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REVIEW ARTICLE

# Homeostatic Control of Stress: Interplay Between Pro and Anti-Stress Modulators

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## ABSTRACT

Stress is characterised as a condition of altered homeostasis, which might be due to psychological or physical factors. As humans face challenges, stress acts as an evolutionarily conserved adaptive reaction that helps organisms maintain homeostasis. However, several clinical illnesses, such as neuropsychiatric, metabolic, and neurodegenerative disorders, are caused by dysregulation of stress pathways. The continuity, severity and unpredictability of stress can produce numerous pathologies. The sympathetic-adrenomedullary (SAM) process and the hypothalamic-pituitary-adrenal (HPA) axis, which coordinate central and peripheral adaptations, are the key mediators of the stress response. A dynamic balance between pro-stress and anti-stress modulators, such as catecholamines, cytokines, reactive oxygen species, glucocorticoids, antioxidant systems, heat shock proteins, and transcriptional regulators like peroxisome proliferator-activated receptors, appears to control stress physiology. To comprehend the foundation of stress biology and to find novel biomarkers, it is essential to look at the insights of pro- and antistress modulators. The present review emphasizes the significance of their balance in defining physiological resistance vs disease susceptibility by offering a thorough insight into traditional and modern viewpoints on stress modulators. The understanding of these stress modulators helps researchers to identify specific stress biomarkers and plan treatment strategies, accordingly.

***KEYWORDS:*** Stress modulators, ROS, Glucocorticoids, HPA-axis, neurodegenerative disorders.

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## Introduction

Stress is a universal biological phenomenon experienced by all living organisms. It represents a coordinated set of physiological and behavioural responses to environmental challenges, which may be either threatening or rewarding in nature. Various regulatory systems within the body are triggered and coordinated by different brain responses to enhance the organism's capacity to respond to environmental (both internal and external) alterations. These responses are essential for survival, as they facilitate adaptation by reallocating energy resources and optimizing organismal performance. However, it is increasingly recognized that a substantial proportion of chronic illnesses, estimated at 70–80%, are associated with stress or stress-related mechanisms.[1]

The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenomedullary (SAM) arrangement are two interrelated systems that play a main role in mediating the stress response. The activation of these systems brings about a series of neuroendocrine and autonomic alterations that support adaptive responses. Acute activation of these pathways is advantageous, but dysregulated or chronic stimulation has detrimental effects, including as neurodegeneration, metabolic problems, and systemic inflammation.[2,3]

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Numerous conditions, such as colitis, asthma, hypertension, depression, cancer, inflammation, and other neurological disorders, have been linked to stress-related dysregulation.[4,5] The combined effect of various physiological systems altered by ongoing stressors leads to allostatic load. This highlighted the significance of the regulatory balance of various pro- and anti-stress modulators in maintaining health.[6]

Stress responses are multifactorial, modulating through various central and peripheral pathways such as the HPA axis, catecholamines, antioxidant systems, immunomodulators, cytokines, neurotrophic factors, mitochondrial perturbations, etc. Hence, it is essential to first understand the intricate regulations between these pro- and anti-stress modulators to understand the biological basis of stress outcomes at the physiological level. Secondly, in order to target the stress-induced pathologies, it is also relevant to examine the potential of such biomarkers to identify various stress-induced conditions for specific targets and

treatment strategies. Several studies indicated that using mono drugs or targeting only one pathway or mechanism may not be enough for successful treatment of stress-induced pathologies; rather, a multitarget approach is required. Hence, in the present review, we have emphasised providing insights about the numerous pro- and antistress modulators in terms of their maintenance of haemostasis and identifying them as potential biomarkers.

## Organization of the Stress System

The brain structure, like the hypothalamus, is involved in mediating neural circuits initiating, propagating, and inhibiting stress responses. The key modulators of the HPA axis are the paraventricular nucleus (PVN) of the hypothalamus, which comprises corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) neurons. They interact meticulously with the locus coeruleus–norepinephrine (LC-NE) system, forming a bidirectional network that participates in neuroendocrine and autonomic responses.[7,8]

These intricate central and peripheral connections for mounting an appropriate stress response are mediated by various higher brain regions such as the hippocampus, striatum, prefrontal cortex, and amygdala. The hippocampus regulates negative feedback through glucocorticoids and mineralocorticoids on their respective receptors. The prefrontal cortex mainly helps in cognitive control and decision-making, while the amygdala is involved in mediating fear and emotional responses. Together, these structures play a vital role in modulating stress responses both for its initiation, producing the fight or flight response and in terminating it so that stress-induced pathologies may not harm the body. Figure 1 explains the above-mentioned central and peripheral pathways to modulate the stress responses.

It is to be noticed that along with the HPA axis, the SAM system is another important peripheral element of the stress response, primarily interconnected through glucocorticoids, neurotransmitters, and their impact on a wide range of immunological perturbations, biochemical processes, and brain activity. To be specific, the SAM system facilitates the traditional "fight-or-flight" response by mediating quick reactions through the release of catecholamines.[1,3,8]

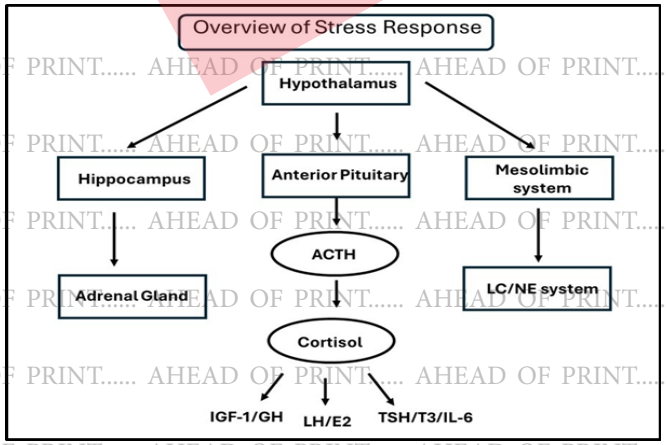


**Figure 1**: The diagram represents various central and peripheral circuits for the modulation of the stress response.

## Pro-Stress Modulators

### (i) Catecholamines and Monoaminergic Systems

Stress responses are mostly mediated by catecholamines, such as norepinephrine, dopamine, and adrenaline. Increased arousal and alertness during stress are caused by the noradrenergic system, which arises from the locus coeruleus. While prolonged activation can result in immunological suppression, anxiety, and cardiovascular problems, acute activation increases adaptive responses. Fast-acting neurotransmitters and hormones called catecholamines, primarily norepinephrine (noradrenaline) and adrenaline (epinephrine), assist the body in mobilizing resources and modifying respiratory, circulatory, and metabolic processes during stressful situations.

The raphe nuclei give rise to the serotonergic system, which controls HPA axis activity and modifies emotional reactions. Serotonin signalling dysregulation has been connected to anxiety disorders, depression, and poor stress coping strategies. In a similar vein, motivation, reward processing, and cognitive function are all influenced by the dopaminergic system, namely the mesolimbic and mesocortical pathways. Dopamine signalling changes brought on by stress can lead to anhedonia, cognitive impairments, and heightened susceptibility to substance abuse.[1,8,9]

### (ii) Cytokines and Neuroimmune Interactions

Cytokines are signalling proteins that allow the immune system to interact with the neurological system. They are mostly secreted by immune cells, but they are also released by glia and certain brain-resident cells. The reciprocal effects of cytokines and immunological activity on neuronal and glial function are known as neuroimmune interactions. Stress is linked to immune system activation, which releases inflammatory-inducing cytokines such as TNF-alpha and IL-6 etc. These cytokines affect neuroendocrine function and interact with the CNS, which causes the emergence of systemic diseases and mood disorders.[10-12]

### (iii) Oxidative and Nitrosative Stress

Excess reactive oxygen species cause oxidative stress, while excess reactive nitrogen species cause nitrosative stress. They frequently work together to produce peroxynitrite, which damages lipids, proteins, and DNA extensively, usually because of inflammation and malfunctioning mitochondria. Stress-induced oxidative and nitrosative stress causes oxidative damage to cellular constituents.

Oxidative stress has been linked to neurodegenerative diseases and mental disorders and impacts mitochondrial activity, calcium homeostasis, and neuronal integrity. Because of its fast metabolic rate and high lipid content, the brain is especially vulnerable to oxidative injury.[13,14]

## Anti-Stress Modulators

### (i) Antioxidant Défense Systems

To combat oxidative stress, the body uses an advanced antioxidant defence mechanism. To neutralize reactive species, enzymatic antioxidants such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) are essential. Redox balance is further maintained by non-enzymatic antioxidants like glutathione. By preventing, reducing, or repairing damage brought on by reactive oxygen species (ROS) and reactive nitrogen species (RNS), antioxidant defence systems safeguard cells. SOD, which transforms superoxide into hydrogen peroxide, and CAT and GPx, which detoxify hydrogen peroxide (and lipid peroxides) into water or corresponding alcohols, are important enzymatic defences. They work in tandem with the glutathione (GSH) system and associated thioredoxin pathways, which use reducing equivalents (such as NADPH) to regenerate oxidized antioxidant molecules. While cellular signalling networks (redox-sensitive transcription and stress-response pathways) upregulate antioxidant genes during oxidative challenge, non-enzymatic antioxidants like vitamin C, vitamin E, carotenoids, and uric acid also scavenge free radicals. Lastly, repair and removal mechanisms (like proteasome-mediated degradation and DNA repair) aid in the restoration of function following oxidative damage. Cellular damage and the advancement of illness can result from the disruption of these processes.[1,4,8]

### (ii) Heat Shock Proteins

Heat shock proteins (HSPs) are examples of molecular chaperones that guarantee correct protein folding and stop aggregation to shield cells from harm brought on by stress. By assisting other proteins in folding correctly, preventing misfolding and aggregation, and facilitating the refolding or destruction of damaged proteins, HSPs shield cells from stress. Stressors include heat, oxidative/nitrosative stress, hypoxia, inflammation, and exposure to toxins, which cause their expression to increase quickly. HSP70, HSP90, and tiny HSPs are major families that bind unfolded proteins and preserve cellular proteostasis. HSPs can also alter signalling pathways related to apoptosis and survival. HSPs enhance cell resilience and impact recovery following stress by maintaining protein integrity and facilitating the removal of aberrant proteins; when overburdened or dysregulated, compromised HSP function is linked to the advancement of diseases, such as neurodegeneration and other chronic inflammatory conditions. Among these, HSP-70 is a biomarker of cellular stress and highly inducible. HSPs are crucial elements of the cellular stress response because they also protect mitochondria and prevent apoptosis.[8,15-17]

### (iii) Glucocorticoids and Feedback Regulation

The stress response is modulated through a negative feedback mechanism by mineralocorticoids and glucocorticoids at various brain regions like the hippocampus, frontal cortex, amygdala, and hypothalamus, etc. By exerting negative feedback on the HPA axis, glucocorticoids prevent overreaction to stressors. However, sustained exposure to high glucocorticoid levels might have negative consequences, such as immunological suppression and neuronal atrophy.[3,5,18,19]

### (iv) Neuropeptides and CRH Signalling

CRH is the starting ligand of the HPA-axis. It integrates neuroendocrine, autonomic, and behavioural aspects of the stress response, making it a crucial regulator. CRH receptors, which are distributed throughout the central and peripheral nerve systems, mediate its actions, primarily through CRF1 and CRF2. Anxiety and stress-related disorders have been linked to dysregulation of CRH signalling and differential expression of CRF1 and CRF2.[3,5,7]

### (v) PPAR Signalling and Metabolic Regulation

Nuclear transcription factors called peroxisome proliferator-activated receptors (PPARs) control inflammation, metabolism, and mitochondrial activity. It has been demonstrated that PPAR pathway activation has neuroprotective benefits by lowering oxidative stress and neuroinflammation. These pathways are modulated by pharmaceuticals like metformin and thiazolidinediones, although their clinical effectiveness is still context-dependent.[20] PPAR-gamma is lately used as one of the important biomarkers of stress to examine the role of various antistress agents.[21]

## Integration of Pro- and Anti-Stress Systems

The body's synchronised pro- and anti-stress mechanisms, which strike a balance between quick adaptation and harm prevention, integrate stress responses. Pro-stress pathways mobilize energy, modify cardiovascular and immunological function, and change physiology toward survival amid acute stresses (e.g., sympathetic nervous system activation and the HPA axis leading to cortisol production). The intensity and duration of these reactions are then controlled by anti-stress systems: cortisol gives the HPA axis negative feedback, regulatory immune circuits and anti-inflammatory cytokines limit excessive immune activation, and cellular stress defences (like heat shock proteins and antioxidant systems) prevent damage from oxidative and nitrosative stress. Thus, it can be concluded that there exists a dynamic equilibrium between various activating and inhibitory pathways/ molecules modulating the physiological stress response under normal scenarios. For example, for coping with acute stress responses, mobilisation of energy and the

facilitation of adaptive behaviour predominate. However, continued stress leads to an imbalance in antistress pathways, resulting in pathological disorders marked by oxidative perturbations, neuroendocrine dysfunction, and heightened inflammation. Thus, it is relevant to understand these intricate processes regulating stress response by focusing on the interactions between neurotransmitters, glucocorticoids, immunological mediators, and biochemical regulators.[9,13,22-24]

## Future Perspectives

Future studies should focus on understanding both pro- and antistress processes at biochemical, molecular and behavioural levels to understand the detailed biological basis of stress responses under normal physiological conditions and during severity and continuity of stress, where the balance between such pathways is perturbed, leading to various central and peripheral stress-induced pathologies. Another aspect of these pro-and antistress processes/ pathways/ molecules is to establish them as stress biomarkers under different stressful physiological and pathological conditions. This will open new areas of focus with stress-induced changes, including immunometabolism, the gut–brain axis, and epigenetic regulation

## CONCLUSION

The understanding of the pro- and anti-stress modulators at the central, peripheral, neuroendocrine, immunomodulatory, monoamine and other biochemical processes help researchers to identify specific stress biomarkers and plan treatment strategies accordingly.

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