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Sex, Stress, and Steroids: Rethinking Cortisol Through a Gendered Lens

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Abstract
Cortisol, a vital glucocorticoid hormone, plays an essential role in the body's stress response, metabolic regulation, immunomodulation, and circadian rhythm maintenance. "Cortisol is synthesized in the adrenal cortex and regulated via the hypothalamic-pituitary-adrenal (HPA) axis in response to stress and circadian cues." While its biological significance has been well established, the effects and patterns of cortisol secretion vary by biological sex, a factor often underrepresented in historical research. This discrepancy has contributed to incomplete understandings of stress-related conditions, such as anxiety and depression, which present differently in males and females. Understanding the sex-specific differences in cortisol reactivity and regulation can shed light on the pathophysiology and treatment of these disorders. In healthy individuals, cortisol follows a circadian rhythm composed of two main phases: the cortisol awakening response (CAR) and the diurnal cortisol slope (DCS). Disruptions in these patterns are linked to negative mental health outcomes. Research has shown that males tend to exhibit higher daytime cortisol levels than premenopausal females, though this sex-based difference declines after age 50, suggesting the influence of estrogen and other sex hormones on cortisol regulation. Estrogenic milieu lowers mean cortisol levels in premenopausal females, with estrogen increasing cortisol-binding globulin (CBG), thereby decreasing levels of active cortisol. These physiological patterns extend into psychopathology: males with depression often exhibit elevated baseline cortisol, while females more frequently show blunted or irregular cortisol responses, a difference that may reflect underlying hormonal or receptor-based mechanisms. At the molecular level, glucocorticoid and mineralocorticoid receptor expression also differs between sexes, influencing how cortisol modulates stress feedback loops. High cortisol levels are a risk factor for both genders, regardless of their receptor affinity, however, low cortisol may be a protective factor for males only. These differences highlight the importance of incorporating sex as a biological variable in both clinical and preclinical cortisol research. Doing so can improve the accuracy of diagnoses, enhance treatment efficacy, and provide a more nuanced understanding of the diverse effects of stress hormones across populations.

Keywords: cortisol; sex differences; HPA axis; Stress; estrogen; testosterone; circadian rhythm; mental health; hormonal regulation

Introduction and Definition

"Cortisol is a steroid hormone primarily produced in the adrenal cortex and regulated by the hypothalamic-pituitary-adrenal (HPA) axis, with additional synthesis occurring in peripheral tissues such as the skin"[1]. It plays a central role in stress response, metabolism, immunoregulation, and cognitive function, with its bioavailability and effects varying by circadian rhythm, sleep, hormonal status, body composition, and sex [2].

While research has significantly advanced society's understanding of cortisol's functions, much of this work has been derived from studies with predominantly male and racially homogenous samples [2, 3]. This historical bias has left gaps in the comprehension of how cortisol behaves across different populations—particularly females—whose physiological and hormonal environments differ substantially from males. Females, for example, often exhibit different patterns of cortisol regulation, stress reactivity, and mental health vulnerability, which are shaped by interactions between cortisol and sex hormones such as estrogen, progesterone, and testosterone [3, 4]. Despite these differences, female-specific mechanisms have often been overlooked or generalized based on male-centered data.

Cortisol synthesis and regulation, the influence of sex hormones on its bioavailability and signaling, and emerging evidence of sex-specific stress reactivity and psychopathology together underscore the importance of integrating sex as a biological variable in neuroendocrine research and mental health science [5]. Integrating findings from both endocrine and neurobehavioral research help to uncover how cortisol contributes differently to health and disease in males and females. Such efforts not only expand

the scientific understanding of cortisol but also advocate for more equitable research practices that account for sex and gender diversity in human health studies.

Body

Cortisol Synthesis and Regulation

Cortisol synthesis is primarily regulated by the hypothalamic-pituitary-adrenal axis, the central neuroendocrine system that is essential for maintaining homeostasis and coordinating the body's response to stress. In response to environmental or psychological stressors, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH subsequently acts on the adrenal cortex, promoting cortisol production through enzymatic pathways that depend on steroidogenic enzymes such as 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) [5]. In addition to adrenal synthesis, extra-adrenal production of cortisol occurs in peripheral tissues such as the skin. This local synthesis is activated by proinflammatory cytokines like interleukin-1 (IL-1), particularly in response to tissue injury, highlighting cortisol's tissue-specific functions in immune regulation and local homeostasis [6].

Cortisol secretion is tightly governed by a circadian rhythm, orchestrated by the suprachiasmatic nucleus of the hypothalamus. Two main components define this rhythm: the cortisol awakening response (CAR)—a sharp rise in cortisol levels within 30 to 45 minutes of waking—and the diurnal cortisol slope (DCS)—a gradual decline in secretion throughout the day. These patterns regulate metabolic, cognitive, and immune functions and help synchronize physiological processes with daily environmental cycles [7].

Biological sex significantly influences cortisol regulation. Males tend to exhibit higher levels of unbound cortisol than females, a difference linked to lower concentrations of cortisol-binding globulin (CBG) and variations in sex hormone levels [8]. These sex-specific hormonal milieus affect cortisol bioavailability and receptor interactions, contributing to differences in stress reactivity and susceptibility to disease. Moreover, cortisol metabolism is modulated by sex hormones such as estrogen. The hormone is broken down in the liver and adipose tissue by A-ring reductases and regenerated from inactive cortisone in the liver, fat, and skeletal muscle by 11β-hydroxysteroid dehydrogenase (11β-reductase). Estrogen has been shown to influence the activity of these enzymes, further contributing to sex differences in cortisol dynamics [9].

Altogether, understanding cortisol synthesis and regulation requires integrating molecular pathways, circadian control, and sex-specific endocrine dynamics to fully capture the hormone's multifaceted influence on both health and disease**.**

Hormonal Influences on Cortisol Regulation

Hormonal fluctuations exert a profound influence on cortisol regulation, with sex and age shaping both its bioavailability and physiological impact. One of the key mechanisms involves the modulation of cortisol-binding globulin (CBG), which regulates the proportion of free (biologically active) cortisol in circulation. Estrogen increases CBG levels, raising total cortisol concentrations but lowering free cortisol availability, complicating the interpretation of physiological data and hormone measurement [10]—particularly in premenopausal females and those using hormonal contraceptives or undergoing hormone therapy. In clinical populations, such as females with metastatic breast cancer, disrupted vagal tone and poor sleep quality are associated with dysregulated cortisol rhythms [11].

In males, testosterone and cortisol interact in a tightly regulated balance. Testosterone typically exerts an inhibitory influence on cortisol secretion, and with aging, declining testosterone levels are associated with altered HPA axis function. This hormonal shift has been linked to disrupted sleep architecture and metabolic dysregulation, suggesting that a breakdown of the testosterone–cortisol relationship may underlie age-related vulnerabilities in stress and endocrine balance [12].

Taken together, these insights emphasize the importance of adopting a sex-specific lens when assessing cortisol. These findings highlight how hormonal and autonomic systems intersect in sex-specific ways to influence cortisol output and stress vulnerability. Hormonal context—whether shaped by age, reproductive status, or disease state—profoundly alters cortisol dynamics and should be integrated into models of stress physiology and endocrine health.

Sex Differences in Cortisol Reactivity in Stress and Mental Health

Sex differences in cortisol reactivity to both acute and chronic stress have profound implications for mental health outcomes. Males tend to show elevated cortisol levels compared to females in anticipation of a psychologically stressful situation, even in the absence of task performance [13] . In contrast, females often exhibit more variable, blunted, or delayed cortisol responses, which may arise from sex-specific regulatory mechanisms such as the modulatory influence of estrogen and progesterone on glucocorticoid receptor sensitivity [3].

In the context of chronic stress and mental illness, sex differences in cortisol regulation become even more pronounced. Females with depression or cancer often display a flattened diurnal cortisol rhythm, a reduced cortisol awakening response (CAR), and overall dysregulated secretion—markers associated with increased fatigue, immune disruption, and functional disability [14]. Similarly, in posttraumatic stress disorder (PTSD), males and females may show opposing cortisol patterns: males often display elevated basal cortisol, whereas females more frequently

present with lower cortisol levels, a paradoxical response possibly reflecting sex-specific adaptations to trauma [3].

These distinct hormonal trajectories underscore the importance of implementing sex-specific approaches in diagnosing and treating stress-related disorders. In clinical practice, interventions aimed at stabilizing HPA axis function in females and limiting cortisol overexposure in males may yield more effective and personalized outcomes.

Current Research and Clinical Implications

Contemporary research on cortisol is increasingly focused on unraveling the biological mechanisms underlying sex-specific regulation, bioavailability, and stress reactivity. Recent work has revealed that cortisol is synthesized not only in the adrenal cortex but also locally in tissues such as the skin, where it responds to inflammatory signals like interleukin-1, indicating tissue-specific regulation [6]. Additionally, attention has turned to circadian and pulsatile cortisol patterns, with findings that disruptions in the cortisol awakening response (CAR) and diurnal slope are associated with poor mental and metabolic outcomes, particularly in females with conditions such as breast or ovarian cancer [2]. Clinically, these insights hold significant implications for diagnosis and treatment. For instance, blunted cortisol rhythms in females may go unrecognized without sex-specific reference values, leading to underdiagnosis or misclassification of disorders such as depression or PTSD [3].

To advance both scientific understanding and healthcare equity, it is essential that future studies explicitly incorporate sex as a biological variable. This includes accounting for hormonal status, menstrual phase, contraceptive use, and menopausal stage in study design. Such sex-informed approaches will not only improve diagnostic precision and treatment efficacy but also foster more inclusive and personalized models of stress physiology and endocrine health.

Conclusion

Sex-based differences in cortisol biology are both profound and clinically meaningful. Males generally exhibit higher levels of free circulating cortisol, greater HPA axis reactivity to acute stress, and elevated basal cortisol in chronic conditions such as depression and PTSD [3, 13]. In contrast, females often display more variable or blunted cortisol responses, especially under chronic stress, with patterns influenced by hormonal fluctuations, menstrual cycle phase, contraceptive use, and menopausal status [4]. These differences are shaped by the modulatory effects of sex steroids—estrogen, progesterone, and testosterone—on cortisol synthesis, binding protein levels, receptor sensitivity, and feedback regulation [9, 10]. Such biological divergence contributes to distinct vulnerabilities and symptom profiles in stress-related disorders across sexes. For example, females are more likely to present with dysregulated cortisol rhythms in the context of anxiety, depression, or cancer, while males may show sustained cortisol elevation linked to cardiovascular and metabolic risk [11, 14, 15]. These patterns have important implications for diagnosis, biomarker interpretation, and treatment response.

A sex-specific lens is therefore essential in cortisol-related research and clinical application. Relying on male-dominant models can obscure critical hormonal and physiological differences, leading to incomplete or misleading conclusions. Incorporating sex as a biological variable—alongside considerations of hormonal status and life stage—not only improves scientific accuracy but also enhances the equity and effectiveness of healthcare interventions. As cortisol continues to serve as a key biomarker in stress and endocrine research, future studies must prioritize inclusive design and analysis that reflects sex-based variability. Doing so will refine our understanding of stress biology and pave the way for more personalized, precise, and equitable approaches to human health.

List of Abbreviations

ACTH: adrenocorticotropin hormone
CAR: cortisol awakening response
CBG: cortisol-binding globulin
CRH: corticotropin-releasing hormone
CYP11B1: 11β-hydroxylase
CYP11B2: aldosterone synthase
DCS: diurnal cortisol slope
HPA: hypothalamic-pituitary-adrenal
IL-1: interleukin-1
PTSD: posttraumatic stress disorder

Conflicts of Interest

The authors declare that they have no conflict of interests.

Authors' Contributions

LA: made contributions to the design of the encyclopedia, collected and analysed data, drafted the manuscript, revised, and gave final approval of the version to be published.
ES: contributed to study design and planning, assisted with the collection and analysis of data, revised, and gave final approval of the version to be published.

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