THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN THE REGULATION OF MOOD AND EMOTION

Benedikta Diah Saraswati, S.Si., M.Biomed.

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The Hypothalamic–Pituitary–Adrenal Axis in the Regulation of Mood and Emotion

Benedikta Diah Saraswati[1]

[1]Faculty of Medicine, IPB University, Bogor, Indonesia

Email: benediktadiah@apps.ipb.ac.id

ABSTRACT

The hypothalamic-pituitary-adrenal (HPA) axis serves as the body's primary stress response system, coordinating hormonal cascades that influence mood and psychological well-being. This network involves the hypothalamus, pituitary gland, and adrenal cortex, releasing corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol in response to stress. While normally protective, chronic HPA axis activation in modern environments creates pathological conditions impacting mental health. HPA axis hyperactivity in mood disorders, characterized by elevated cortisol levels that negatively affect mood, cognition, and neuronal structure. This dysregulation creates a cycle where stress hormones exacerbate symptoms, triggering further activation. HPA axis dysfunction is linked to increased suicide risk independent of other psychiatric conditions. Anxiety disorders manifest as heightened stress sensitivity with exaggerated cortisol responses. Recent discoveries reveal gut microbiota influences on HPA axis activity through microbial metabolites, establishing a gut-brain-HPA connection. Sex differences significantly impact stress responses, with females exhibiting more pronounced reactions, contributing to higher prevalence of stress-related disorders in women. HPA axis dysregulation impairs prefrontal cortex functioning and hyperactivates the amygdala, resulting in poor decision-making and emotional dysregulation. Future therapeutic approaches emphasize personalized medicine incorporating biomarker testing, genetic screening, and digital health technologies for real-time stress monitoring, transforming the HPA axis into a pathway for targeted intervention.

Keywords: HPA Axis, Mood, Emotion, Endocrine System

HPA Axis and Mood Regulation

Within the intricate landscape of human physiology, few systems command as much influence over our emotional well-being as the hypothalamic-pituitary-adrenal (HPA) axis. This remarkable biological network serves as the body's primary stress response system, orchestrating a complex symphony of hormonal cascades that profoundly shape our mood, cognition, and overall psychological state. Like a sophisticated conductor directing an orchestra, the HPA axis coordinates the delicate interplay between our central nervous system and endocrine system, creating a dynamic feedback loop that can either maintain emotional equilibrium or, when disrupted, lead to significant psychological distress.

The story of the HPA axis begins deep within the brain, in a small but mighty region called the hypothalamus. Here, specialized neurons continuously monitor the body's internal environment and external stressors, acting as sentinels that detect threats to our psychological and physiological homeostasis. When these neural guardians perceive stress, they initiate a cascade of events that ripples throughout the entire body. The hypothalamus releases corticotropin-releasing hormone (CRH), a powerful chemical messenger that travels to the pituitary gland, often referred to as the "master gland" of the endocrine system.

Upon receiving this signal, the pituitary gland responds by secreting adrenocorticotropic hormone (ACTH) into the bloodstream. This hormone then journeys to the adrenal glands, perched atop the kidneys like small caps, where it stimulates the production and release of cortisol, often dubbed the "stress hormone." This entire process, from initial stress perception to cortisol release, typically occurs within minutes, demonstrating the remarkable efficiency of this ancient survival mechanism.

Under normal circumstances, this HPA axis activation serves a vital protective function. Cortisol mobilizes energy stores, sharpens focus, and prepares the body for action in the face of threats. However, the modern human experience often subjects us to chronic, persistent stressors that our evolutionary programming never anticipated. When the HPA axis remains activated for extended periods, the very system designed to protect us can become a source of harm, particularly to our mental health and emotional well-being.

In the realm of mood disorders, the HPA axis often performs a discordant symphony, with its usual harmonious rhythms replaced by chaotic, dysregulated patterns. Research has consistently demonstrated that the HPA axis is often hyperactive in individuals with mood disorders, leading to elevated cortisol levels, which can negatively impact mood, cognition, and neuronal structure (Watson & Mackin, 2006). This hyperactivity creates a vicious cycle where elevated stress hormones exacerbate mood symptoms, which in turn trigger further HPA

axis activation. Dysregulation of the HPA axis is linked to increased risk of suicide, independent of other psychiatric conditions, suggesting its significant role in mood regulation (Berardelli et al., 2020). This finding underscores the profound impact that biological stress systems can have on our most fundamental survival instincts, highlighting the critical importance of understanding and addressing HPA axis dysfunction in mental health treatment.

Recent scientific discoveries have revealed surprising new players in HPA axis regulation, expanding our understanding beyond traditional stress pathways. The gut microbiota has been identified as a potential influencer of HPA axis activity, with certain microbial metabolites capable of modulating the stress response (Misiak et al., 2020). This gut-brain-HPA axis connection represents a fascinating frontier in mood disorder research, suggesting that the trillions of microorganisms residing in our digestive systems may be silent partners in our emotional well-being.

The Cognitive and Emotional Cascade

Beyond its direct effects on mood, HPA axis dysregulation creates a cascade of cognitive and emotional consequences that further compound psychological distress. The HPA axis is involved in regulating neurocognitive functions and emotional responses, with disruptions leading to heightened stress and mood disturbances (Robayo, 2023). This involvement extends to virtually every aspect of mental functioning, from basic attention and memory processes to complex emotional regulation and decision-making abilities.

The prefrontal cortex, our brain's executive control center, also suffers under chronic HPA axis activation. This region, responsible for planning, decision-making, and emotional regulation, can become impaired when constantly bathed in stress hormones. The result is often poor judgment, impulsivity, and difficulty managing emotions, symptoms commonly seen in mood disorders. The amygdala, our brain's alarm system, becomes hyperactive under chronic stress, leading to heightened emotional reactivity and increased perception of threats in the environment.

Different Regulation between Gender

The HPA axis doesn't operate identically across all individuals, with sex differences representing one of the most significant sources of variation in stress response patterns. Sex differences in HPA axis regulation have been observed, with females generally exhibiting a more pronounced stress response, which may contribute to the higher prevalence of stress-related disorders in women (Leistner et al., 2020). These differences emerge from a complex

interplay of hormonal, genetic, and social factors that begin before birth and continue throughout the lifespan.

Estrogen and testosterone exert opposing effects on HPA axis functioning, with estrogen generally amplifying stress responses while testosterone tends to dampen them. This hormonal influence helps explain why mood disorders often fluctuate with reproductive events in women's lives, such as menstruation, pregnancy, postpartum periods, and menopause. During these times, dramatic shifts in sex hormone levels can destabilize HPA axis functioning, creating windows of vulnerability for mood disorder onset or exacerbation.

The social context of stress also differs significantly between men and women, influencing how the HPA axis responds to environmental challenges. Women often face unique stressors related to caregiving responsibilities, workplace discrimination, and societal expectations that can create chronic activation of their stress response systems. Additionally, women may be more likely to internalize stress and ruminate on negative experiences, prolonging HPA axis activation and increasing vulnerability to mood disorders.

The Promise of Personalized Medicine

As our understanding of HPA axis functioning continues to evolve, the future of mood disorder treatment lies in increasingly personalized approaches that take into account individual differences in stress system functioning. Biomarker testing may eventually allow clinicians to assess HPA axis functioning directly, guiding treatment selection and monitoring recovery progress. Genetic testing could identify individuals at higher risk for HPA axis dysfunction, enabling preventive interventions before mood disorders develop (Ring 2025).

The integration of digital health technologies offers exciting possibilities for real-time monitoring of stress responses and personalized intervention delivery. Wearable devices that track cortisol levels, heart rate variability, and other biomarkers of stress could provide continuous feedback about HPA axis functioning, allowing for immediate adjustments to treatment strategies (Jerath *et al*. 2023)

The HPA axis represents both a window into the biological foundations of mood disorders and a promising target for therapeutic intervention. As we continue to unravel its complexities, we move closer to a future where mental health treatment is truly personalized, addressing not just symptoms but the underlying biological mechanisms that drive emotional suffering. In this future, the HPA axis may transform from a source of vulnerability into a pathway toward healing, offering hope for the millions of individuals who struggle with mood disorders worldwide.

References

Watson, S., & Mackin, P. (2006). HPA axis function in mood disorders. *Psychiatry*, *5*(5), 166-170.

Berardelli, I., Serafini, G., Cortese, N., Fiaschè, F., O'Connor, R. C., & Pompili, M. (2020). The involvement of hypothalamus–pituitary–adrenal (HPA) axis in suicide risk. *Brain sciences*, *10*(9), 653.

Misiak, B., Łoniewski, I., Marlicz, W., Frydecka, D., Szulc, A., Rudzki, L., & Samochowiec, J. (2020). The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota?. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *102*, 109951.

Robayo, A. M. M. (2024). Hypotalamus-pituitary-adrenal (HPA) axes and their relationship with stress, mood, personality, and neurocognitive functioning. In *The Theory of Mind Under Scrutiny: Psychopathology, Neuroscience, Philosophy of Mind and Artificial Intelligence* (pp. 341-365). Cham: Springer Nature Switzerland.

Leistner, C., & Menke, A. (2020). Hypothalamic–pituitary–adrenal axis and stress. *Handbook of clinical neurology*, *175*, 55-64.

Ring, M. (2025). An Integrative Approach to HPA Axis Dysfunction: From Recognition to Recovery. *The American Journal of Medicine*.

Jerath, R., Syam, M., & Ahmed, S. (2023). The future of stress management: integration of smartwatches and HRV technology. *Sensors*, *23*(17), 7314.