

DOI: <https://doi.org/10.36719/2663-4619/114/186-189>

Esmer Mirabova

Azerbaijan Medical University
master student

<https://orcid.org/0009-0008-7838-5007>
esmermirabova@gmail.com

Gulnara Vahabova

Azerbaijan Medical University
PhD in Biology

<https://orcid.org/0009-0006-5528-0136>
gulnaravahabova@yahoo.com

Cortisol as a Stress Hormone

Abstract

Cortisol, a critical glucocorticoid hormone produced by the adrenal glands, plays a pivotal role in various physiological processes. Its release is finely orchestrated by the suprachiasmatic nucleus, governing the circadian rhythm and activating the intricate hypothalamic–pituitary–adrenal (HPA) axis, a vital neuroendocrine system responsible for stress response and maintaining homeostasis. Disruptions in cortisol regulation due to chronic stress, disease, and aging have profound implications for multiple bodily systems. The presented article provides detailed information about the amount of cortisol in saliva and its effect on cognitive functions

Keywords: *cortisol, chronic stress, hypothalamic–pituitary–adrenal (HPA) axis, cognitive impairment, Cushing syndrome, glucocorticoid*

Əsmər Mirabova

Azərbaycan Tibb Universiteti
magistrant

<https://orcid.org/0009-0008-7838-5007>
esmermirabova@gmail.com

Gülənər Vahabova

Azərbaycan Tibb Universiteti
biologiya üzrə fəlsəfə doktoru

<https://orcid.org/0009-0006-5528-0136>
gulnaravahabova@yahoo.com

Stress hormonu kimi kortizol

Xülasə

Böyrəküstü vəzilər tərəfindən istehsal olunan kritik bir qlükokortikoid hormonu olan kortizol müxtəlif fizioloji proseslərdə əsas rol oynayır. Onun sərbəst buraxılması sirkadiyalı ritmi idarə edən və stressə cavab vermək və homeostazı saxlamaq üçün cavabdeh olan həyati vacib neyroendokrin sistemi olan mürəkkəb hipotalamo-hipofiz-adrenal (HPA) oxunu aktivləşdirən supraxiazmatik nüvə tərəfindən incə şəkildə tənzimlənir. Xroniki stress, xəstəlik və qocalma səbəbiylə kortizol tənzimlənməsindəki pozğunluqlar çoxlu bədən sistemləri üçün dərin təsirlərə malikdir. Təqdim olunan məqalədə tüpürçəkdəki kortizolun miqdarı və onun idrak funksiyalarına təsiri haqqında ətraflı məlumat verilir.

Açar sözlər: *kortizol, xroniki stress, hipotalamo-hipofiz-adrenal (HPA) oxu, koqnitiv pozğunluq, Cushing sindromu, qlükokortikoid*

Introduction

Cortisol, a type of steroid hormone, is produced from cholesterol and synthesized in the zona fasciculata of the adrenal cortex. The anterior pituitary releases adrenocorticotrophic hormone (ACTH), which boosts the expression of LDL receptors and enhances the activity of cholesterol desmolase. This enzyme converts cholesterol into pregnenolone, marking the rate-limiting step in cortisol synthesis. Most glucocorticoids in the body circulate in an inactive state, bound to proteins like corticosteroid-binding globulin (CBG) or albumin. Inactive cortisol is activated by 11-beta-hydroxysteroid dehydrogenase 1 (11-beta-HSD1) in various tissues, while 11-beta-HSD2 deactivates cortisol back into cortisone in organs like the kidney and pancreas (Angelousi, Margioris, Tsatsanis, 2020).

Research

Cortisol secretion is regulated by the hypothalamus-pituitary-adrenal (HPA) axis. The paraventricular nucleus (PVN) of the hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotrophic hormone (ACTH). ACTH then triggers the adrenal cortex to produce cortisol. In a negative feedback mechanism, adequate levels of cortisol inhibit the secretion of both ACTH and CRH. The HPA axis operates on a circadian cycle, resulting in high cortisol levels in the morning and lower levels at night (Gozansky, Lynn, Laudenslager, Kohrt, 2005). Steroid hormones, such as cortisol, are primary messengers. They can cross the cytoplasmic membrane because of their fat-soluble properties. Cell membranes are composed of phospholipid bilayers; these prevent fat-insoluble molecules from passing through. Once cortisol passes through the cell membrane and enters into the cell, it binds to specific receptors in the cytoplasm. In the absence of cortisol, the glucocorticoid receptor binds to an Hsp90 chaperone protein in the cytosol. The binding of cortisol to the glucocorticoid receptor dissociates the Hsp90. The cortisol-receptor complex then enters the nucleus of the cell and affects gene transcription.

Stress response. The human body is constantly reacting to both internal and external stressors. It processes stressful stimuli and generates a response based on the perceived level of threat. The autonomic nervous system consists of the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). During stressful situations, the SNS becomes active, initiating the fight-or-flight response, which triggers various hormonal and physiological changes. The amygdala plays a key role in processing fear, arousal, and emotional signals, deciding the appropriate response. If needed, the amygdala sends a stress signal to the hypothalamus (Kadmiel, Cidlowski, 2013). The hypothalamus then activates the sympathetic nervous system (SNS), prompting the adrenal glands to release catecholamines, like epinephrine. This leads to responses such as an elevated heart rate and faster breathing. If the body continues to sense the stimuli as a threat, the hypothalamus engages the HPA axis. Cortisol is released from the adrenal cortex, helping the body remain on high alert. In the short term, cortisol's catabolic effects provide the body with the necessary energy to cope with the situation (Lila, Sarathi, Jagtap, Bandgar, Menon, Shah, 2011).

Cortisol also influences brain function. It heightens activity in the right frontal region while decreasing approach motivation (Meyer, Smeets, Giesbrecht, 2015). It was strongly linked to midfrontal delta-beta coupling and showed a correlation with both slow-wave (delta) and fast-wave (beta) activity and was associated with anxiety and behavioral inhibition (Yehuda, Seckl, 2011). Stress triggers the activation of the HPA axis and brain function, leading to increased asymmetry in frontal activity (Oakley, Cidlowski, 2013). Additionally, MCI patients with cerebrovascular damage show increased delta power and reduced alpha2 power. Moderate hippocampal atrophy is linked to the greatest rise in alpha2 and alpha3 power, while a higher theta/gamma ratio is strongly correlated with amygdala atrophy. Moreover, the alpha3/alpha2 ratio is closely associated with hippocampal atrophy (Raff, Carroll, 2015).

Salivary cortisol measurement has been introduced as an alternative to plasma cortisol measurements in recent years. It offers advantages such as easy collection and being unaffected by

stress factors since it does not require venipuncture, and a strong correlation has been reported between salivary and serum cortisol levels. Cortisol in saliva exists in its bioactive form. Salivary cortisol is also in harmony with the 24-hour rhythm of serum cortisol. Furthermore, there is a balance between salivary cortisol and free cortisol, which is independent of the amount of saliva. Instant changes in free cortisol are reflected in salivary cortisol concentrations within a few minutes. Accordingly, the cortisol level detected in saliva collected within a 2-3 minute sampling period accurately reflects the free plasma (blood) cortisol level (Ramamoorthy, Cidlowski, 2016). For the saliva test, the normal range for adults is: 10.2-27.3 nanograms per milliliter (ng/mL) in the morning, 2.2-4.1 ng/mL at night (Schutter, Honk, 2005).

Hypercortisolism. Cushing syndrome develops when the body is exposed to elevated cortisol levels over a prolonged period. The causes of Cushing syndrome are classified as either ACTH-dependent or ACTH-independent. In ACTH-dependent cases, the excess of ACTH is usually caused by a pituitary tumor or an ectopic source, such as a neuroendocrine tumor (Tops, Peer, Wester, et al., 2006). In both instances, excessive ACTH production triggers the adrenal glands to release an abnormal amount of cortisol. In ACTH-independent subtypes, the causes can be endogenous or exogenous. The endogenous cause typically involves a tumor on the adrenal gland, resulting in increased cortisol production, while the exogenous cause arises from overuse of oral or injectable corticosteroids (WebMD). The symptoms of Cushing syndrome vary depending on the degree of cortisol elevation. Common signs of excess cortisol include weight gain, particularly in the face and abdomen, fat accumulation between the shoulder blades, diabetes, high blood pressure, excessive hair growth in women (hirsutism), muscle weakness in the upper limbs, and osteoporosis (Yılmaz, Zorlu, 2022).

Hypocortisolism. Several neuropsychiatric disorders linked to stress, such as posttraumatic stress disorder (PTSD) and chronic pain and fatigue syndromes, paradoxically show lower levels of the stress hormone cortisol in the blood. This effect is most pronounced in individuals who experienced trauma early in life, suggesting a form of developmental programming that may contribute to both reduced cortisol levels and increased susceptibility to mental health disorders. The reduced cortisol in these cases is not due to adrenal or pituitary gland malfunction. Instead, two key processes are likely at play. First, target cells become more sensitive to glucocorticoids, particularly in how they provide negative feedback to the hypothalamic-pituitary-adrenal (HPA) axis. This is thought to be caused by changes in the number of glucocorticoid receptors, which aligns with research showing that early life challenges can permanently alter these receptors in specific tissues. These changes are driven by epigenetic mechanisms. Second, early life trauma or starvation causes a long-term reduction in the breakdown of glucocorticoids, particularly due to enzymes like 5 α -reductase type 1 (mainly found in the liver) and 11 β -hydroxysteroid dehydrogenase type 2 (in the kidneys). This has been observed in both humans and experimental models. These changes may be an adaptive response from early life, aimed at increasing the persistence of active cortisol in the liver (to boost energy production) and kidneys (to improve salt retention) without raising overall cortisol levels in the blood. This avoids harmful effects on the brain and muscles. As a result, modestly lower circulating cortisol levels and increased vulnerability to stress-related disorders may occur. This idea suggests that a vulnerable early-life profile could be identified and treated with mild glucocorticoid replacement. In fact, early clinical trials with cortisol have shown some promise.

Conclusion

It has been determined that high cortisol is associated with the impairment of memory, language, reaction speed, social cognition, as well as overall cognitive function. In animals, the administration of glucocorticoids has resulted in cognitive disorders and abnormal behaviors. In cognitively healthy subjects, high cortisol levels have been linked to an increased risk of cognitive decline and autonomic dysreflexia. Research has also observed elevated cortisol levels in cases of dementia and delirium. High cortisol levels may exacerbate the effects of stressful life events, high

neuroticism, depression, and sleep disorders on cognitive performance, neurodegeneration, and the decline of cognitive abilities. Additionally, it can increase oxidative stress and amyloid β peptide toxicity, having a neurotoxic effect on the hippocampus.

References

1. Angelousi, A., Margioris, A. N., & Tsatsanis, C. (2020). ACTH action on the adrenals. In K. R. Feingold, B. Anawalt, M. R. Blackman, A. Boyce, G. Chrousos, E. Corpas, W. W. de Herder, K. Dhatriya, K. Dungan, J. Hofland, S. Kalra, G. Kaltsas, N. Kapoor, C. Koch, P. Kopp, M. Korbonits, C. S. Kovacs, W. Kuohung, B. Laferrère, M. Levy, E. A. McGee, R. McLachlan, M. New, J. Purnell, R. Sahay, A. S. Shah, F. Singer, M. A. Sperling, C. A. Stratakis, D. L. Trencé, & D. P. Wilson (Eds.), *Endotext* [Internet]. MDText.com, Inc. <https://www.endotext.org>
2. Gozansky, W. S., Lynn, J. S., Laudenslager, M. L., & Kohrt, W. M. (2005). Salivary cortisol determined by enzyme immunoassay is preferable to serum total cortisol for assessment of dynamic hypothalamic-pituitary-adrenal axis activity. *Clinical Endocrinology* (Oxford), 63(3), 336-341. <https://doi.org/10.1111/j.1365-2265.2005.02349.x>
3. Kadmiel, M., & Cidlowski, J. A. (2013). Glucocorticoid receptor signaling in health and disease. *Trends in Pharmacological Sciences*, 34(9), 518-530. <https://doi.org/10.1016/j.tips.2013.07.004>
4. Lila, A. R., Sarathi, V., Jagtap, V. S., Bandgar, T., Menon, P., & Shah, N. S. (2011). Cushing's syndrome: Stepwise approach to diagnosis. *Indian Journal of Endocrinology and Metabolism*, 15(Suppl 4), S317-S321. <https://doi.org/10.4103/2230-8210.90289>
5. Meyer, T., Smeets, T., Giesbrecht, T., et al. (2015). The role of frontal EEG asymmetry in post-traumatic stress disorder. *Biological Psychology*, 108, 62-77. <https://doi.org/10.1016/j.biopsycho.2015.03.008>
6. Yehuda, R., & Seckl, J. (2011). Stress-related psychiatric disorders with low cortisol levels: A metabolic hypothesis. *Endocrinology*. <https://doi.org/10.1210/en.2011-1016>
7. Oakley, R. H., & Cidlowski, J. A. (2013). The biology of the glucocorticoid receptor: New signaling mechanisms in health and disease. *Journal of Allergy and Clinical Immunology*, 132(5), 1033-1044. <https://doi.org/10.1016/j.jaci.2013.08.004>
8. Raff, H., & Carroll, T. (2015). Cushing's syndrome: From physiological principles to diagnosis and clinical care. *The Journal of Physiology*, 593(3), 493-506. <https://doi.org/10.1113/jphysiol.2014.281535>
9. Ramamoorthy, S., & Cidlowski, J. A. (2016). Corticosteroids: Mechanisms of action in health and disease. *Rheumatic Disease Clinics of North America*, 42(1), 15-31. <https://doi.org/10.1016/j.rdc.2015.09.003>
10. Schutter, D. J. L. G., & Honk, J. (2005). Salivary cortisol levels and the coupling of midfrontal delta-beta oscillations. *International Journal of Psychophysiology*, 55, 127-129. <https://doi.org/10.1016/j.ijpsycho.2004.07.001>
11. Tops, M., Peer, J. M., Wester, A. E., et al. (2006). State-dependent regulation of cortical activity by cortisol: An EEG study. *Neuroscience Letters*, 404, 39-43. <https://doi.org/10.1016/j.neulet.2006.06.022>
12. WebMD. (n.d.). Cortisol test. Retrieved April 9, 2025, from <https://www.webmd.com/a-to-z-guides/cortisol-test>
13. Yılmaz, S., & Zorlu, M. (2022). Subclinical hypercortisolism: An important, unrecognized dysfunction. *International Journal of Molecular Sciences*, 23(2), 673. <https://doi.org/10.3390/ijms23020673>

Received: 07.01.2025

Accepted: 02.04.2025