, HADS-cAD was positively associated with living at altitude ≥ 2000 m (AOR = 2.32)	(Risal et al., 2016)
110 soldiers (gender not specified); lowlanders and native Tibetans stationed at Shangri-La (3800 m) for 3 months; no prior psychiatric condition	HAMA	- 30/209 were rated positive for anxiety (14.35%) and were excluded from the study	(Kong et al., 2015)

The presented references in Table 1 were derived from a systematic PubMed search using the search terms " anxiety " and " high altitude ". Of the identified 86 articles, only articles on adult humans, including more than 10 participants and using standardized psychometric instruments were included. The following standardized instruments were used in the identified studies:
- Self-Rating Anxiety Scale (SAS)
- GAD-7: anxiety scale from patient health questionnaire
- HADS: hospital anxiety and depression scale, HADS-A anxiety subscale
- HADS cDA: combined scoring for depression and anxiety
- STAI: Spielberger state trait anxiety inventory
- HAMA: Hamilton Anxiety Scale

inclusion of gun ownership rates and population density in a multiple regression model (Kim et al., 2011). These authors also report a strong positive correlation of altitude of residence with suicide in South Korea (Kim et al., 2011).

A big limitation of epidemiological studies on suicide and altitude of residence is obviously the influence of numerous potentially confounding factors. Betz and colleagues (Betz et al., 2011) confirm increased suicides at higher altitudes of residence but emphasize that factors not related to oxygen levels likely play an important role in this effect. These factors may include meteorological, sociodemographic or other peculiarities of mountainous regions such as reduced access to psychiatric care (Betz et al., 2011; Burtscher, 2014; Reno et al., 2018). More specifically, the association between depression and altitude residence could be mediated also by the availability of Lithium (Helbich et al., 2013), antidepressant use and material deprivation (Alameda-Palacios et al., 2015). In support of a dependence of altitude-related suicide rates on sociodemographic factors, we and others did not find elevated suicide mortality with increasing altitude of residence (Burtscher et al., 2021c; Selek, 2013). Whether altitude of residence - and especially hypoxia – is an independent risk factor for suicide and depression therefore remains debated (Honigman et al., 2020).

Increased rates of depressive symptoms, major depression and suicide have also been reported for patients of chronic respiratory diseases, again more than in patients of chronic diseases unrelated to hypoxemia (Druss and Pincus, 2000; Goodwin, 2011; Goodwin et al., 2012, 2003; van den Bemt et al., 2009; Webb et al., 2012; Zaeh et al., 2016). Also hypoxemia due to smoking is associated with higher suicide rates (Aubin et al., 2011). Notably, the severity of respiratory diseases is positively correlated with suicide attempts and mortality (Chung et al., 2014; Kuo et al., 2010).

Animal experiments further support the relation of depressive-like behavior and hypoxia. Exposure of rats to 1 week of hypobaric hypoxia (simulating an altitude of 3048 m) for example resulted in depressive-like phenotypes (however, only in females), as assessed by forced swim tests, which was accompanied by cerebral metabolic changes (Bogdanova et al., 2014). Interestingly, most selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine and escitalopram, but not sertraline) were not able to rescue depressive symptoms induced in such manner (Kanekar et al., 2018). Whether this is due to differential modes of pharmacological action of different SSRIs that may help to elucidate the link between hypoxia and depressive disorders remains to be investigated, especially since nothing is known about the situation in humans. However, the oxygen-dependence of serotonin metabolism may be a reason for reduced efficiencies of SSRIs, as outlined below. Importantly, the adoption of a more energy-saving approach by females (that may not be related to depressive-like symptoms) is an alternative explanation for these effects and would also explain the ineffectiveness of most SSRIs.

In summary, hypoxia exerts prominent effects on psychological states, and responses to hypoxic and mental stress are inter-related. As a consequence, high altitude residence is expected to be associated with differences in the susceptibility to anxiety and depressive disorders. Living in hypoxic conditions imposes specific metabolic and physiological strains on individuals that may alter the propensity of mental homeostasis to be disturbed. Small, in normoxia sub-harmful, allostatic loads may then suffice to prevent restoration, or establishing a new, equilibrium. While these relationships are incompletely understood and modulated by many factors (such as socio-economic characteristics above all access to specialized care, individual predispositions, physical activity and nutritional status), the here presented data are in favor for the postulated link (Fig. 3).

Key points
→ Hypoxia exposure can alter mood and emotions
→ Since respiratory diseases and high altitude exposures are frequently associated with anxiety symptoms, a link between hypoxia and anxiety disorders is possible
→ Although high (but not moderate) altitude of permanent residence may be associated with increased risk for depression and suicide, potential confounding factors remain difficult to extract
→ Chronic hypoxia may represent an additional stressor, facilitating the development of stress related diseases

5. Mechanistic links between hypoxia and anxiety and depressive disorders

As hypoxia acutely alters mood (see above), can induce panic attacks (Beck et al., 1999) and like chronic stress may increase inflammation (see below), it could be involved in the development of anxiety or depressive disorders. If overlapping physiological and pathological

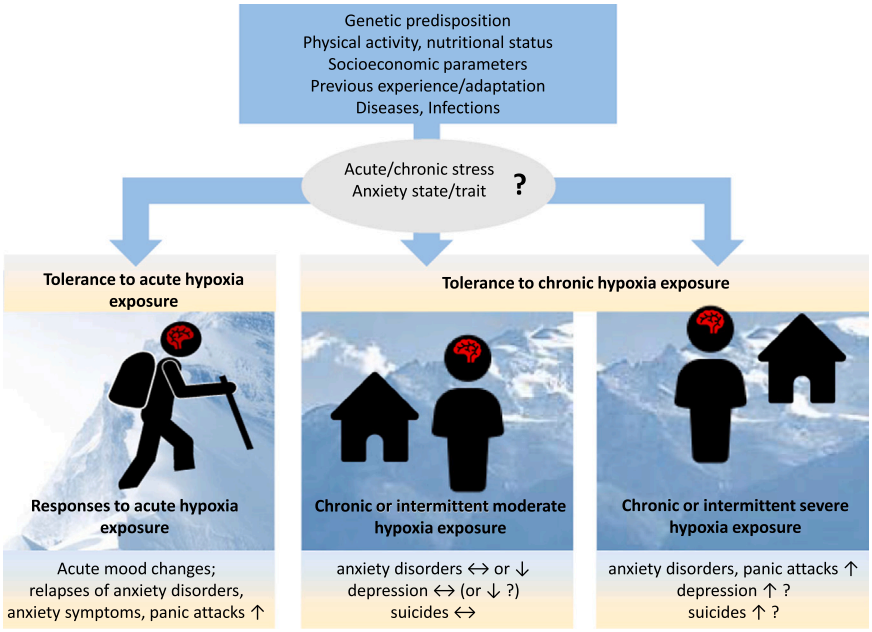

Fig. 3. Effects of acute and chronic exposures to altitude/hypoxia on anxiety and depression-related symptoms. Various individual and situational parameters, as well as the hypoxic dose (severity, duration, frequency of the exposure) may influence the outcome. See text for references.

adaptations to hypoxia and chronic stress play roles in the pathogenesis of these diseases, it seems plausible to speculate that these mechanisms can be targeted to prevent or ameliorate anxiety and depressive disorders. In this section some common patterns of adaptive and maladaptive effects of hypoxia and of chronic stress, anxiety and depressive disorders are discussed.

5.1. *Inflammation*

Chronic social-environmental stress is a major risk factor for anxiety and depressive disorders and is associated with increased inflammation (Slavich and Irwin, 2014). Inflammation and pro-inflammatory cytokines are also involved in the pathogenesis of anxiety and depressive disorders (Miller and Raison, 2016; Slavich and Irwin, 2014) and therefore may link chronic stress to increased vulnerability for these disorders. The upregulation of pro-inflammatory cytokines due to acute or chronic hypoxia exposure therefore could impact on the development of these diseases.

For example, Fan and colleagues demonstrated that chronic hypoxia (10% FiO_2 for 23 h/day over 2 weeks) induced anxiety-like behavior in mice, which was mediated by pro-inflammatory NF-κB activation in hippocampal microglia (Fan et al., 2016). In a recent study, Nguyen and colleagues (Nguyen et al., 2021) exposed rats to moderate altitude (1655 m) and observed increased levels of inflammation markers (increased granulocyte-to-lymphocyte and monocyte-to-lymphocyte ratios, increased levels of circulating monocytes) and depressive-like behaviors.

While inflammation has emerged as an important factor in the pathogenesis of stress-related diseases (Ravi et al., 2021), information on the overlaps with pathways of hypoxia-adaptations are sparse.

5.2. *Serotonin*

Hypoxia obviously leads to reduced oxygen dependent brain processes, including of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis (Kious et al., 2018). The potential role of hypoxia-mediated biogenic amine synthesis, including serotonin, in affective disorders has been suggested almost 40 years ago (Katz, 1982). Inflammation maybe an integral player also from this point of view. Psychoneuroimmunology describes the concept that mental stress-induced alterations in an individual's immunometabolic signature leads to physical and/or mental disease. The best evidence is available for depressive symptoms but similar mechanisms are also applicable for anxiety (Costello et al., 2019; Strasser et al., 2017). When neurotransmitter precursor amino acid levels are used as markers for anxiety and depressive disorders, the serotonin and catecholamine pathways are most relevant. Data from various studies indicate that inflammation has a significant impact on neurotransmitter precursor amino acids and related biogenic amines as well as neurotransmitters such as serotonin and dopamine (Miller et al., 2013). Specifically, the serotonin pathway can be influenced by cytokines which enhance the activity of indoleamine 2,3-dioxygenase or stress hormones which can activate tryptophan 2,3-dioxygenase (Oxenkrug, 2010). This leads to a degradation of tryptophan and shunting of the metabolic processing in favor of the tryptophan catabolite pathway, such as kynurenine, kynurenic and quinolonic acid, rather than serotonin production. Elevated kynurenine-to-tryptophan ratios have been described to mediate anxiety (Hüfner et al., 2015; Lapin, 1996). The catecholamine pathway with its precursors phenylalanine and tyrosine is also influenced by inflammatory reactions and an association of phenylalanine-to-tyrosine ratio with depressive symptoms has been described (Hüfner et al., 2021, 2015). Apart from inflammation the reduced availability of oxygen can directly influence neurotransmitter precursor amino acid levels since the conversion of tryptophan to serotonin by tryptophan hydroxylase, requires molecular oxygen (Katz, 1980). The availability of the enzyme co-factor tetrahydrobiopterin (BH4) which is essential for phenylalanine catabolism involving phenylalanine hydroxylase and also for serotonin synthesis, is reduced in the presence of ROS (Neurauter et al., 2008; Sperner-Unterweger et al., 2014). A deficiency in BH4 can thus lead to systemic deficiencies of serotonin, dopamine, norepinephrine, and epinephrine.

Changes in brain metabolism of serotonin have been found at altitude in animal models (Prioux-Guyonneau et al., 1982; Ray et al., 2011) and selective serotonin reuptake inhibitors (SSRI) are largely ineffective in hypobaric hypoxia in an animal model possibly due to a hypoxia induced serotonin deficit (Kanekar et al., 2018). Effects of gender with females being more vulnerable to the effects of hypoxia in the animal model have also been described (Kanekar et al., 2021). Impaired

serotonin synthesis at low oxygen levels has furthermore been proposed as a mechanism for elevated suicide rates (Young, 2013) and would be in line with the well-established negative association of serotonin levels with suicide probability (Joiner et al., 2005; Mann, 2003) and involvement in depression (Köhler et al., 2016).

5.3. Neuropeptides

Hypoxia has both stimulatory and inhibitory effects on the release of numerous neuropeptides, including oxytocin, vasopressin, orexin and angiotensin-II. Oxytocin and vasopressin are nine amino acid neuropeptides that are produced in the hypothalamic paraventricular nucleus (PVN). They are traditionally known for their peripheral effects, oxytocin for the stimulation of birth and milk letdown, vasopressin for water retention and blood pressure regulation. However, both also exert multiple central actions in the brain; oxytocin is known for its prosocial, anxiolytic and fear-reducing effects, in a delicate balance with the opposing effects of vasopressin (Neumann and Landgraf, 2012). Importantly, receptors for both peptides are expressed in the amygdala, the fear center of the brain, as well as in the bed nucleus of the stria terminalis (BNST), which is thought to play a major role in regulating anxiety. Both nuclei project to a large number of brain stem targets whose activation underlies the various physiological responses that are important for the expression of anxiety and fear. In the amygdala, an interesting mechanism has been described through which vasopressin and oxytocin can oppositely modulate the fear response: Vasopressin receptors have been found on the brainstem projecting neurons in the amygdala, whereas oxytocin receptors are expressed on local GABAergic neurons, that can, in turn, inhibit these vasopressin receptor expressing, brainstem projecting neurons (Huber et al., 2005). It is possible that a similar mechanism in the BNST may allow for an opposite modulation by vasopressin and oxytocin on anxiety.

Importantly, central release of oxytocin and vasopressin is affected by oxygen levels. In the dorsal motor nucleus of the vagus (DMNV), oxytocin release was found to be blunted in a rat model, of chronic intermittent hypoxia-hypercapnia, modeling obstructive sleep apnea (Jameson et al., 2016). This decrease in endogenous oxytocin release in the DMNV could be rescued by optogenetic activation of oxytocinergic fibers that descend from the PVN and in the DMNV restore oxytocin release, as assessed by calcium imaging in brain slices. Interestingly, in this rat model a corresponding chemogenetic stimulation of these descending projections in vivo prevented hypoxia-induced hypertension (Jameson et al., 2016). As vasopressin release is increased under hypoxic conditions (see chapter 3.4) potential opposite regulation of oxytocin and vasopressin release during hypoxia in the BNST and amygdala could contribute to the anxiety and fear responses resulting from hypoxia.

Oxytocinergic neurons further project to the NTS, which - like the DMNV – is a part of the vagal nucleus. These neurons express CRF receptor 2 on their terminals and are thought to modulate hypoxia-induced CRF signaling in the NTS but the physiological underpinnings and outcomes of such putative interactions between CRF and oxytocin signaling remain to be determined (Ruyle et al., 2018). In general, oxytocin may influence peripheral physiology through the modulation of different parts of vagal nerve activity. Oxytocin has also been reported to exert neuroprotective effects during hypoxia: in hippocampal slices that were maintained in hypoxic and low glucose conditions to mimic neonatal hypoxic ischemic encephalopathy, oxytocin prevented cell death by enhancing GABAergic signaling as assessed by electrophysiological recordings (Wu et al., 2021).

Also the neuropeptide orexin seems to be activated by hypoxia and hypercapnia. This peptide is also known as hypcretin-1 or orexin-A, - and like oxytocin is produced in the hypothalamus. It exerts similar mechanistic effects on the vagal and GABAergic systems but with opposite physiological outcome. Orexin-1 enhances GABAergic signaling to neurons controlling cardiac neurons in the nucleus ambiguus, another cell group of the vagal nucleus. It likely acts presynaptically on GABAergic axon terminals descending from the lateral paragigantocellular nucleus that is located in the ventral medulla, to increase both heart rate and blood pressure (Dergacheva et al., 2011). The activation of orexinergic neurons by hypoxia and hypercapnia (Du et al., 2016; Williams et al., 2007) (and possibly orexin-1 signaling in the nucleus ambiguous) together with the inhibition of oxytocin release in vagal nuclei (preventing rises in blood pressure and heart rate) thus may be involved in the regulation of oxygen supply to cells in a low oxygen environment.

In addition, orexin receptor agonists may protect neurons from hypoxia via HIFs. Exogenous orexin-1 induced HIF-1α mediated neuroprotective effects from cerebral ischemia-reperfusion injury in rats (Yuan et al., 2011). In SH-SY5Y human neuroblastoma cells, orexin induces the expression of the HIF 1α target genes vascular endothelial growth factor (VEGF) and erythropoietin (EPO) and thereby promotes cell survival (Feng et al., 2014).

The reduced oxytocinergic and enhanced orexinergic activity during hypoxia could also have consequences on mood and cognition. As mentioned above, oxytocin has profound anxiolytic fear-reducing effects in many parts of the brain, among which the amygdala and BNST (for review see (Triana-Del Río et al., 2018)) and promotes social behavior, in both animals and humans (Lukas and Neumann, 2013; Parker et al., 2014). Orexin-1, on the other hand, increases wakefulness and alertness, especially during stress and possibly also during hypoxia, considering that hypoxic stress activates the HPA axis (Guyenet, 2014) (see also chapter 3.4). However, it is currently not known whether mood and cognition changes during hypoxia are directly mediated by oxytocin and orexin-1.

Angiotensin II, through its effects on blood pressure, may also play an important role during hypoxia. This was found in animal models of hypoxemia associated with sleep apnea, including a sustained hypertension that is maintained during normoxia. It was found that angiotensin II, the most active component of the renin-angiotensin system with both peripheral and central effects, contributes to the increase of blood pressure (Grobe et al., 2008). Angiotensin II signals from the periphery to the brain through angiotensin II type 1 A receptors in the subfornical organ (Saxena et al., 2015), and from there to the PVN, the ventral medulla and the vagal nuclei, as recently reviewed (Marciante et al., 2021). Therefore, it could be that angiotensin II signaling is upstream of oxytocin and orexin-1 signaling under hypoxic conditions and induces hypertension through, amongst others, these neuropeptides, but this hypothesis remains to be tested.

The hypertension as a result of chronic intermittent hypoxia can trigger cognitive decline. Indeed, sleep apnea is a common comorbidity of cognitive decline and Alzheimer's disease (Andrade et al., 2018; Bubu et al., 2020), and it has been suggested that central angiotensin II signaling through angiotensin II type 1 A receptors is enhanced in Alzheimer's patients (Cosardereliogl u et al., 2021). However, the precise links between hypoxia, angiotensin II signaling and neurodegenerative diseases still have to be established.

5.4. Bioenergetics

Hypoxia disrupts cerebral energy metabolism in many ways, most obviously by reduced availability of the final electron acceptor in mitochondrial aerobic respiration, oxygen. In addition, reduced efficiency of the creatine system (Raman et al., 2005), as well as impaired mitochondrial dynamics (Jain et al., 2015) have been demonstrated in rats after chronic hypoxic exposure. Cerebral energy metabolism has been suggested to be involved in the development of depressive disorders and creatine supplementation has been shown to improve depressive-like phenotypes (Allen et al., 2010) as assessed by the forced swim test. Similar to the sex-effects of hypoxia on depression-like behavior in rats (Bogdanova et al., 2014) this was also only the case in female rats. Creatine is also associated with beneficial effects in human depression patients, an overview on these results has been

recently provided (Kious et al., 2018). It is also becoming increasingly acknowledged that mitochondria are integral players in stress adaptations and behavioral consequences (Picard et al., 2018), as well as in anxiety (Filiou and Sandi, 2019) and depressive disorders, although clear cellular specificities, mechanistic underpinnings and variations within patient populations remain to be elucidated (Brasanac et al., 2022). Chronic stress is linked to disturbances of mitochondrial functions (van der Kooij, 2020) and mitochondria have been demonstrated to be altered in highly anxious rodents but also mitochondrial disease is associated with higher rates of anxiety, as recently reviewed (Filiou and Sandi, 2019). The impairment of mitochondria in chronic stress may therefore be a link to the development of anxiety (Daviu et al., 2019). With regard to anxiety, impaired mitochondrial respiration, dynamics and disposal of damaged mitochondria (mitophagy) have been reported in the ventral tegmental area (Gebara et al., 2020; Hollis et al., 2015) and in the amygdala (Duan et al., 2021) of rodents, both brain regions with major roles in anxiety disorders. Furthermore, emerging evidence also implicates mitochondrial dysfunction in the immune system in the pathogenesis of anxiety and depressive disorders, as for example recently shown for T-cells (Gamradt et al., 2021) and in peripheral blood mononuclear cells (Scaini et al., 2021) in patients with major depressive disorder.

How stress can impair mitochondrial functions via the immune and endocrine system has recently been reviewed in more detail (Daniels et al., 2020).

5.5. Glucose metabolism

Hypoxia induces energy-metabolism re-programming, importantly including an upregulation in glucose metabolism to fuel glycolysis in the absence of sufficient oxygen for oxidative phosphorylation. This acutely includes reduced allosteric repression of glycolysis by phosphofructokinase and subsequent HIF-mediated upregulation of glucose transporters and glycolytic enzymes (Kierans and Taylor, 2021). Importantly, also stress alters glucose energy metabolism. Chronic stress in mice has been shown to lead to blood and brain hyperglycemia, increased markers of glucose demand but reduced glucose delivery to the brain (Carneiro-Nascimento et al., 2020; van der Kooij et al., 2018). Hyperglycemia in turn induces a dysregulation of HIF-1α (Catrina et al., 2004) and therefore of adaptations to hypoxia.

Increased glycolysis is associated with higher levels of lactate. Notably, lactate can induce panic attacks in panic disorder patients (Liebowitz et al., 1984). Conversely, visual stimulation in humans has been shown to result in higher lactate accumulations in the visual cortex in patients with panic disorders, further supporting the association of lactate and panic disorders (Maddock et al., 2009).

5.6. Chemoreceptors

Molecular mechanisms of oxygen sensing, stress, anxiety and depressive disorders are profoundly connected. Indeed, chemoreceptors for CO_2 or oxygen not only modulate respiratory control but also can induce a sensation of dyspnea in the absence of variations of CO_2 or oxygen (Buchanan and Richerson, 2009).

Acute hypoxia is sensed by chemoreceptors that regulate breathing and modulate respiratory neuroplasticity (Navarrete-Opazo and Mitchell, 2014). The major peripheral oxygen sensor (carotid body) is also responsive to inflammatory signals and importantly regulates sympathetic (and parasympathetic) nervous system and neural regulation of immunity (Katayama et al., 2021) and therefore may mediate hypoxia-induced effects on mental stress and the pathogenesis of anxiety and depressive disorders. The sympathetic effects following peripheral oxygen sensing are importantly mediated by the nucleus of the solitary tract in the brain stem (Iturriaga et al., 2021). Other brain regions activated by changes in oxygen levels sensed by the carotid bodies include various hypothalamic nuclei as reviewed for animal studies (Horn and Waldrop, 1998) and recently confirmed in humans by functional magnetic resonance imaging (fMRI) (Gerlach et al., 2021), potentially linking consequences of peripheral oxygen sensing to the HPA.

The main brain structure generating breathing rhythm is the pre-Bötzinger complex in the brainstem (Del Negro et al., 2018), which is strongly connected to respiration-associated brainstem nuclei, including the NTS, and less strongly to forebrain regions, but likely is involved in behavioral and emotional control, in particular by innervating thalamic and hypothalamic areas (Yang and Feldman, 2018). Interestingly, the NTS expresses abundant glucocorticoid receptors that have been demonstrated to be fundamentally involved in endocrinal and behavioral stress responses (Ghosal et al., 2014).

The retrotrapezoid nucleus on the ventral medullary surface is a CO2-sensing brain region importantly involved in breathing automatic and directly connected to the preBötzinger complex (Guyenet et al., 2019).

Furthermore, signals for impending suffocation, such as carbon dioxide inhalation or hypoxia, induce the robust activation of anxiety networks in the brain. For CO_2 for example the chemo-sensitive murine acid-sensing ion channel ASIC1a has been demonstrated to mediate induction of anxiety in the amygdala (Coryell et al., 2007; Ziemann et al., 2009), a central brain region in the regulation of anxiety. In line with these findings, the human version of ASIC1a, ACCN2, is a risk gene for anxiety (Smoller et al., 2014). Given the chemosensitivity of the amygdala, its potential involvement in the etiology of AMS is not surprising (Feddersen et al., 2007).

Notably, many other brain regions that have been shown to be chemo-sensitive to CO_2 are important players also in anxiety and depressive disorders; this includes for example serotonergic (and non-serotonergic) neurons in the raphe nucleus (Teran et al., 2014) and noradrenergic neurons in the locus coeruleus (Buchanan and Richerson, 2009). Recently, Batistela and colleagues showed that hypoxia induced robust expression of the immediate early gene c-Fos in non-serotonergic cells in the lateral wings of the dorsal raphe and dorsomedial periaqueductal grey, indicating their activation in response to hypoxia (Batistela et al., 2021). These brain regions are also known to mediate panic-like escape responses in rodents.

While there is evidence for central O_2 sensing from animal models (Buchanan and Richerson, 2009), the absence of a hypoxic ventilatory response in humans with resected carotid bodies (Honda, 1992) indicates a minor role of central O_2 sensing in humans. However, a serotonergic activation (from the raphe nuclei) of the oxygen-sensitive retrotrapezoid nucleus (Mulkey et al., 2007) is a further link between chemosensitivity and anxiety/depression-related serotonergic pathways.

Chemo-sensing is further involved in the regulation of cerebral blood flow (Feddersen et al., 2015; Ogoh et al., 2021) and blood brain barrier integrity (Halder and Milner, 2019), both of which may be impaired by stress and in anxiety (Hasler et al., 2007) and depressive disorders (Dudek et al., 2020).

In conclusion, stress responses overlap with adaptations to hypoxia at different levels, as depicted in Fig. 4.

Key points

→ Adaptations to hypoxia and mental stress partially overlap
→ These overlapping mechanisms may be targeted to treat anxiety and depressive disorders
→ Classical (e.g., serotonin) and peptidergic (e.g., oxytocin and orexin) neurotransmitters mediate both mental and hypoxic stress responses
→ Bioenergetics and glucose metabolism are altered by chronic mental stress and hypoxia and are impaired in anxiety and depressive disorders.
→ Chemosensitive brain regions are involved in (mental and hypoxic) stress-responses and also the regulation/development of anxiety and depression

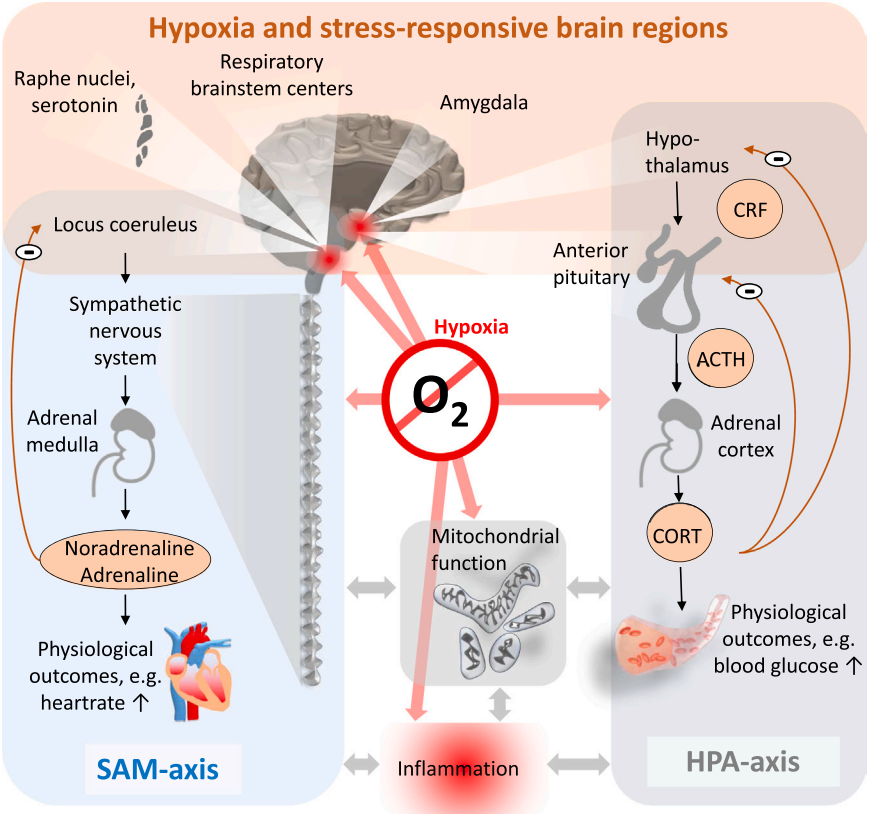

Fig. 4. Hypoxia affects the stress response on multiple levels. Hypoxia or resulting changes in CO2 levels directly and indirectly influence various components of the HPA (hypothalamic–pituitary–adrenal)- and sympatho-adrenomedullary (SAM) axes, as well as chemo-sensitive regions in the brain and have consequences on mitochondrial functions (most directly oxidative phosphorylation and reactive oxygen species generation) and inflammatory processes. CRF; corticotropin-releasing factor, ACTH; adrenocorticotropic hormone, CORT; cortisol.

6. Modulating hypoxia adaptations to counteract anxiety and depressive disorders

Depending on the severity and patterns of hypoxia administration, hypoxia interventions can have different, even opposing effects (Navarrete-Opazo and Mitchell, 2014). While severe hypoxia causes cellular and tissue damage, mild, sub-harmful hypoxia can induce protective adaptations, rendering cells, tissues and the whole organism more resilient to subsequent hypoxia insults (Noble, 1943). This process is called hypoxia conditioning and has great potential as treatment strategy for neurological and psychiatric diseases (Baillieul et al., 2017; Burtscher et al., 2021a) and possibly also in anxiety and depressive disorders as will be discussed in this chapter. In addition, the application of hyperbaric oxygen or the use of breathing methods represent efficient tools to target hypoxia-related responses in chronic stress, anxiety and depressive disorders.

6.1. Hyperbaric oxygen therapy and breathing techniques

It has been suggested that re-establishing normal oxygen levels may be beneficial in conditions of hypoxia-related inflammation (Larrick et al., 2021). Therefore, interventions like hyperbaric oxygen therapy (HBOT) may also be efficient to treat anxiety and depressive disorders. Emerging evidence from recent mouse studies confirms this potential for anxiety (Lin et al., 2019; Luo et al., 2020). Results from HBOT application against depression (Krzystanek et al., 2021), for example in post-stroke depression (Liang et al., 2020), also indicate efficiency of this approach.

The modulation of breathing – a way of willfully modulating oxygen-supply – is another tool to reduce stress, anxiety and depressive symptoms (Jerath et al., 2015). This may be related to benefits of the repeated controlled experience to dyspnea (Meuret et al., 2018), which in turn may reduce sensitivity to stressors, possibly based on physiological adaptations to hypoxia, as discussed in the next section.

6.2. Hypoxia conditioning

Assuming that hypoxia facilitates the development of mood disorders, hypoxia conditioning consequently may be protective and could increase resistance to mental stress, anxiety and depressive symptoms (Rybnikova et al., 2008).

In line with this rational, antidepressant effects by hypoxia conditioning have been observed in rat models of depression, including models of learned helplessness (Rybnikova et al., 2007, 2008) and unpredictable chronic mild stress (Kushwah et al., 2016).

Testing rats in models of depression, including the forced swim test, chronic mild stress and novelty suppressed feeding, Zhu et al. (2010) identified BDNF mediated hippocampal neurogenesis modulation as a mechanisms involved in antidepressant effects of hypoxia conditioning. Indeed, hypoxia conditioning has also been reported to increase neurogenesis in cerebral cortical cultures (Jin et al., 2002). Impaired neurogenesis has also been linked to depression (Drew and Hen, 2007) and is crucially implicated in rodent chronic stress models, for example glucocorticoid elevating models (David et al., 2009).

In humans some early preliminary studies (original work published in Russian) also point to an efficacy of hypoxia conditioning in the treatment of depression, as summarized by Basovich (2010).

Based on these findings, Rybnikova et al. (2008) hypothesized that hypoxia conditioning may be a promising treatment strategy for post-traumatic stress disorder. Indeed, anti-anxiety effects of hypoxia conditioning have been shown in several recent animal studies modelling post-traumatic stress disorders (Ding et al., 2019; Manukhina et al., 2020, 2018).

Rybnikova and Samoilov (2015) attribute the beneficial effects of hypoxia (pre-) conditioning to enhanced HPA-responses and adaptation to mild stressors, as well as to the potentiation of negative glucocorticoid feedback. Hypoxia conditioning protocols have also been reported to reduce inflammation (Gangwar et al., 2019) and may represent new strategies for anxiety and depressive disorders also due to this effect. The

emerging link of deficits in mitochondrial respiration (Hollis et al., 2015) and mitochondrial dynamics (Gebara et al., 2020) with trait anxiety and depressive-like phenotypes in mouse models, also supports a dysregulation of oxygen metabolism associated with anxiety and depressive disorders. It furthermore is suggestive for another mechanism through which hypoxia conditioning may exert its beneficial effects; boosting mitochondrial efficiency and resilience (Burtscher et al., 2021b). Hypoxia conditioning has furthermore been demonstrated to partly prevent the autonomic imbalance associated with acute stress like hypoxia or exercise (Bernardi et al., 2001; Burtscher et al., 2004a). For example, Bernardi and colleagues showed that 2 weeks of hypoxia conditioning (3–4 periods of 7 min hypoxia exposure at rest during 1 h per day) elicited reduced vagal withdrawal (and increased hypoxic ventilatory response) during subsequently applied progressive hypoxia stress (Bernardi et al., 2001). Burtscher et al. (2004b) used a similar hypoxia-conditioning protocol over 3 weeks in older individuals, which resulted in reduced increases of heart rate, systolic blood pressure, blood lactate concentration, and the rating of perceived exertion during subsequent sub-maximal exercise (cycling at 1 W/kg) in normoxia when compared to pre-conditioning and the control group as well. Lower sympathetic tone after hypoxia conditioning, indicated by reduced resting heart rate and blood pressure values in cardiac patients, has recently been confirmed by a meta-analysis (Glazachev et al., 2021). Provided that major depression and anxiety disorders (Sanchez-Gonzalez et al., 2013; Vinkers et al., 2021) are associated with increased sympathetic nervous system activity, therapeutic benefits from hypoxia conditioning may be reasonably assumed. Another mechanism by which hypoxia conditioning may impart its favorable effects is the control of HIF-pathways: a persistent upregulation of HIF-1α was observed in rodents exposed to psycho-emotional stress but could be prevented by hypoxia conditioning (Baranova et al., 2017; Rybnikova et al., 2013).

Anxiety is also a common comorbidity of neurodegenerative diseases, including the most common form of dementia, Alzheimer's disease (Leung et al., 2021), and one with massive impacts on the quality of life. Meng et al. (2020) and Correia et al. (2021) demonstrated in mouse models of Alzheimer's disease that hypoxia conditioning not only improved cognition but also reduced anxiety symptoms. Hypoxia conditioning protocols and outcomes on anxiety and fear parameters in rodent models of post-traumatic stress disorder and neurodegenerative diseases are summarized in Table 2.

Importantly, hypoxia may be a core trigger or facilitator of neurodegenerative diseases (Burtscher et al., 2021a, 2021b, 2021d). This could contribute to an explanation for the increased occurrence of anxiety and depressive disorders in neurodegenerative diseases, as well as for the effectiveness of hypoxia conditioning.

6.3. Exercise

Motor-cognitive challenges have been shown to be associated with increased neuronal activity leading to higher oxygen demands and "functional" hypoxia in the brain and in particular in the hippocampus (Butt et al., 2021; Tang et al., 2010). While speculative at this point, such "functional", endogenous hypoxia may at least partly be responsible for the well-established cognitive (Hillman et al., 2008) and anxiolytic and antidepressive (Aylett et al., 2018; Carek et al., 2011) capacities of exercise via beneficial hypoxia adaptations.

6.4. Pharmacological approaches

It is well known that hypoxia-induced HIF activation ameliorates oxygen supply by improving vascularization and erythropoiesis via induction of VEGF and EPO, respectively. In addition, HIF-1 is a potent inducer of glycolysis, another means to secure cellular energy production in hypoxic conditions. On the other hand, HIF-1 upregulation mediates inflammatory responses and may be involved in the pathogenesis of anxiety and depressive disorders. The rapidly evolving field of HIF inhibitor development against cancers (Fallah and Rini, 2019) will provide also the only just emerging field of hypoxia-adaptations in anxiety and depressive disorders with valuable tools for preclinical trials.

Also- the potential role of central chemosensors in the development of anxiety and depressive disorders and their pharmacological modulation to target these diseases merits further research, as previously suggested (Baldwin et al., 2017).

Other pathways involved in hypoxia adaptations are those revolving around adenosine receptors, for example erythrocyte adenosine receptor A2B, the activation of which elicits beneficial metabolic reprogramming

Table 2
Outcomes and protocols of hypoxia conditioning for the treatment of anxiety and fear symptoms.

Model	Conditioning protocol	Main results	Reference
Rat PTSD model	3 sessions of 10% O_2 for 2 h every 24 h (pre or after experimental PTSD induction)	HIF-1α expression after restress ↑ Conditioning (pre and after) reduced HIF-1α overexpression and reduced anxiety-like behavior	(Baranova et al., 2017), (Rybnikova et al., 2013)
Rat PTSD model	14 days at simulated altitude with altitude and duration progressively increasing from 1000 m for 30 min on day 1–4000 m (about 12.6% O_2) for 4 h on day 5	Conditioning reduced anxiety-like behavior and fear symptoms evoked by experimental PTSD, mitigated damage to the adrenal glands, alleviated PTSD-induced metabolic and structural injury and reduced oxidative stress in various organs. Conditioning was also anxiolytic in the (non-PTSD) control group	(Manukhina et al., 2018), (Manukhina et al., 2020)
Mouse PTSD model	Over 2 weeks the mice were exposed daily to 4 h at 3000 m (about 14.2% O_2)	Conditioning reduced fear and anxiety-like behavior, reduced activation of various brain areas in PTSD and increased brain protein expression of HIF-1α, VEGF and BDNF	(Ding et al., 2019)
APP/PS1 mice (Alzheimer's disease model)	4 h hypoxia (5000 m, about 11.2% O_2) per day for 15 consecutive days	Conditioning decreased anxiety-like behaviors (and improved cognition). It increased hippocampal neurogenesis and BDNF expression and inhibited apoptosis-related protein expression	(Meng et al., 2020)
3 ×Tg-AD mice (Alzheimer's disease model)	Over 2 weeks 9 hypoxic episodes (each either 2 or 4 h long) were administered at either 8% or 11% O_2	Conditioning improved cognition and decreased anxiety-like behaviors, it also reduced cortical levels of amyloid-β and improved various parameters of brain energy metabolism 3 ×Tg-AD mice	(Correia et al., 2021)

PTSD; posttraumatic stress disorder, O2; oxygen, BDNF; brain derived neurotrophic factor

in the brain in response to hypoxia (Qiang et al., 2021), and its downstream affector AMP-activated protein kinase (AMPK). AMPK has been demonstrated to decrease as a result of the unpredictable chronic mild stress model in mice and possibly is involved in the development of anxiety- and depressive-like phenotypes (Zhu et al., 2014). Despite some promising results of modulating AMPK for example with metformin (Sarkaki et al., 2015), the potential of targeting these pathways for the treatment of anxiety and depressive disorders needs to be further explored.

Key points

→ Training or modulation of the hypoxic response may be beneficial in anxiety and depressive disorders
→ Hyperoxia can counteract anxiety and depressive symptoms in humans
→ Controlled hypoxia exposure (hypoxia conditioning) induces adaptations that were beneficial in animal models of anxiety and depression
→ Exercise-induced "functional hypoxia" may partially account for anxiolytic and antidepressive effects of exercise
→ An expanding toolset to pharmacologically modulate or mimic hypoxia adaptations is becoming available

7. Conclusions and perspectives

Although oxygen deprivation and fear of suffocation are primordial inducers of stress, panic, anxiety and possibly depression, converging adaptive mechanisms to hypoxic and mental stressors are only beginning to be acknowledged. The role of chemo-sensitive brain regions in mental stress and the parallel involvement of classical neurotransmitters, neuropeptides, transcriptomic alterations orchestrated by central transcription factors and metabolic responses in adaptations to hypoxic and mental stressors are only some of these overlaps. Based on these shared mechanisms, it is possible that the modulation of physiological systemic and cellular responses to either type of stress may affect the outcome of both hypoxic and mental stress with implications for stress-related diseases, such as anxiety and depressive disorders. Considering how physiological responses to hypoxia can influence stress response pathways (Fig. 4), it is likely that hypoxic insults or exposure to severe hypoxia can result in dysfunction of these pathways, including the SAM- and HPA-axes, and contribute to the development of stress-related diseases. Conversely, dysfunctional stress responses associated with diseases such as anxiety and depressive disorders could influence physiological responses to hypoxia, for example via impacting integral pathways for hypoxic stress adaptations, such as HIFs. This could have consequences on the tolerance to hypoxia and may affect the development of AMS and other high-altitude diseases – however, experimental and observational data on this topic are controversial. Furthermore, theoretically inter-dependent effects of stress pathways and responses to hypoxic stress may cooperatively facilitate the development of stress-related diseases. It is even possible that such synergistically acting hypoxic and mental stress responses – either acutely or by long-lasting stress-induced changes – can trigger other neuropsychiatric diseases, such as neurodegenerative diseases. Recently, increasing interest has arisen for the role of hypoxia in the pathogenesis of various neurodegenerative diseases (Burtscher et al., 2021a, 2021d; Correia and Moreira, 2021). Anxiety and depressive symptoms are common comorbidities and potential risk factors in these diseases, for example in Parkinson's (Kalia and Lang, 2015) and Alzheimer's disease (Becker et al., 2018; Cassimjee, 2007; Rosenberg et al., 2013). Although this is currently only speculative and will require experimental elucidation, hypoxic insults may be risk factors for anxiety and depressive symptoms, as well as – or thereby – for neurodegenerative diseases. In addition, chronic stress-derived vulnerabilities of shared stress pathways to hypoxia (or hypoxia-induced impairments of stress pathways) could facilitate neurodegenerative processes.

While there are indeed indications from epidemiological studies that the prevalence of anxiety and depressive disorders is influenced by for example the altitude of residence - and thus by variations in atmospheric oxygen pressures – these studies are inconsistent, probably due to the existence of a broad array of potential confounding factors (including socio-economic and other physical characteristics of high altitude environments). However, those observations are supported by (limited) evidence from animal experiments demonstrating noteworthy implications of hypoxia in models of anxiety and depression. In addition, some reports suggest an efficiency of hypoxia conditioning for related diseases, in particular post-traumatic stress disorder. This suggests that specific responses to hypoxia could be targeted to treat stress-related disorders, either by pharmacological means or by modulation of oxygen levels, e.g., using HBOT or hypoxia conditioning.

Among the vulnerabilities that can result from both severe hypoxia or from maladaptive stress responses are mitochondrial dysfunction, oxidative stress and inflammation, all of which could be pharmacological targets beside molecules targeting HIFs or adenosine receptors (as discussed above). They are also all thought to be amenable to hypoxia conditioning (Mallet et al., 2020).

Possibly one of the greatest impediments of translational research using oxygen modifications to target cerebral functions, neurological and psychiatric diseases is the hazardous nature of oxygen and especially the lack of it, in particular to the brain. It is thus important to consider hypoxia as a hormetic stressor; at adequate concentrations - and depending on other environmental and individual characteristics - it induces beneficial effects but a too high dose (composite of severity, duration and frequency) it is detrimental to the brain. Also, this aspect is similar to mental stress; while acute stress responses can be physiologically highly useful (for example by fueling rapid responses to immediate threat), excessive or persisting stress is harmful.

Summary

→ Systemic and cellular responses to hypoxic and mental stressors affect the outcome also of the respective other stressor
→ Hypoxic insults can result in dysfunction of stress-pathways and trigger stress-related diseases
→ Dysfunctional stress responses associated with diseases such as anxiety and depressive disorders could compromise hypoxia responses and promote mountain-sicknesses
→ Improving hypoxia adaptations (e.g., by hypoxia conditioning) may improve stress-related diseases
→ Mechanistically hypoxia conditioning improves overlapping outcomes of hypoxic and mental stress, including mitochondrial function and cellular defenses against oxidative stress and inflammation
→ Determination of the optimal hypoxic dose for various clinical applications of hypoxia conditioning will be a major research challenge

Submission declaration and verification

The article has not been published previously and is not under consideration for publication elsewhere. All authors have read the final version of the article and approved its publication.

Declaration of interest

The authors declare no conflicts of interest.

Data Availability

No data was used for the research described in the article.

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