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Research Article

The Interplay Between Stress and Endocrine Regulation: Mechanisms, Biomarkers, and Physiological Consequences

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Introduction

Stress represents a multifaceted physiological and psychological response to internal or external stimuli that challenge the stability of the internal environment and disrupt homeostasis. This adaptive response is orchestrated through a highly integrated network involving the nervous, endocrine, and immune systems, with the endocrine system serving as a central regulatory axis. Through complex hormonal signaling pathways, the endocrine system enables the organism to perceive, process, and respond to stressors in a coordinated and time-dependent manner. Among these mechanisms, the hypothalamic–pituitary–adrenal (HPA) axis is recognized as the principal neuroendocrine system governing the stress response [1,2]. In response to stress, the hypothalamus secretes corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH subsequently acts on the adrenal cortex, triggering the synthesis and release of cortisol, a key effector hormone that mediates systemic adaptation [3].

Cortisol, the primary glucocorticoid in humans, exerts pleiotropic effects across multiple organ systems. It plays a critical role in maintaining energy homeostasis by promoting gluconeogenesis, mobilizing amino acids, and facilitating lipolysis. Simultaneously, cortisol modulates immune responses by exerting anti-inflammatory and immunosuppressive effects, thereby preventing excessive tissue damage during acute stress [4]. Furthermore, cortisol influences cardiovascular function by regulating vascular tone and blood pressure, and it affects central nervous system processes including cognition, mood, and memory. While these actions are essential for immediate survival and adaptation, their persistence under conditions of chronic stress can become maladaptive. Sustained elevation of cortisol levels is associated with impaired glucose metabolism, increased visceral adiposity, endothelial dysfunction, and alterations in neurotransmitter systems, collectively contributing to the pathogenesis of metabolic syndrome, depression, and anxiety-related disorders [5,6].

Beyond the HPA axis, stress exerts significant modulatory effects on other endocrine axes, highlighting the systemic nature of the

stress response. The Hypothalamic–Pituitary–Thyroid (HPT) axis is particularly sensitive to prolonged stress exposure. Chronic stress can suppress Thyroid-Stimulating Hormone (TSH) secretion and reduce peripheral conversion of thyroxine (T4) to Triiodothyronine (T3), leading to a state of functional hypothyroidism. This alteration may serve as an energy-conserving adaptation; however, it is often accompanied by fatigue, reduced metabolic rate, and impaired thermoregulation [7,8].

Similarly, the Hypothalamic–Pituitary–Gonadal (HPG) axis is adversely affected by stress. Elevated glucocorticoid levels inhibit the secretion of Gonadotropin-Releasing Hormone (GnRH), which in turn reduces Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) release. As a consequence, the production of sex steroids such as estrogen and testosterone declines, leading to disruptions in reproductive function. Clinically, this may manifest as menstrual irregularities, anovulation, decreased libido, and impaired spermatogenesis [7].

At a broader level, the interaction between stress and the endocrine system is characterized by bidirectional communication and feedback regulation. Hormones released during stress not only mediate physiological responses but also influence brain function and behavior, thereby modulating the perception of stress itself. Additionally, emerging evidence highlights the role of molecular mechanisms such as glucocorticoid receptor sensitivity, epigenetic modifications, and inflammatory signaling pathways in shaping individual variability in stress responsiveness. These mechanisms contribute to either resilience or vulnerability, determining whether stress exposure leads to adaptive outcomes or pathological conditions.

Taken together, the endocrine response to stress represents a dynamic and finely tuned system that balances immediate survival needs with long-term physiological stability. However, when this balance is disrupted by persistent or excessive stress, it can result in widespread endocrine dysregulation and increased susceptibility to chronic disease. Therefore, a deeper understanding of the complex and interconnected nature of stress-related endocrine pathways is essential for advancing both preventive strategies and therapeutic interventions [9].

Materials and Methods

This study was designed as a comprehensive narrative review aimed at synthesizing current knowledge on the interaction between stress and endocrine regulation by integrating evidence from experimental, clinical, and epidemiological investigations. A structured literature search was conducted using major scientific databases, including PubMed, Scopus, and Web of Science, to identify relevant peer-reviewed publications from 2015 to 2025. The search strategy was developed to ensure both sensitivity and specificity, combining key terms such as “stress,” “endocrine system,” “HPA axis,” “cortisol regulation,” “neuroendocrine response,” and “chronic stress disorders.”

To enhance the quality and relevance of the review, clearly defined inclusion and exclusion criteria were applied. Eligible studies included original experimental research, randomized and non-randomized clinical trials, and high-impact review articles that examined the physiological, biochemical, or molecular aspects of stress-related endocrine responses in human subjects or established animal models [10,11]. Particular emphasis was placed on studies investigating both acute and chronic stress paradigms, alterations in hormonal profiles, and their association with pathological conditions such as metabolic syndrome, endocrine disorders, and neuropsychiatric diseases. Studies published in English with clearly described methodologies and statistically validated findings were prioritized.

Key variables extracted from each study included endocrine parameters such as circulating cortisol, ACTH, thyroid hormones (T3, T4, TSH), and sex steroids (estrogen, testosterone), as well as physiological and clinical outcomes related to stress exposure. Information regarding study design, sample characteristics, duration of stress exposure, and analytical techniques was also recorded [12]. Where applicable, molecular-level data, including gene expression patterns, receptor sensitivity, and inflammatory markers, were incorporated to provide a deeper mechanistic understanding.

A comparative analytical approach was employed to identify converging evidence, inconsistencies, and potential gaps in the literature. Studies were evaluated based on methodological rigor, including sample size adequacy, control of confounding variables, and reproducibility of results. Greater weight was given to studies with robust experimental design, longitudinal follow-up, and well-defined outcome measures. This integrative approach allowed for the identification of consistent trends across different research domains while also highlighting areas requiring further investigation.

Results and Discussion

The collected evidence demonstrates that stress exerts profound and system-wide effects on endocrine homeostasis, primarily mediated through activation of the hypothalamic–pituitary–adrenal (HPA) axis [2,13]. In the context of acute stress, activation of this axis results in a rapid yet tightly regulated increase in circulating cortisol levels. This transient hormonal surge promotes immediate adaptive changes, including enhanced gluconeogenesis, increased cardiac output, and redistribution of blood flow toward essential organs such as the brain and skeletal muscles. Concurrently, physiological processes that are not critical for immediate survival—such as digestion, growth, and reproduction—are temporarily downregulated [4]. These coordinated responses are evolutionarily conserved and are crucial for maintaining organismal integrity under short-term stress

conditions.

However, when stress becomes chronic or repetitive, the regulatory mechanisms of the HPA axis may become dysregulated. In many cases, this leads to sustained hyperactivation, characterized by persistently elevated cortisol levels, although some individuals may exhibit a paradoxical blunted or hypoactive response due to feedback desensitization [14]. Chronic exposure to elevated glucocorticoids has far-reaching metabolic consequences. It promotes insulin resistance by impairing insulin signaling pathways, enhances adipocyte differentiation particularly in visceral fat depots, and disrupts lipid metabolism, thereby contributing to central obesity and dyslipidemia. These alterations collectively increase the risk of developing metabolic syndrome and type 2 diabetes mellitus [15]. Moreover, prolonged cortisol elevation negatively affects pancreatic β-cell function and may exacerbate hyperglycemia.

In addition to metabolic effects, chronic stress significantly compromises immune competence. While acute glucocorticoid release has anti-inflammatory properties, prolonged exposure leads to immune suppression, reduced lymphocyte proliferation, and impaired cytokine balance. This immunological shift increases susceptibility to infections, delays tissue repair, and may even facilitate the progression of inflammatory and autoimmune disorders [16]. At the same time, low-grade chronic inflammation may paradoxically persist, indicating a complex dysregulation rather than simple suppression of immune activity.

The impact of stress extends beyond the HPA axis to other endocrine systems, particularly the hypothalamic–pituitary–thyroid (HPT) axis. Chronic stress has been associated with decreased peripheral conversion of thyroxine (T4) to the more active triiodothyronine (T3), along with alterations in Thyroid-Stimulating Hormone (TSH) dynamics. This condition, often referred to as non-thyroidal illness syndrome, may represent an adaptive mechanism aimed at conserving energy during prolonged stress exposure [17]. Nevertheless, it frequently manifests clinically as fatigue, reduced metabolic rate, cognitive slowing, and decreased thermogenic capacity, thereby impairing overall functional performance.

Similarly, the Hypothalamic–Pituitary–Gonadal (HPG) axis is highly sensitive to stress-related hormonal changes. Elevated glucocorticoid levels inhibit hypothalamic secretion of Gonadotropin-Releasing Hormone (GnRH), leading to downstream suppression of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) [18]. As a result, the production of sex steroids such as estrogen and testosterone declines, adversely affecting reproductive physiology. In females, this may present as menstrual irregularities, anovulation, and decreased fertility, while in males it may lead to reduced spermatogenesis, decreased libido, and alterations in androgen-dependent functions.

At the molecular level, the effects of stress on endocrine regulation are mediated through several interconnected pathways. Glucocorticoid receptor signaling plays a central role, influencing gene transcription across multiple tissues. Chronic stress can alter receptor sensitivity and expression, thereby modifying cellular responsiveness to hormonal signals. In addition, epigenetic mechanisms—including DNA methylation and histone modifications—have been shown to modulate stress-related gene expression, potentially contributing to long-term changes in endocrine function and stress susceptibility [19]. Inflammatory pathways also play a significant role, as chronic stress is associated with increased production of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha. These mediators can interfere with endocrine signaling and further disrupt hormonal balance, establishing a self-perpetuating cycle of endocrine and immune dysregulation [20].

Importantly, the physiological impact of stress is not uniform across individuals. Variability in genetic background, early-life environmental exposures, lifestyle factors, and psychosocial context all influence the sensitivity and adaptability of endocrine responses. This heterogeneity underscores the complexity of stress-related disorders and highlights the need for individualized approaches in both research and clinical practice.

In conclusion, the interaction between stress and the endocrine system is highly complex and involves multiple layers of regulation, ranging from systemic hormonal responses to molecular and epigenetic modifications. While acute stress responses are essential for survival and adaptation, chronic stress represents a major risk factor for endocrine imbalance and a wide spectrum of associated diseases. Future research should prioritize the identification of sensitive and specific biomarkers of stress-related endocrine dysfunction, as well as the development of targeted therapeutic strategies aimed at restoring hormonal homeostasis and improving long-term health outcomes.

Acknowledgement

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Conflict of Interest

None.

References

1. McEwen BS, Akil H (2020) Revisiting the Stress Concept: Implications for Affective Disorders. J Neurosci 40(1): 12-21.
2. Herman JP, Tasker JG (2016) Paraventricular Hypothalamic Mechanisms of Chronic Stress Adaptation. Front Endocrinol (Lausanne) 7: 137.
3. Sheng JA, Bales NJ, Myers SA, Bautista AI, Roueinfar M, et al. (2021) The Hypothalamic-Pituitary-Adrenal Axis: Development, Programming Actions of Hormones, and Maternal-Fetal Interactions. Front Behav Neurosci 14: 601939.

4. Cain DW, Cidlowski JA (2017) Immune regulation by glucocorticoids. Nat Rev Immunol 17(4): 233-247.

5. Russell G, Lightman S (2019) The human stress response. Nat Rev Endocrinol 15(9): 525-534.

6. Tafet GE, Nemeroff CB (2016) The Links Between Stress and Depression: Psychoneuroendocrinological, Genetic, and Environmental Interactions. J Neuropsychiatry Clin Neurosci 28(2): 77-88.

7. Ortiga-Carvalho TM, Chiamolera MI, Pazos-Moura CC, Wondisford FE (2016) Hypothalamus-Pituitary-Thyroid Axis. Compr Physiol 6(3): 1387-1428.

8. Stagnaro-Green A, Pearce E (2012) Thyroid disorders in pregnancy. Nat Rev Endocrinol 8(11): 650-658.

9. Yaribeygi H, Panahi Y, Sahraei H, Johnston TP, Sahebkar A (2017) The impact of stress on body function: A review. EXCLI J 16: 1057-1072.

10. Kim JJ, Diamond DM (2002) The stressed hippocampus, synaptic plasticity and lost memories. Nat Rev Neurosci 3(6): 453-462.

11. Daviu N, Bruchas MR, Moghaddam B, Sandi C, Beyeler A (2019) Neurobiological links between stress and anxiety. Neurobiol Stress 11: 100191.

12. O'Connor DB, Thayer JF, Vedhara K (2021) Stress and Health: A Review of Psychobiological Processes. Annu Rev Psychol 72: 663-688.

13. Ulrich-Lai YM, Herman JP (2009) Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 10(6): 397-409.

14. Lei AA, Phang VWX, Lee YZ, Kow ASF, Tham CL, et al. (2025) Chronic Stress-Associated Depressive Disorders: The Impact of HPA Axis Dysregulation and Neuroinflammation on the Hippocampus-A Mini Review. Int J Mol Sci 26(7): 2940.

15. Hackett RA, Steptoe A (2017) Type 2 diabetes mellitus and psychological stress - a modifiable risk factor. Nat Rev Endocrinol 13(9): 547-560.

16. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, et al. (2019) Chronic inflammation in the etiology of disease across the life span. Nat Med 25(12): 1822-1832.

17. Van den Berghe G (2014) Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid 24(10): 1456-1465.

18. Acevedo-Rodriguez A, Kauffman AS, Cherrington BD, Borges CS, Roepke TA, et al. (2018) Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling. J Neuroendocrinol 30(10): e12590.

19. Zannas AS, Chrousos GP (2017) Epigenetic programming by stress and glucocorticoids along the human lifespan. Mol Psychiatry 22(5): 640-646.

20. Segerstrom SC, Miller GE (2004) Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull 130(4): 601-630.