Review Article

Influences of Microbial Infections on Hormonal Balance

Wafaa Hazim Salih [1,*], Huda S. H. Al-Khalidy [2]

[1] Department of Microbiology, Al-Kindy College of Medicine, University of Baghdad, Baghdad 10071, Iraq

[2] Department of Clinical Biochemistry, Al-Kindy College of Medicine, University of Baghdad, Baghdad 10071, Iraq

[*] Corresponding author: wafaahazim@kmc.uobaghdad.edu.iq

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Abstract

Although considerable knowledge exists on bacterial infections' ability to alter the immune response, significantly less is understood about their impact on hormonal regulation, specifically concerning the stress hormone cortisol. Cortisol is a vital hormone in an organism's stress response, its levels are precisely controlled by hypothalamic-pituitary-adrenal axis. It is triggered during bacterial infections, leading to disrupted cortisol secretion, which impairs the body's innate reaction to stress, both acute and chronic. This review elucidates the mechanisms by which bacterial infections affect cortisol levels, beginning with the disruption of normal cortisol production due to acute or chronic infection. Cortisol serves a dual function in regulating the immune response: it functions as an inflammation reducing agent, while its dysregulation frequently results in heightened inflammatory damage. The significant implications of alterations in cortisol levels for stress-related disorders, including anxiety and depression, as well as cardiovascular diseases, have been examined. It also examines the influence of several bacterial pathogens on cortisol modulation, indicating that distinct infections may elicit divergent responses in cortisol dynamics. A comprehensive understanding of the interplay between bacterial infections and cortisol regulation will yield significant insights into stress management, immunological responses, and potential therapeutic targets.

Keyword: Cortisol, Stress and bacterial infection, HPA axis.

Introduction

The immune and endocrine systems are among the most intricate and vital in the body. Recent research during the past decade has shown their remarkable interaction, demonstrating several bidirectional communication pathways and reciprocal regulatory mechanisms [1]. Dysregulations of the immune system are associated with endocrine disorders like autoimmune thyroiditis, diabetes types 1 and 2, osteoporosis, and dysfunctions of the HPA axis. Thyroid cancer and other endocrine malignancies are associated with immune system impairment [2]. Stress has unambiguous and diverse effects on cognitive performance, mostly attributable to cortisol's impact on brain function. Stress impacts cognitive function in multiple manners [3]. Stress and the hypothalamic suprachiasmatic nucleus (SCN) activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the secretion of cortisol from the adrenal cortex into the circulation [4, 5]. Human cognitive abilities can be influenced by both acute and chronic amounts of cortisol. The effects may be positive or negative, contingent upon cognitive function, cortisol timing, and dosage [6]. The impact of

cortisol on various activities is contingent upon the quantity and kind of cortisol receptors present in brain regions associated with cortisol [7]. There are two intracellular cortisol receptors present in the body. These are receptors for glucocorticoids (GR) and mineralocorticoids (MR). Mineralocorticoids are found specifically in the brain, kidneys, colon, heart, and sweat glands, while glucocorticoids are distributed throughout most tissues [8, 9, 10]. This review focuses on evaluating how bacterial infections influence cortisol levels and the body's natural reaction to physiological stress. It explores the interaction between bacterial pathogens and HPA axis, detailing the mechanisms by which infections alter cortisol production and regulation. Gaining insight into cortisol's role in managing inflammation and stress responses is crucial for addressing both acute and chronic stress-related health conditions.

Understanding Cortisol and the Stress Response

An increase in cortisol production peaks twenty to forty minutes after the stressor starts. This surge is caused by the triggering of HPA axis. The cortisol secretion in response to stress varies greatly from one person to the next. Some researchers have hypothesized that stress-induced mental disorders, including anxiety and depression, are strongly correlated with cortisol levels and the HPA axis's proper functioning [11, 12].The HPA axis is the principal element of the physiological reaction to stress in the central nervous system (CNS). The HPA axis's physiological response to acute stressors ensures our survival in potentially life-threatening situations [13]. The termination of the cascade initiated by a stressor is essential for human well-being, whereas dysfunctions in this area contribute to allostatic load and increased vulnerability to stress [14]. Selye discovered that the body's mechanisms for responding to stress not only safeguard and rejuvenate the body but can also inflict harm [15]. Cortisol is recognized as a principal stress hormone secreted by the adrenal gland, playing an important function in managing the response of the body to stress, immunological regulation, and homeostasis [16]. Cortisol release during stress regulates energy management by enhancing glucose availability to enhance physical and mental endurance [17]. It is essential in regulating immunological responses by suppressing pro-inflammatory cytokines and increasing anti-inflammatory pathways. Cortisol maintains homeostasis by inhibiting the release of other hormones through negative feedback mechanisms. It influences blood pressure, metabolism, and fluid equilibrium [18, 19]. Persistently elevated cortisol levels lead to immunological suppression by inhibiting interleukin synthesis through a negative feedback mechanism, hence increasing susceptibility to infections [20]. Chronic elevated cortisol levels can disrupt the body's homeostatic systems, leading to hypertension, insulin resistance, and metabolic syndrome. Cortisol operates as an intermediary between stress responses and essential life functions; its dysregulation can result in numerous health problems [21, 22].

Mechanisms of Bacterial Infections and Immune Activation

Bacterial infections elicit a series of immune-logical responses that defend against invading pathogens. Bacteria emit PAMPs, including lipopolysaccharides and peptidoglycans, in response to infection, which are detected by pattern recognition receptors on immune cells such as macrophages, dendritic cells, and neutrophils [23, 24]. Recognition via pattern

recognition receptors (PRRs) triggers the activation of innate immunity, characterized by a cytokine-driven pro-inflammatory response featuring TNF-α and IL-6 aimed at recruiting more leukocytes to the infection site and initiating inflammation and bacterial phagocytosis [25, 26]. Adaptive immunity also encompasses antigen-presenting cells, which convey bacterial antigens to T-cells. The T-cells develop into several subsets to combat the virus. T-helper cells stimulate B-cells to generate neutralizing antibodies that recognize and eliminate germs [27, 28]. Certain bacteria have the capability to evade the immune system by forming biofilms, modifying surface proteins, and secreting toxins that disrupt host immunological function [29]. The immune response to bacterial infections significantly involves cytokine release, which can either aid in disease management or prove detrimental if poorly managed [30,31]. Immune cells detect infections during bacterial invasion using PRRs, particularly Toll-like receptors (TLRs), which specifically recognize lipopolysaccharides and other bacterial components [32]. The activation of intracellular cascades, specifically the NF-κB pathway, triggers secretion of pro-inflammatory cytokines including IL-1, IL-6, and TNF-α [33, 34]. The secreted pro-inflammatory cytokines facilitate the immune response by attracting neutrophils and macrophages, along with other immune cells, to the infection place. This localized inflammation result in the eradication of the encapsulated bacteria [35]. Nonetheless, substantial cytokine releases, known as a cytokine storm, cause extensive inflammation and may result in grave consequences, such as sepsis [36]. Additional signaling mechanisms, including the JAK-STAT pathway, further modulate cytokine production and the differentiation of immune cells, especially guiding the response to particular bacteria [37, 38]. Significant alterations in hormone release linked to the induction of immune system activity in response to infections or stressors are intended to regulate bodily defense mechanisms and preserve homeostasis [39, 40]. Upon exposure to pathogens, immune cells may generate pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, that not only recruits additional immune cells to inflammation site but may also activate the HPA axis, resulting in the release of stress hormones such as cortisol and adrenaline [41]. Cortisol regulates the immune response by inhibiting excessive inflammatory reactions, facilitating the function of immune cells, and curbing excessive immunological activity that may result in tissue damage [20,42].

Impact of Bacterial Infections on Cortisol Levels

The presence of bacterial infection triggers interactions with the hypothalamic-pituitary-adrenal axis, a critical pathway in the stress response, which in turn result in cortisol secretion [43]. Immune cells trigger the secretion of pro-inflammatory cytokines, such as interleukins 1 and 6 (IL-1, IL-6), and tumor necrosis factor-alpha (TNF-α), upon detecting bacterial components during bacterial invasion [34]. These cytokines migrate to the brain, where they stimulate the hypothalamus to synthesize corticotropin-releasing hormone (CRH). CRH triggers the pituitary gland to release adrenocorticotropic hormone (ACTH), which subsequently activates the adrenal glands to release cortisol [44, 45]. Cortisol exerts an anti-inflammatory impact, thereby attenuating or regulating the immune response by inhibiting further cytokine production to prevent an excessive inflammatory reaction [46, 47]. In cases of severe or chronic infections, continuous cytokine stimulation might result in sustained

cortisol release, ultimately inhibiting immune function and hindering bacterial elimination [48, 49]. The cortisol response to infection signify-cantly varies based on the type, length of time, and severity of the infection [43, 50]. Acute bacterial infections typically elicit an acute stress response in the body, characterized by a rapid increase in cortisol to defend against excessive inflammatory reactions and to mobilize energy reserves. A mild infection often induces a slight elevation in cortisol levels, sufficient to manage immunological activation without causing suppression [51, 52]. Conversely, severe or systemic infections, such as sepsis, exhibit significantly elevated cortisol levels for extended durations, partly due to the persistent stimulation of cytokines and the activation of the HPA axis [36,53]. Chronic or recurring infections cause variations in cortisol levels, typically elevated at first but later diminished as the HPA axis may become dysregulated due to persistent stimulation, occasionally resulting in what is termed "adrenal fatigue." [49,54,55,56]. Further-more, the inherent characteristics of the infectious pathogen affect cortisol variability. Bacterial infections typically elicit a more pronounced reaction, but viral or fungal infections frequently generate a distinct and perhaps less marked cortisol response [57, 58]. IL-6 and TNF-α are significant inflammatory mediators that modulate cortisol levels by activating HPA axis as a result of infections and inflammatory disorders [16]. These cytokines, upon activation by a pathogen or tissue injury, stimulate the hypothalamus to enhance the release of CRH, a hypothalamic releasing hormone. CRH prompts the pituitary gland to secrete ACTH, which in turn activates the adrenal glands to synthesize and release cortisol [59, 60]. IL-6 is particularly effective in activating HPA axis through cortisol secretion due to its capacity to communicate directly with the hypothalamus and exert influence at the pituitary level [46]. TNF-α similarly facilitates the activation of the HPA axis while also regulating other cytokines implicated in the comprehensive inflammatory response. Cortisol is secreted through a feedback system to regulate inflammation by inhibiting additional cytokine synthesis, thereby safeguarding tissues from inflammatory damage [61, 62].

Bacterial Infections and Cortisol Modulation:

In sepsis and systemic bacterial infection, cortisol levels fluctuate significantly as the body attempts to regulate the intense inflammatory response and preserve homeostasis. Sepsis is recognized for precipitating a fast elevation of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α. It swiftly stimulates the hypothalamic-pituitary-adrenal axis, resulting in a significant surge in cortisol production, essential for regulating inflammation, sustaining blood pressure, and mobilizing glucose to facilitate vital organ function during acute physiological stress. Nonetheless, this cortisol surge may be dysregulated in extended or severe sepsis [63, 64, 65]. Elevated cortisol levels initia-lly inhibit excessive inflammation; however, with the progression of sepsis, the adrenal glands fail to sustain cortisol production due to adrenal fatigue or compromised HPA axis signaling [66, 67]. This syndrome is termed relative adrenal insufficiency, characterized by inadequate cortisol levels despite ongoing inflammation, exacerbated immune suppression, hypotension, and organ failure. In sepsis, the body's inability to regulate cortisol levels underscores the hormone's critical role in modulating immune responses and overall survival during systemic infections [68, 69]. Gastrointestinal infections, especially those caused by *E. coli, Salmonella*,

and *Clostridium difficile*, can significantly affect cortisol levels via modifications in the gut flora and direct immune activation. The gut microbiota is crucial for regulating immunological responses and modifying the HPA axis. Gastrointestinal infections affect the microbiome, resulting in diminished levels of beneficial bacteria coupled with an increase in pathogenic bacteria, which subsequently heightens gut permeability and inflammation [70, 71, 72]. This then induces an imbalance and inflammation, which in turn cause the secretion of pro-inflammatory cytokines, such as IL-6 and TNF-α, which activate the HPA axis and increase cortisol production [73, 74]. Conversely, although elevated cortisol may mitigate local inflammation in the gastrointestinal tract, prolonged cortisol release undermines gut immunity and could result in the survival of pathogens [65, 75]. Furthermore, cortisol induces additional alterations in the microbiome population, resulting in a decline in microbial diversity and beneficial species. Thus, this detrimental cycle of elevated cortisol and microbiome disturbance may exacerbate gastrointestinal symptoms and hinder recovery, as cortisol's immunosuppressive properties undermine the capacity to properly eliminate the infection [71, 76]. During a respiratory infection, the lung immune cells swiftly generate pro-inflammatory cytokines, such as IL-6 and TNF-α, thereby activating the hypothalamic-pituitary-adrenal axis. This activation leads to cortisol synthesis, which is essential for regulating inflammation, reducing lung tissue edema, and maintaining blood pressure which are all vital for respiration during infection [77, 78, 79]. Elevated cortisol levels during respiratory infections serve to mitigate excessive inflammation that could potentially damage lung tissues. If the infection is more severe or prolonged, elevated cortisol levels might inhibit immunological activities and hinder the body's ability to eliminate the infection [80, 81].

Long-Term Hormonal Effects of Chronic Bacterial Infections

Chronic bacterial infections ultimately result in prolonged hormonal disruption, affecting the endocrine system and subsequently altering the equilibrium of biological systems [82]. Chronic bacterial infections typically result in prolonged immunological activation, leading to persistent inflammatory responses. This is known as chronic inflammation, which induces the persistent secretion of pro-inflammatory cytokines, hence activating the HPA axis. This activation elevates cortisol synthesis, an essential hormone for modulating stress and inflammatory reactions. Prolonged increased cortisol levels, however, have numerous adverse impacts on bodily systems, including immunological suppression, insulin resistance, and compromised thyroid function [83, 20, 26]. Chronic infection can negatively impact thyroid function, as the hypothalamus and pituitary regulate thyroid hormones through the HPA axis, and prolonged, subacute inflammation may induce alterations in thyroid hormones, potentially resulting in hypothyroidism or other thyroid problems [84, 85]. The chronic bacterial infection will disrupt the secretion of growth hormone and prolactin, adversely impacting tissue repair, growth, and general metabolic health [86].

Interplay Between Cortisol, Stress, and Immune Response During Infection:

Cortisol, linked to stress and immunological response during infection, serves as a crucial component of the body's defenses. Upon the onset of any illness, an immune response is promptly activated, leading to the secretion of

pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α. These then activate the cascade that commences the hypothalamic-pituitary-adrenal axis, which subsequently triggers the adrenal glands to secrete cortisol. It is a steroid hormone crucial for regulating the immune response by optimally balancing inflammation and immunological control to effectively address threats. Cortisol regulates its functions by inhibiting specific cytokines and averting excessive immunological activation to prevent tissue damage, hence sustaining immune homeostasis [41, 42, 43]. Nonetheless, the relationship between cortisol and immunological response is not one-dimensional. Cortisol is recognized for its ability to enhance the immune response in the short term by supplying energy and facilitating the effective operation of immune cells at infection sites, particularly during acute infections. Cortisol safeguards the body against the adverse consequences of sustained inflammation, such as cytokine storms that can result in tissue damage and potential organ failure. Cortisol has a crucial balancing role in survival during infection [87, 88, 54]. Conversely, chronic stress or infection leads to persistently elevated cortisol levels [46, 89]. Prolonged exposure of the immune system to cortisol ultimately inhibits its functioning, hence diminishing the body's capacity to eliminate infections and heightening susceptibility to secondary infections. Prolonged rise of cortisol result in metabolic alterations such as insulin resistance and weight gain, which subsequently impact immunological function [16, 90, 91,92].

Conclusion

Cortisol levels, a primary component of the body's stress response, are significantly influenced by bacterial infections. The link between immune activity and hormone control is intricate, although it is vital concerning the severity and progression of infection. Immune responses to bacterial infections influence the HPA axis, correlating with changes in cortisol levels. These alterations can influence not only the stress response but also several physiological functions, including immune function, metabolism, and behavior. Chronic bacterial infections may lead to prolonged dysregulation of cortisol levels, potentially contributing to the genesis of anxiety, depression, and cardiovascular disease. Understanding the intricate relationship between bacterial infection and hormone regulation, especially cortisol, may enhance clinical results for patients with persistent infections or stress-related disorders.

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