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ENVIRONMENTAL STRESSORS AND NEUROENDOCRINE INTEGRATION: MECHANISTIC PATHWAYS LINKING HYPOXIC EXPOSURE TO BRAIN AND SYSTEMIC HEALTH OUTCOMES

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ABSTRACT

Growing numbers of environmental stressors are affecting human health. Although air pollution, psychological stress, high-altitude exposure, and traffic noise differ widely, each elicits responses deep within the body's regulatory systems. Activation of the hypothalamic-pituitary-adrenal axis, along with the sympathetic-adrenal medullary system, is a common outcome under these conditions. This neuroendocrine activation mediates diverse effects, including cognitive dysfunction, emotional dysregulation, neuroinflammation, blood-brain barrier, cardiometabolic disease, immune dysregulation, and accelerated biological aging. Chronic activation adds burden that steers physiology toward long-term imbalance. Most responses vary because age, genetics, or sex shape how individuals react under chronic conditions. Hypoxic conditions, which may occur at high altitudes, because of climate change, or in the context of disturbed sleep breathing, offer particularly valuable insight into how the body detects, reacts to, and frequently fails to adapt to environmental stress. Organ injury, neurological symptoms, and adrenal signals are all connected to oxygen sensors via hypoxia-inducible factor pathways. Clinical findings, data from air pollution, notions from altitude research, and neural stressors link along to form a thread: some people survive in hypoxic hypoxia, while others are incapable. Rather than combating complicated chemical mixtures, hypoxia presents just one measurable factor - the partial pressure of oxygen. This review expands on these concepts and suggests that further understanding of the neuroendocrine system involved may help define future directions for research and intervention.

Keywords: Hypoxia, Stress, HPA axis, SAM system, Allostatic load, high altitude, Acclimatization, Adaptation, Neuroinflammation, Glucocorticoids, Resilience, HIF pathway, Environmental health, Air pollution, Neuroendocrine regulation

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Abbreviations

ACTH Adrenocorticotropic hormone

AMS Acute Mountain sickness

AVP Arginine vasopressin

BBB Blood-brain barrier

BDNF Brain-derived neurotrophic factor

BOLD Blood oxygen level-dependent

CRH Corticotropin-releasing hormone

CRP C- reactive protein

FMRI Functional magnetic resonance imaging

GR Glucocorticoid receptor

HACE High-altitude cerebral edema

HAPE High-altitude pulmonary edema

IL-6 Interleukin-6

IL-1 beta Interleukin-1 beta

HIF Hypoxia-inducible factor

HPA Hypothalamic-pituitary-adrenal

GBA Gut- brain-axis

MMP Matrix metalloproteinase

MR Mineralocorticoid receptor

TNF alphaTumor necrosis factor alpha

PaO_2 Partial pressure of oxygen

PHD Prolyl hydroxylase domain

PVN Paraventricular nucleus

SAM Sympathetic-adrenal medullary

SCN Suprachiasmatic nucleus

VEGF Vascular endothelial growth factor

VHL Von Hippel-Lindau protein

1. Introduction

Across the globe, people face growing exposure to various environmental stresses - low oxygen levels, extreme temperatures, air pollution, and psychological issues. Around 25% of worldwide diseases may stem from such exposures, according to the World Health Organization.[1] Despite their differing sources and mechanisms, these stresses affect individuals and often lead to similar bodily dysfunctions. Oxidative damage, faulty mitochondria, heightened immune responses, and imbalances in hormone signaling appear repeatedly. Clarity about how distinct stressors influence overlapping body systems can reveal deeper links between shifting environments and human health problems.[1]

Among bodily systems, the neuroendocrine network stands key in managing reactions to varied outside stressors.[2,3] Exposure to polluted air, much like traditional stressors, turns on hormonal stress circuits - effects ripple well past respiratory issues alone.[2,4] This perspective carries important implications: when different environmental stressors converge into overlapping neurohumoral routes, understanding one may clarify another; fixing shared paths might shield against many threats at once.

Although many factors strain physiological systems, hypoxic hypoxia stands out within clinical medicine and basic physiological study alike. This condition arises when tissues receive too little oxygen because blood oxygen levels are diminished. This drop often follows prolonged time at high altitude, respiratory disorders, restricted blood flow, deficient red blood cell count, or interference from toxic substances.[5,6] One reason high altitude hypoxia draws attention in laboratory settings lies in how easily researchers can control and observe its effects. Where psychosocial stress challenges precise quantification, oxygen availability lends itself to quantification. Rather than combating complicated chemical mixtures, hypoxia presents just one measurable factor - the partial pressure of oxygen. Because of this straightforward nature, scientists can trace direct links between stimulus and response, untangling effects often obscured in complicated stress models. Exposure to high altitudes, research shows, reshapes several bodily processes - cognitive performance dips even as respiratory patterns shift and renal function adjusts, together aiding acclimatization.[7-9]

When a threat appears, the brain acts, shaping how the body reacts.[10,11] Central to this process is the hypothalamic-pituitary-adrenal axis. Facing stress - be it physical (e.g., hypoxia) or psychological (e.g., social threats) - nuclei in the hypothalamus

paraventricular nucleus region release corticotropin-releasing hormone; this triggers cortisol production by the adrenal glands.[12-14] At nearly the same time, the sympathetic-adrenal medullary pathway in parallel releases catecholamines that shift energy supplies and reroute circulation toward vital organs.[15-17] Such shifts prove beneficial during stress, aligning bodily functions with what survival demands. Chronic stress builds up over time because the body's systems stay active too long. Instead of an acute burst, it is constant reuse that would be detrimental. This ongoing strain, called allostatic load, was described by McEwen and Wingfield.[18,19] Their concept helps explain how chronic stress contributes to disease states.

A significant gap exists in the integrative understanding of environmental stress research. Although researchers studying air pollution now often acknowledge roles of the neuroendocrine system in health outcomes,[2,3] findings from high altitude hypoxia are rarely integrated.[20] This fragmentation limits our understanding of how multiple environmental challenges interact, why individuals differ in their responses, and how acute adaptive mechanisms transfer to maladaptation.

Recent findings highlight the value of integrated approaches. While studying high-altitude populations, Brutsaert's team noticed Nepali Sherpa often have larger spleens, along with stronger contractions when active - traits possibly enhancing oxygen delivery.[21] Holmström and colleagues extended this finding, showing how Sherpa and people from lower elevations react differently when breathing extra oxygen, revealing distinct spleen behaviors.[22] While much of the mechanistic data comes from animal models,[2,4] human research has mostly relied on cross-sectional designs;[20] meanwhile, single-stressor trials struggle to reflect complex real-world patterns.[1] These findings require cautious interpretation.

This review pulls together insights from environmental physiology, stress neurobiology, and air pollution research findings to construct a comprehensive framework for understanding how environmental stressors—particularly hypoxia as a translational model—engage neuroendocrine pathways to impact brain and systemic physiology. By tracing mechanisms from molecular oxygen sensing through integrated physiological responses to clinical outcomes, this review highlights next steps in the management of stress impacts.

Before proceeding, it is important to define the scope and boundaries of this review. The primary focus is on neuroendocrine integration pathways—specifically the hypothalamic-pituitary-adrenal axis, the sympathetic-adrenal medullary system, and hypoxia-inducible factor signaling—as common mediators of environmental stress. We do not provide comprehensive, stressor-specific coverage of topics such as particulate matter chemistry, detailed high-altitude pulmonary physiology, climate modeling, or individual psychiatric diagnoses. Rather, we emphasize convergent pathways across multiple stressors - air pollution, climate change, psychosocial stress, and noise, to reveal shared mechanisms. Hypoxia is presented as a translational model to illustrate these pathways in depth, not as an exhaustive topic. Readers seeking stressor-specific comprehensive reviews are directed to excellent prior work.[2,5,23] This deliberate breadth-over-depth approach is intended to highlight therapeutic targets common to seemingly unrelated environmental threats.

2. Environmental Stressors: Convergence on Common Pathways

2.1 THE NEUROBIOLOGY OF HYPOXIA

Starting at 1,500 meters, low oxygen levels trigger predictable body reactions. As altitude increases up to 3,500 meters, symptoms shift from mild discomfort to severe illness.[23] Instead of improving, symptoms worsen further, correlating with the duration of exposure and degree of hypoxia. Acute mountain sickness, when ascending quickly, may lead to life-threatening high-altitude pulmonary edema and high-altitude cerebral edema.[23,24] The worse the oxygen shortage becomes, so does the risk to vital

functions. Acute hypoxia, as experienced by a traveler arriving at high altitude, triggers increased heart rate, rapid breathing, and elevated blood pressure.[23,25,26] Though these shifts help enhance tissue oxygenation, they impose metabolic costs. Research led by McMorris reported that high altitude impairs cognitive function, especially on tasks requiring planning or multitasking - the harder the activity, the sharper the decline.[27,28]

Chronic hypoxia, characterized by prolonged exposure at high altitude or advanced lung disease, often presents a different physiological profile. A sudden surge in sympathetic activity might be a more subtle dysregulation - hypothalamic-pituitary-adrenal axis changes and shifts in metabolism. Persistent neuropsychological deficits, including impairments in memory, attention, and processing speed, were reported by Virués-Ortega's team.[29] In intermittent hypoxia, which characterizes obstructive sleep apnea and repeated high-altitude sojourns, adaptive demands occur with each transition. Swenson detailed the complex pulmonary vascular responses to this pattern, including sustained pulmonary hypertension that can persist during normoxic intervals.[5,6]

Hypoxia classification (acute, chronic, intermittent) oversimplifies real-world exposure continua. Heterogeneity in severity, duration, and onset complicates cross-study comparisons.[5,6] In vitro findings may not generalize to real-world conditions involving cold and psychosocial stress.[7]

2.2 AIR POLLUTION AS A NEUROENDOCRINE STRESSOR

Stress pathways respond to airborne pollutants via several routes - direct sensory irritation triggering sympathetic reflexes, pulmonary inflammation inducing circulating cytokines, and translocated particles that may directly affect central stress circuits.[2,4,30] The "stress boundary" concept suggests that the effects of air pollution cannot be fully understood without considering neurohormonal stress responses.[2] Pollutants, including ozone, particulate matter, and diesel exhaust, activate both the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal medullary system, leading to glucocorticoid and catecholamine release, shifting cardiovascular, metabolic, and immune function. Thomson further linked air pollution exposure to allostatic load, demonstrating how systemic and central nervous system impacts are interconnected.[31] Rentschler and Kodavanti provided mechanistic insights into neuropsychiatric and neuropathologic manifestations, highlighting that developmental exposures may be particularly consequential, with programmed stress reactivity persisting throughout life.[32]

A persistent challenge in air pollution research is disentangling direct pollutant effects from indirect effects mediated by neuroendocrine activation.[2,4] Studies using adrenalectomy or receptor antagonists have established causality in animal models, but analogous approaches in humans are infeasible.[2] Furthermore, particulate matter composition varies substantially by source and location, raising concerns about the generalizability of findings from single-pollutant studies.[32]

2.3 CLIMATE CHANGE AS A STRESS MULTIPLIER

Though climate change brings novel environmental stressors, it also worsens existing ones. In their analysis, Heidari and Lawrence looked at how shifting climate stressors and physiological dysregulations are connected, pointing out overlapping rather than separate effects.[1] For example, high temperatures often come together with poor air quality; meanwhile, forced relocation due to extreme weather carries deep psychosocial stress. Notably, moderate hypothermia may shield brain tissues against ischemic injury,[33-36] suggesting that temperature regulation interacts with hypoxic stress responses. Warming climates shift ecological balances, especially in mountainous areas facing combined heat and oxygen loss. In such settings, Johnson's observations of how lowland groups adjust differently from Tibetans gain deeper meaning. Genetic adaptations - once fully suited to ancient conditions - might now fall short when confronted by emerging environmental challenges.[9]

Beyond direct physiological effects, climate change may exert indirect neuroendocrine consequences through food and water insecurity, forced migration, and socioeconomic disruption. Emerging evidence indicates that climate-related disasters—including wildfires and floods—are associated with sustained elevations in stress biomarkers, with effects persisting months to years after the event.[1] These findings suggest that the neuroendocrine burden of climate change may extend far beyond direct thermal or hypoxic stress. The mental health consequences of climate anxiety, particularly among younger populations, represent an additional dimension of stress exposure that remains less understood.[1]

Because health effects often stem from multiple overlapping factors, attributing them solely to climate shifts - rather than broader societal or environmental trends - is difficult.[1] Studies typically observe patterns at a population level, which weakens conclusions about cause and effect. Furthermore, the field lacks standardized metrics for quantifying cumulative climate-related stress exposure, impeding efforts to establish dose-response relationships.[1,9]

2.4 PSYCHOSOCIAL AND ECOLOGICAL EXPOSURES

Slavich's Social Safety Theory provides a biological framework for understanding how social and ecological threats engage conserved stress responses.[37,38] Rather than acting alone, psychological stress triggers mirror bodily reactions seen during physical stressors. This suggests that diverse environmental stressors may interact through common neuroendocrine and inflammatory mechanisms. Urban living brings new challenges - noise pollution, artificial illumination after dark, and crowded spaces - that dysregulate circadian rhythms and stress axes. Supporting this idea, Recio et al. studied how vehicle noise impacts cardiovascular, respiratory, and metabolic health, linking these effects through neuroendocrine pathways.[39] Circadian rhythms shape brain-based biological clocks, according to Saper - these internal signals align with stress hormone secretion.[40] Cowell and Wright reported interactions between stress factors, emphasizing that cumulative stressor effects depend on developmental stage, sex, and genetic background.[41]

The conceptual distinction between "psychosocial" and "physical" stressors, while analytically useful, may not reflect the integrated nature of real-world experiences.[37,38] Many environmental challenges simultaneously involve physical and psychological dimensions—for example, high-altitude exposure combines hypoxemia with the psychological stress of perceived danger and social isolation.[7] Research that artificially separates these dimensions may underestimate the compounded effects of combined exposures.

2.5 CONVERGENCE OF STRESS PATHWAYS

Though varied in nature, environmental stressors often impact similar biological mechanisms, leading frequently to inflammation. Protection via inflammation was outlined by Medzhitov,[42] whereas persistent forms linked to chronic illness were detailed by Nathan and Ding.[43] Hypoxia-induced gene expression is tied to inflammation, driven by hypoxia-inducible factor-dependent pathways;[44-47] similarly, air pollution shows parallel effects.[2,4] When cells face hypoxia or related challenges, oxidation becomes evident - mitochondrial reactive oxygen species trigger cellular damage and activate stress-responsive signaling pathways.[46] Stress of many kinds reprograms metabolism; here, hypoxia-inducible factor guides a change from oxidative phosphorylation to glycolysis.[47-49] Metabolic reprogramming, much like that seen under psychosocial stress, shows up when people face air pollution, driven by stress hormones such as cortisol and catecholamine.[50,51] At the core, neuroendocrine activation reacts in tandem - whether the trigger is psychological or environmental toxins, both pathways - the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal medullary system - become engaged.[16,17,52]

Although convergence seems straightforward, it might hide distinct impacts of specific stressors that matter in practice.[2,4] Take hypoxia - it triggers

hypoxia-inducible factor mechanisms, something psychosocial stress does not do on its own. To design targeted interventions, researchers must map shared as well as separate biological routes.

3. The Neuroendocrine Stress Response

3.1 THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Stress triggers set off varied brain routes ending at the paraventricular nucleus. The hypothalamic-pituitary-adrenal axis function is initiated in the paraventricular nucleus of the hypothalamus, where corticotropin-releasing hormone and arginine vasopressin are synthesized. Once these hormones are released into the hypophyseal portal circulation, they stimulate the anterior pituitary to release adrenocorticotropic hormone into the systemic circulation, which in turn drives glucocorticoid secretion from the adrenal cortex.[12-15, 53] While bodily threats like low oxygen reach the paraventricular nucleus through signals rising from the brainstem, psychological stressors pull in higher cortical networks instead.[51] From stimulus to response, the pathway shifts based on threat type. Starting differently each time, chemical irritants like air pollutants may involve multiple pathways.[2,4] Notably, glucocorticoids are released in circadian rhythm - layered with pulsatile ultradian oscillations - a setup vital for regulating target tissue responses.[14,54,55]

Most studies assess hypothalamic-pituitary-adrenal function using single-time-point cortisol measurements or limited sampling protocols, which fail to capture the pulsatile nature that may be critical for biological effects.[14] The relationship between peripheral cortisol measures and central glucocorticoid receptor activation remains incompletely understood, particularly in the brain, where local 11β-hydroxysteroid dehydrogenase activity modifies hormone availability.[56]

3.2 THE SYMPATHETIC-ADRENAL MEDULLARY SYSTEM

Parallel to hypothalamic-pituitary-adrenal activation, environmental stressors trigger the sympathetic-adrenal medullary pathway, resulting in rapid catecholamine release. These chemicals drive adaptive changes such as increased heart rate, bronchodilation, and mobilization of energy substrates.[17,18] Far from operating alone, the sympathetic-adrenal medullary and hypothalamic-pituitary-adrenal axes interact - catecholamines amplify hypothalamic-pituitary-adrenal activity, just as glucocorticoids shape catecholamine production, aligning bodily reactions.[16] The neurovisceral integration model proposed by Thayer and Lane explains how the prefrontal cortex manages signals sent to both autonomic and neuroendocrine outflows.[57,58] When challenges like hypoxia or air pollution impair prefrontal control, those regulatory networks may fail, causing exaggerated sympathetic output.[7,59]

Even though catecholamine levels are measured in blood, these levels may not accurately reflect sympathetic nervous system activity at specific end organs, given regional differences in innervation and receptor density.[17] Moreover, the rapid metabolism of catecholamines complicates their use as biomarkers of cumulative stress exposure.

3.3 THE HYPOTHALAMUS AS MASTER INTEGRATOR

Some brain nuclei clusters sort both external and internal signals. Stress handling relies heavily on the paraventricular nucleus, where its neuroendocrine neurons project to the median eminence and its pre-autonomic neurons project to sympathetic centers.[13,51] Rhythmic cycles across each day depend on steady work by the suprachiasmatic nucleus. Environmental stressors that disrupt light exposure patterns can desynchronize suprachiasmatic nucleus outputs, contributing to hypothalamic-pituitary-adrenal dysregulation.[40,60] Metabolic and stress signals merge inside the arcuate nucleus, which might reduce hunger if oxygen levels drop low enough.[61]

3.4 GLUCOCORTICOID SIGNALING

Although glucocorticoids interact with mineralocorticoid receptors and glucocorticoid receptors alike, the mineralocorticoid receptors bind cortisol with higher affinity, shaping baseline activity; in contrast, the glucocorticoid receptors drive

stress-responsive effects.[61,62] Because sensitivity to these hormones differs by tissue, and hinges partly on 11β-hydroxysteroid dehydrogenase and FKBP5, individuals respond to stress in distinct ways.[56] Sapolsky outlined not only the permissive and suppressive but also stimulatory and preparative actions of glucocorticoids.[56] Recent work has revealed their signals entwined with those responding to hypoxia - notably promoting hypoxia-inducible factor-1α stabilization[63] along with hypoxia-inducing gene expression.[64]

Though the difference between mineralocorticoid receptor and glucocorticoid receptor roles appears straightforward in theory, real-world complexity arises because of their co-expression in many cell types and their ability to form heterodimers with distinct transcriptional properties.[61,62]

3.5 ALLOSTATIC LOAD

Stability through change defines allostasis, a process essential for survival. Overactivation of these adaptive systems, however, exerts cumulative effects known as allostatic load.[18,19,52] Load can manifest when challenges repeat, adaptation fails, or responses are prolonged.[19] Biomarker reviews by Juster et al. point to cortisol, catecholamines, and inflammatory markers as central players, along with downstream effects.[66] Exposure to air pollution ties directly into this load, according to Thomson's analysis.[20,31] One study linked allostatic load to long-term stress buildup - cardiovascular disease, diabetes, cognitive decline, and mortality.[67] Another study proposed that cumulative stress exposure accelerates biological aging through telomere attrition, epigenetic changes, and mitochondrial dysfunction.[68]

Even after thorough testing, measures of allostatic load remain inconsistent - different research projects apply distinct sets of biological markers and calculation approaches.[66,67] Because these methods differ so widely, combining results across studies becomes difficult, which also slows clinical implementation. What is more, researchers usually assess allostatic load just once per person, meaning they miss how physiological responses dysregulate gradually through life. Figure 1

4. Hypoxic Stress: A Window into Neuroendocrine Integration

4.1 THE MOLECULAR OXYGEN SENSING MECHANISM

The discovery of hypoxia-inducible factors revolutionized the understanding of cellular oxygen sensing. When oxygen levels are normal, prolyl hydroxylase domain enzymes add hydroxyl groups to hypoxia-inducible factor-α, marking it for breakdown. During hypoxia, prolyl hydroxylase domain enzymes work poorly - allowing hypoxia-inducible factor-α to build up, translocate to the nucleus, and then initiate transcription of numerous genes involved in erythropoiesis, angiogenesis, metabolism, and cell survival.[47-49,69,70] Such gene activation forms an organized shift that helps cells adapt. Depending on tissue type, different isoforms of hypoxia-inducible factor-α have distinct expression patterns, allowing graded responses.[47,71] Hypoxia-inducible factor-3α may act to suppress the functions of both hypoxia-inducible factor-1α and hypoxia-inducible factor-2α. While hypoxia-inducible factor-1α handles immediate shifts in metabolism, it is hypoxia-inducible factor-2α that manages prolonged processes tied to erythropoietic and vascular responses.[47,71]

Most studies of hypoxia-inducible factor signaling have been conducted in cell culture or animal models, with limited direct evidence from human data on how individual isoforms react to low oxygen levels.[47,69] The extent to which hypoxia-inducible factor pathway activation differs between acute and chronic hypoxia in humans remains largely unknown. Because some hypoxia-inducible factor isoforms play contrasting roles, tweaking their pathways with pharmacological manipulation demands close attention to these differences. Figure 2

4.2 HYPOXIA-INDUCIBLE FACTOR-GLUCOCORTICOID INTERACTION

Recent findings point to a bidirectional interaction between hypoxia-inducible factor and glucocorticoid signaling. Bailey and colleagues reported that

glucocorticoids promote hypoxia-inducible factor-1α stabilization through increased breakdown of von Hippel-Lindau protein.[63] From another angle, Kodama's team observed that glucocorticoids directly influence hypoxia-dependent gene expression, showing physical binding between glucocorticoid receptor and hypoxia-inducible factor-1α.[64] This crosstalk may coordinate systemic and cellular responses to combined stressors, enhancing acclimatization during high-altitude ascent.[61] Still, if hypoxia-inducible factor stays active too long, trouble may follow, as disrupted metabolism and cancer growth have been tied to its prolonged activity.[47]

How exactly hypoxia-inducible factor and glucocorticoids interact in human bodies is not fully understood. Most mechanistic studies have used transformed cell lines or non-mammalian models.[63] Whether those results apply to human physiology, especially in brain tissue where both systems operate, remains unclear. Timing adds another layer: stress hormones act fast, within minutes or hours, while hypoxia-inducible factor signals unfold more slowly, across many hours or even days - making their overlap messy for straightforward theories. Figure 2

4.3 NEUROINFLAMMATION

Hypoxia triggers hypoxia-inducible factor signals, which regulate the expression of cytokines, chemokines, and adhesion proteins - creating inflammation in hypoxic tissues.[44,71] Within the central nervous system, such shifts spark microglia and prompt reactive changes in astrocytes.[71] Alongside these effects, oxidative stress builds up; it intensifies neuroinflammation by creating feed-forward loops.[42,43,46]

What counts as adaptive or maladaptive neuroinflammation is often ambiguous - identical molecules act differently based on circumstances.[42,7] Though microglia may protect neurons during mild hypoxic conditions, they turn into neurodegenerative cells when stress is severe or prolonged. Telling these phases apart through measurable signs still demands attention.

4.4 THE BLOOD-BRAIN BARRIER

Under hypoxic conditions, the blood-brain barrier faces functional strain. Formed by brain endothelial cells alongside pericytes and astrocytes, this structure maintains neural environment stability.[73,74] When oxygen drops, these lining cells detect change - triggering hypoxia-inducible factor-related shifts like modified junction proteins and greater immune cell infiltration across blood vessels.[71,75] Though short-term tissue hypoxia may support survival, extended phases damage the tissue - a point highlighted by Taylor and Colgan.[75]

Starting with molecular shifts, low oxygen levels trigger hypoxia-inducible factor-1α activation, which blocks production of claudin-5 and occludin - key elements in cell barrier seals - and at the same time upregulates matrix metalloproteinase-2 and matrix metalloproteinase-9, enzymes known to break the basement membrane.[75,76] Instead of stabilizing connections, hypoxia prompts blood vessel cells to release vascular endothelial growth factor, a signal that increases paracellular permeability via Src kinase-dependent phosphorylation of junctional proteins.[76] Not far behind, pericytes begin to become nonfunctional when deprived of adequate oxygen; these supporting cells then detach from endothelial-lined vessels, resulting in reduced coverage, weakening microvessel strength, and opening paths for leukocyte infiltration.[74] Swelling and retraction - this is what astrocytic end-feet do when they lose their usual role in supporting endothelial cells, weakening the blood-brain barrier even more.[74] Exposure to air pollution damages the blood-brain barrier using comparable pathways; tiny particles translocate into the brain, resulting in pericyte dysfunction.[4,32]

Human blood-brain barrier research often relies on animals or lab-grown cells, which might miss key features of actual human physiology.[73,74] Species differences in blood-brain barrier properties—including tight junction protein expression and pericyte coverage—complicate translation. Furthermore, the functional consequences of blood-brain barrier disruption likely depend on which

specific components are affected and the duration of impairment.

4.5 THE GUT-BRAIN AXIS IN ENVIRONMENTAL STRESS

Appearing central to how environmental stressors affect bodily systems, the gut-brain axis shapes both neuroendocrine and neuroinflammatory outcomes. Exposure to hypoxia, air pollution, or psychological stress shifts the balance of microbes living in the digestive tract.[77,78] When oxygen levels drop, certain helpful bacteria - like Lactobacillus and Bifidobacterium - decline, whereas types linked to inflammation grow more dominant.[77] Because of these disruptions, the lining of the intestine weakens, allowing bacterial products, especially lipopolysaccharide, to escape into the bloodstream.[78] Once there, lipopolysaccharide turns on immune sensors called toll-like receptor 4, found not only in circulating cells but also in circumventricular organs, triggering widespread inflammatory signals - including inside the nervous system via vagal afferent routes.[77,78] Lipopolysaccharide transport into the brain through this nerve rooted in the gut lining creates a channel linking gut-based cues to stress-related brain networks.[78] From there, inflammatory signals travel along the vagus route to the hypothalamus, modulating how the hypothalamic-pituitary-adrenal axis responds.[79,80]

Sex differences in gut-brain axis function: Resilience in gut microbes after stress seems more pronounced in females than in males. During stress exposure, their microbiomes react differently - females maintain stability better. Hormonal activity tied to estrogen affects how the gut lining works, also shaping bacterial behavior inside. These biological distinctions may clarify why stress-related gastrointestinal and mood disorders differ between sexes. Studies point to these patterns consistently across experiments involving rodents.[81]

5. Brain Outcomes: From Molecules to Behavior

5.1 COGNITIVE DSYFUNCTION

Among those affected by hypoxic exposure, cognitive impairment is documented consistently. Work by Hornbein's team highlighted deficits in memory, attention, and decision-making abilities.[7] The prefrontal cortex may be especially vulnerable - Virués-Ortega found steady declines in short-term memory and planning skills.[29] At even mid-level high altitude, higher-order thinking suffers, according to McMorris's meta-analyses.[27,28] Spending more time at high altitude affects people differently, Li found when reviewing meta-analysis on climbers.[82] Brain functions tied to the prefrontal cortex decline more sharply, a pattern Dhungel's team noticed using a series of cognitive function tests - likely because those regions are more metabolically active than other parts of the cerebral cortex.[59]

When people face these tests multiple times at high elevation, practice gains often skew results. After coming back to normal oxygen levels, it is still debated whether brain function fully recovers.[7,29]

5.2 EMOTIONAL DSYREGULATION

Under low oxygen conditions, how emotions are managed shifts noticeably. Lupien reviewed the vulnerability of limbic structures—particularly the hippocampus and amygdala—tied to memory and fear—to chronic glucocorticoid exposure.[83] Liston demonstrated that stress-induced dendritic remodeling occurs in the prefrontal cortex, providing cellular evidence for structural plasticity underlying emotional dysregulation.[84] Arnsten elucidated stress signaling pathways that impair prefrontal function while disinhibiting limbic structures.[85] Pruessner et al. found that people with larger amygdalae tended to release more cortisol when facing psychosocial stress.[86] This imbalance may underlie the anxiety and irritability frequently associated with high altitude.[87] Dhungel and colleagues reported altered cerebral function in climbers exposed to different extreme altitudes, with frontal lobe changes correlating with self-reported cognitive disturbances.[59] Animal studies demonstrate that hypobaric hypoxia induces depressive-like behaviors associated with hippocampal neuroinflammation and reduced neurogenesis.[87]

Starting with oxygen-sensitive pathways, activity of hypoxia-inducible factor-1α within the amygdala

strengthens how fear memories form, possibly increasing vulnerability to anxious states.[85] When glucocorticoid receptors in the hippocampus fail to function properly, control over the body's stress system weakens, leading to prolonged stress responses.[61] In low-oxygen environments, diminished production of serotonin - caused by suppressed tryptophan hydroxylase - might play a role in emotional instability.[85] Within limbic regions, inflammation triggers shifts in chemical signaling via cytokines, influencing patterns linked to depression.[72]

Most research on the emotional impacts of hypoxia has relied on self-report measures, which can be affected by participants' expectations and physical sensations.[59,87] It is still difficult to distinguish the direct emotional effects of hypoxia from indirect responses related to discomfort, disrupted sleep, and situational stress.

5.3 STRUCTURAL BRAIN CHANGES

Hypoxia may lead to focal cortical and subcortical lesions. Weeks following low-oxygen conditions, Kühn documented shrinkage in gray matter in the hippocampus, prefrontal cortex, and cerebellum.[88] Instead of focal damage, Popa-Wagner suggested these episodes might speed up degenerative patterns linked to aging.[89] Sönksen described climbers who responded very differently despite similar altitudes, revealing wide variability in tolerance.[90]

Most brain imaging studies are limited by small sample sizes and a lack of pre-exposure baseline scans.[88,90] It is still unknown whether the differences seen represent permanent damage or reversible plasticity.

5.4 NEUROVASCULAR COUPLING

Under hypoxic stress, cerebral blood flow decreases despite high metabolic demand. This balance depends on the neurovascular unit integrity. This unit ensures that active brain regions receive adequate oxygen.[91,92] Iadecola reviewed how hypoxic stress challenges this unit through endothelial dysfunction, pericyte loss, and astrocytic swelling.[76,93] Østergaard developed the concept of capillary dysfunction, which limits oxygen delivery even when total blood flow is preserved.[94] Scans using functional magnetic resonance imaging reveal altered blood oxygen level-dependent signals after high-altitude exposure.[95]

6. Systemic Health Consequences

6.1 CARDIOMETABOLIC EFFECTS

Hypoxic stress has profound effects on cardiovascular and metabolic function. Eckel reviewed that metabolic syndrome results from sympathetic activation, glucocorticoid excess, and inflammatory activation.[50,51] Bärtsch and Gibbs reviewed altitude effects on the heart and lungs, including the possibility of right ventricular hypertrophy from chronic hypoxia.[60] Swenson detailed further hypoxic pulmonary vasoconstriction.[5,6] Another type of environmental stressor - air pollution - produces analogous cardiometabolic effects mediated through similar neuroendocrine activation.[2,4,39]

Though much research exists, how changes in oxygen levels affect cardiovascular and metabolic function is still unclear because studies use very different methods.[5,60] Whether these effects are reversible after exposure ends - or lead to long-term structural shifts in the cardiovascular system - remains uncertain.

6.2 IMMUNE DSYREGULATION

Every aspect of immune activity is modulated under low oxygen. Through hypoxia-inducible factor pathways, antimicrobial peptides, phagocytic receptors, and inflammatory cytokines are regulated.[42,43,94] Eltzschig and Carmeliet highlighted common pathways linking oxygen availability to inflammatory status across organ systems.[45] Cain and Cidlowski reviewed immune regulation by glucocorticoids, which can be pro- or anti-inflammatory depending on context.[96] Palazon and colleagues further examined the role of hypoxia-inducible factor transcription factors in inflammation and immunity, noting that metabolic reprogramming toward glycolysis is essential for pro-inflammatory activation of macrophages and T cells.[48]

Immune responses under low oxygen conditions can either strengthen protection or raise vulnerability - it hinges on how long someone is exposed and their personal traits, though these aspects are not fully understood yet.[44,45] Research so far has mostly tested single types of immune cells in vitro; such setups might miss how immunity really works inside living bodies.

6.3 ENDOCRINE IMBALANCE

Starting with hypoxic exposure, one clear shift appears in thyroid activity - less hormones in body tissues, possibly saving energy during acclimatization. Though not always obvious, the same conditions often dampen gonadal hormone output, leading to lower reproductive function. Instead of steady patterns, growth hormones shift unpredictably, influencing how the body manages metabolism and tissue repair. When stress pathways engage deeply with endocrine axes, chronic stress tends to boost hypothalamic-pituitary-adrenal activity while quieting systems tied to growth and reproductive axes - a point highlighted by Chrousos.[43,54] Much like a hypoxic state, air pollution triggers comparable disruptions across these internal balances.[4,32]

Endocrine effects of hypoxia have been studied primarily in male subjects, with limited data on women.[41] The clinical significance of moderate endocrine alterations during high-altitude exposure remains uncertain.

6.4 LONG-TERM DISEASE RISK

Though less obvious at first glance, hypoxic stress ties closely to increasing risk for cardiovascular, metabolic, and neurodegenerative diseases. The allostatic load framework here provides a conceptual model for these associations.[51,66] Polsky, Rentscher, and Carroll point toward additional mechanistic insight into stress-induced biological aging.[68] Guidi confirmed strong associations between allostatic load and major chronic diseases.[67]

7. Adaptive Versus Maladaptive Responses. Table 1

7.1 RESILIENCE

Resilience is an active process shaped by various adaptive mechanisms. Feder, Nestler, and Charney examined the psychobiological foundations of resilience, pointing to well-regulated hypothalamic-pituitary-adrenal axis function and adequate neurotrophic support as critical components.[68] In their studies, Southwick and Charney highlighted factors linked to resilient outcomes, such as cognitive flexibility and strong social connections.[69] Kalisch outlined a comprehensive framework that underscores resilience mechanisms operating across multiple levels of functioning.[70] Russo identified important molecular contributors, including brain-derived neurotrophic factor and neuropeptide Y, as central mediators.[71] Resilience at the population level was found in Johnson's work on Tibetans adapted to high altitude.[9]

Some scholars argue that studies on resilience often overlook systemic sources of stress, focusing too narrowly on personal traits.[68,69] Whether interventions can truly boost resilience - or if it mostly stems from fixed differences between people - is still debated.

7.2 EPIGENETIC MODULATION

A molecular interface between physiological function and environmental experience is provided by epigenetic processes. Meaney and Szyf reported a paradigm for the epigenetic programming of stress reactivity through maternal care.[95,96] McGowan applied these discoveries to humans, showing that those with a history of childhood abuse have epigenetic modulation of the glucocorticoid receptor.[97] In their analysis of FKBP5, Klengel and colleagues showed that gene-environment interactions are mediated by allele-specific epigenetic alterations.[98] In their analysis of the epigenetic control of stress susceptibility, Zannas and West further pointed out that changes may be reversible.[99] Other studies revealed epigenetic changes brought on by

hypoxia that are linked to tissue fibrosis and altered gene expression.[100,101] Similar epigenetic modifications result from exposure to air pollution.[4,32]

Epigenetic research tied to environmental stress often relies on samples like blood or saliva – these may not reflect brain-specific epigenetic changes.[95,97] Though shifts in methylation show up frequently, their actual biological impact remains unclear.

7.3 INDIVIDUAL SUSCEPTIBILITY

Individual differences in stress outcomes are striking. Some of this comes down to genes. In one study, people with serotonin transporter polymorphism showed stronger relationships between life stress and depression.[102] Research on FKBP5 reveals how it shapes responses under stress and links to psychiatric disorders.[103,104] A framework by Boyce and Ellis suggests that some individuals are more susceptible to environmental influences due to heightened reactivity.[105] At developmental stages, males and females may react in distinct ways - this timing matters greatly, according to Cowell and Wright.[41]

In females, estrogen enhances glucocorticoid receptor expression, thereby altering hypothalamic-pituitary-adrenal axis negative feedback and promoting rapid recovery from stress.[41,105] Progesterone might heighten sensitivity to stressful events. When inflammation is encountered, immune cells in the female brain tend to react more intensely.[105] Instead of syncing tightly, these patterns shift across life phases - before puberty, reactions differ sharply from those seen later in adulthood.[41] Gut microbes in the digestive tract vary by sex, shaped in part by how estrogen influences microbial composition.[105] After menopause, some advantages linked to estrogen fade, altering protection once present. Though early life shows distinct regulation, adult hormonal states reshape how systems respond overall.[41]

The extent to which genetic factors identified in psychiatric populations generalize to environmental stress responses in healthy individuals remain uncertain.

8. Clinical and Translational Implications

8.1 BIOMARKERS

Biomarkers that consistently signal biological changes remain essential for applying stress research to clinical practice. Though alternatives exist, cortisol - measured via saliva or hair - continues to dominate studies of hypothalamic-pituitary-adrenal axis activity.[106,107] Instead of focusing on single markers, researchers also track inflammation through proteins such as C-reactive protein and interleukin-6, which link chronic stress to disease processes.[108] Rather than isolating one system, allostatic load scores bring together measures across multiple regulatory systems to capture cumulative dysregulation.[51,66] Emerging attention has turned toward hypoxia-inducible factor-associated mechanisms and epigenetic shifts, revealing how cells respond to oxygen fluctuations and prolonged environmental stress.[47,48,72,99,100]

Even with much study, not one biological marker - or combination of markers - has proven reliable enough for clinical use to predict how a person will respond to stress.[66,106] Biomarker variability within individuals over time limits their utility for risk stratification.

8.2 RISK STRATIFICATION

Identifying individuals more likely to face adverse effects could allow targeted prevention. Pre-exposure risk stratification might consider genetic factors, prior stress history, baseline hypothalamic-pituitary-adrenal function, and pre-existing medical conditions. Prior stress history and baseline hypothalamic-pituitary-adrenal function predict stress reactivity.[109,110,66] Sex and developmental stage are critical modifiers.[41]

8.3 PREVENTION

Prevention means limiting contact with stressors while building acclimation over time, alongside aiding recovery. Graded exposure gives time to adapt gradually.[9] Air quality management and individual-

level interventions like air filtration can reduce exposure.[4,32] Sleep optimization is particularly important since high altitude often disturbs sleep patterns deeply.[111,30] Nutritional support and psychosocial support could buffer against allostatic load.[109,110]

8.4 THERAPEUTIC MODULATION

Therapeutic interventions often target a return to neuroendocrine stability when maladaptive patterns emerge, aiming also to reduce allostatic load while supporting recovery. Although various types of interventions appear helpful, research supporting them is still in the early stages.

Pharmacological Interventions: Pharmacological approaches commonly focus on restoring balance within the neuroendocrine system when unhealthy patterns develop. They also seek to reduce the impact of prolonged stress and support the body's natural recovery processes. While a range of investigations show promise, the scientific evidence behind them is still developing and remains limited. Though acetazolamide stands as the established choice for preventing and managing acute mountain sickness,[112,100] more recent approaches are increasingly being recognized as effective. Instead of relying solely on traditional methods, researchers have observed mifepristone (RU-486) counteracting metabolic and mental disruptions caused by glucocorticoids in early-stage research.[61,65] While selective agents acting on the glucocorticoid receptor are being explored,[62] their medical use is still cautious due to potential risks. An alternative approach focuses on inhibiting FKBP5, a regulatory protein that affects the sensitivity of the glucocorticoid receptor. Animal research indicates FKBP5 blockers help stabilize hypothalamic-pituitary-adrenal activity while easing signs of anxious behavior.[103,104] Instead of enhancing blood flow, drugs like sildenafil and tadalafil reduce hypoxic pulmonary vasoconstriction and improve oxygenation at high altitude.[5,6] Antioxidant supplementation with N-acetylcysteine helps increase glutathione levels and reduces hypoxic-induced oxidative damage in animal models.[46] Results involving vitamin C remain inconsistent across trials.[89] Omega-3 fatty acids reduce circulating inflammatory markers such as C-reactive protein, interleukin-6, and interleukin-1 beta, and attenuate stress-related hormonal responses, including reduction in cortisol and adrenocorticotropic hormone elevation during experimental stress.[96]

Non-Pharmacological Interventions: Early results suggest that cognitive training targeting executive functions may help preserve cognitive performance during simulated altitude exposure.[27,28] Mindfulness practices lower cortisol responses when facing laboratory stressors while also reducing levels of inflammation in the bloodstream.[69,70] Though subtle, these shifts reflect measurable physiological change under controlled conditions. Vagus nerve stimulation turns on cholinergic routes linked to calming inflammation, possibly reducing brain-related inflammatory reactions during stress.[57,58] Exercise training enhances cardiorespiratory fitness and improves hypoxic tolerance through increased capillary density, mitochondrial biogenesis, and improved autonomic regulation.[60] Laboratory research shows probiotics aimed at the gut-brain connection can lower stress sensitivity while stabilizing hypothalamic-pituitary-adrenal axis activity.[79,80]

9. Future Directions

Future research should embrace system-level approaches, combining molecular, physiological, and behavioral measurements. Multi-omics technologies offer unprecedented opportunities to characterize individual stress responses. Wearable sensors might track behavior patterns through digital signals, revealing how lifestyle shapes health. Instead of one-size-fits-all approaches, genetic analysis offers clues tailored to individuals. Biomarkers tied to environmental influences appear capable of guiding timing for treatments. Body responses measured over time add depth beyond genetics alone.

Tracking epigenetic shifts over time when people face certain exposures might reveal moments best

suited for medical or behavioral adjustments. Attention turns naturally toward how modifications in gene expression link to the brain's ability to reorganize itself. Rigorous investigation of sex-specific differences in hormone-mediated neural responses to stress necessitates robust experimental design, including adequately powered sample sizes to reliably detect biologically meaningful distinctions between males and females.[41,105]

Imaging tools like functional magnetic resonance imaging reveal shifts over time after contact with certain agents. Blood flow patterns, tracked through spin labeling methods, show evolving brain activity. Over months, repeated scans capture how these effects unfold gradually. Such techniques highlight real-time responses within neural networks.

Because heat stress affects bodily systems, city planning must consider how hormones and nerves respond. Climate change adaptation, urban planning, occupational medicine, travel medicine, and public health interventions should incorporate understanding of neuroendocrine pathways.[1,7,41,39,65]

10. Conclusion

Despite its role in linking surroundings to bodily function, the neuroendocrine system shapes health outcomes through stress-responsive networks. Not only does it engage the hypothalamic-pituitary-adrenal axis, but it also activates the sympathetic-adrenal medullary system alongside oxygen-sensitive molecular routes. These mechanisms convert external cues into internal adjustments - provided timing and scale remain balanced. Yet if activation persists beyond necessity, injury begins to accumulate slowly. Over time, such strain disrupts equilibrium, paving the way for illness.

Looking at different environmental stressors - like low oxygen, air pollution, constant sound, and psychological stress - it becomes clear they all affect similar brain-body communication routes. What stands out is how consistent this pattern remains across species and conditions. These overlapping mechanisms suggest new ways to tackle public health through unified strategies. Still, caution is needed because much of what we know comes from lab animals, human research often lacks controlled settings, and key groups such as elderly people and females have been left out too often.

With climate shifts speeding up, cities growing denser, and people moving into new habitats, handling environmental pressures demands broader strategies. Studies ahead should combine system-wide methods and tailored medical models alongside real-world implementations. Sex-based variations and early life influences, although often overlooked, require focused analysis. Epigenetic processes matter just as much. Because stressors multiply, so does the urgency for unified scientific responses.

Conflict of interest statement:

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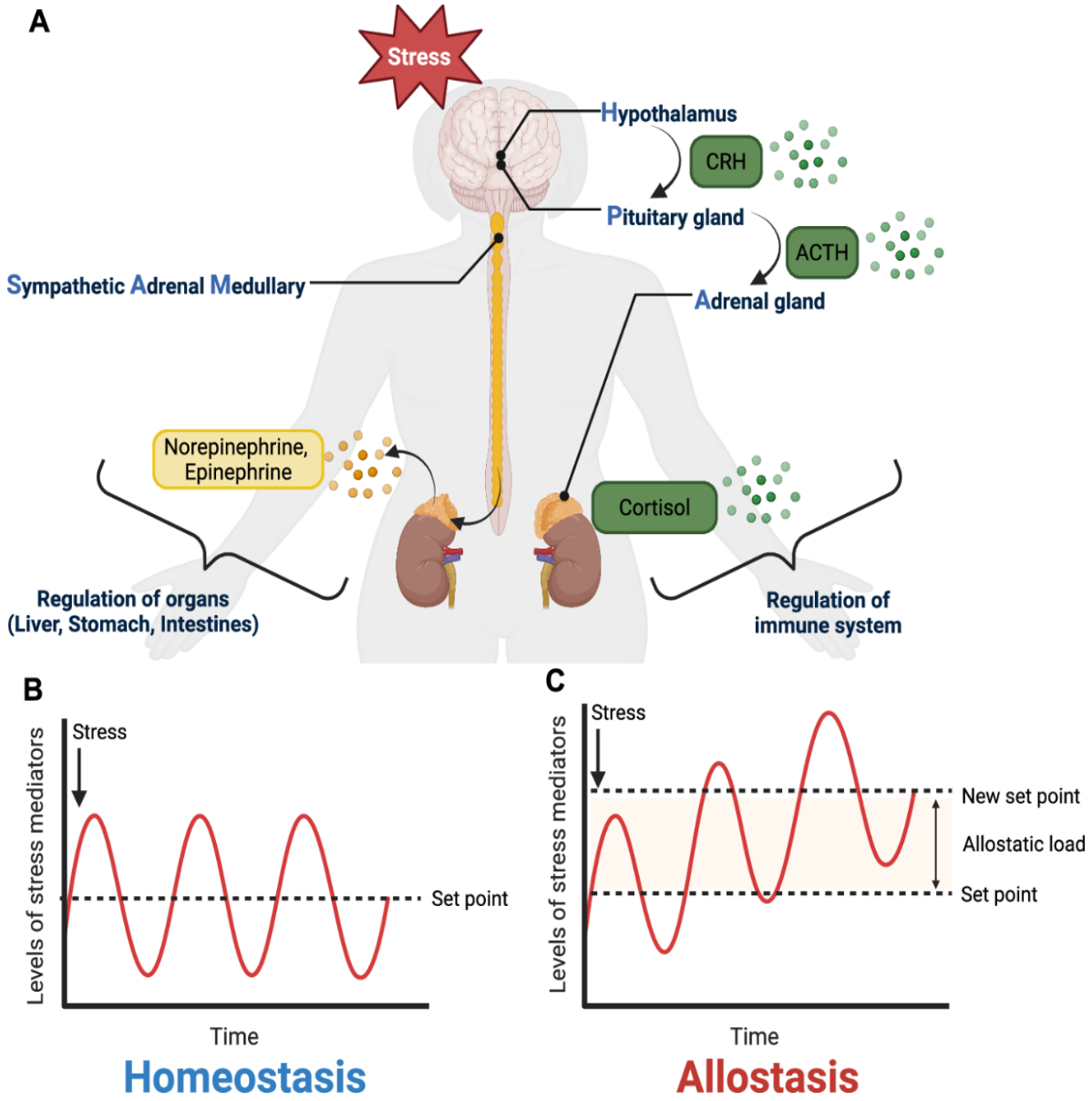
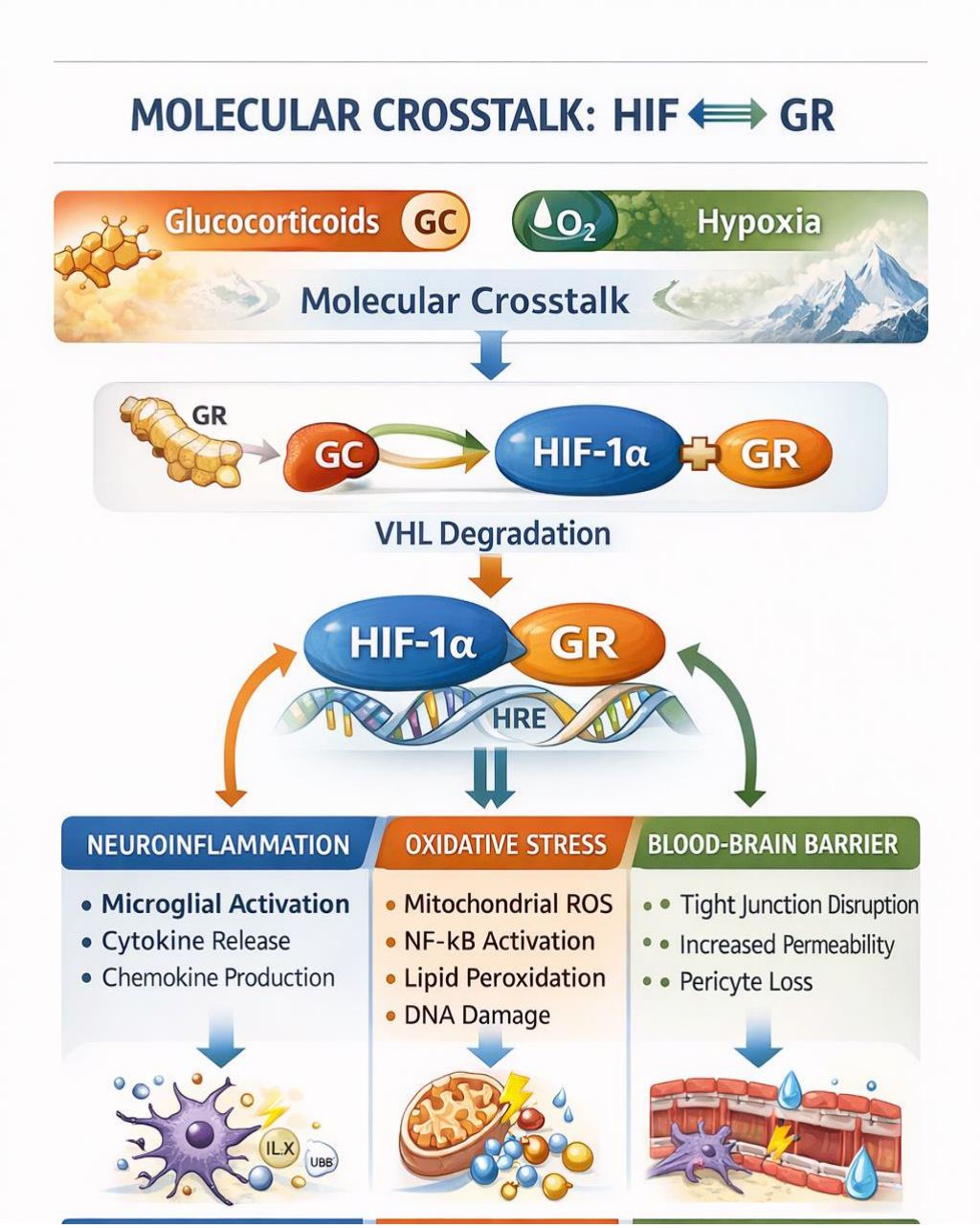


(A) Stress activates the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary system (epinephrine, norepinephrine), regulating immune and visceral functions. (B) Homeostasis shows adaptive oscillations of stress mediators around a stable set point. (C) Chronic stress shifts this set point upward (allostasis), increasing variability and sustained mediator levels. The cumulative burden of this shift constitutes allostatic load and contributes to multisystem dysregulation.

Figure 1. Neuroendocrine stress response and allostasis



Crosstalk between hypoxia-inducible factor and glucocorticoid signaling is bidirectional and context-dependent, as an integrated regulatory network coordinating oxygen sensing and systemic stress responses,[113,114] with downstream effects on neuroinflammation, oxidative stress, and blood-brain barrier integrity, contributing to neurovascular and neuroimmune dysfunction.[115-117]

Figure 2. Hypoxia-inducible factor-glucocorticoid crosstalk during hypoxic stress

Table 1. Adaptive vs Maladaptive Neuroendocrine Responses to Hypoxic Stress

Feature / Level	Adaptive Response	Maladaptive Response	Clinical / Functional Consequences
HPA Axis Activity	Transient cortisol elevation; rapid feedback inhibition	Chronic cortisol elevation; impaired feedback sensitivity	Maintains energy homeostasis vs. allostatic overload, metabolic dysregulation
SAM System	Controlled catecholamine release; efficient cardiovascular adaptation	Persistent sympathetic overdrive; elevated heart rate and BP	Supports perfusion vs. hypertension, vascular stress
Molecular / Cellular	HIF stabilization → angiogenesis, erythropoiesis; antioxidant upregulation; mitochondrial resilience	Excessive HIF signaling → ROS accumulation, oxidative stress; mitochondrial dysfunction	Promotes adaptation vs. endothelial injury, neuronal vulnerability
Neuroinflammation	Transient microglial activation; cytokine regulation	Chronic neuroinflammatory signaling; cytokine dysregulation	Supports repair vs. BBB disruption, corticolimbic damage
Cognitive / Emotional Function	Preserved attention, learning, and mood regulation	Impaired cognition, memory deficits, emotional dysregulation	Maintains brain function vs. neurobehavioral vulnerability
Immune / Endocrine Integration	Balanced immune tone; transient metabolic adjustments	Dysregulated immunity; insulin resistance; adipose redistribution	Short-term defense vs. systemic disease risk
Resilience Mechanisms	Epigenetic plasticity; efficient stress recovery; prior acclimatization	Epigenetic maladaptation; impaired stress recovery; susceptibility to repeated stress	Supports long-term adaptation vs. increased disease susceptibility
Clinical Correlates (High-Altitude Examples)	Successful acclimatization; normal cerebral perfusion	Acute Mountain Sickness (AMS), High-Altitude Cerebral Edema (HACE), chronic maladaptation	Demonstrates translational relevance of neuroendocrine trajectories

Key adaptive responses enable short-term survival and long-term resilience through tightly regulated hypothalamic-pituitary-adrenal axis activity, sympathetic modulation, and cellular homeostasis. Maladaptive responses arise from chronic or excessive stress signaling, leading to oxidative stress, neuroinflammation, endothelial dysfunction, cognitive and emotional impairment, and systemic disease susceptibility.

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