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The Interplay Between Blood Pressure and Cortisol: A Review of Current Evidence

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التفاعل بين ضغط الدم والكورتيزول: مراجعة للأدلة الحالية

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Abstract:
Cortisol, the body's principal glucocorticoid hormone, is a vital component of the stress response and plays an essential role in maintaining homeostasis. During periods of physical or psychological stress, cortisol secretion is upregulated as part of the hypothalamic-pituitary-adrenal (HPA) axis activation. One of cortisol's key physiological effects is its influence on cardiovascular function, specifically, its ability to modulate blood pressure (BP) through multiple mechanisms, including vascular tone regulation, fluid retention, and interaction with the renin-angiotensin-aldosterone system (RAAS). Accumulating evidence has shown that persistently elevated cortisol levels, whether due to chronic stress, dysregulation of the HPA axis, or pathological conditions like Cushing's syndrome, are strongly associated with the development of hypertension. This review critically examines the complex relationship between cortisol and blood pressure, bringing together insights from clinical research, endocrine physiology, and experimental models. It outlines how enzymes such as 11β-hydroxysteroid dehydrogenase (11β-HSD), which regulate intracellular cortisol activity, and the sensitivity of mineralocorticoid receptors (MRs) in key organs such as the kidneys, play central roles in mediating cortisol's pressor effects. The review also highlights key gaps in current understanding, including individual variability in hormonal response, genetic predispositions, and the challenge of differentiating physiological from pathological cortisol elevations. By integrating mechanistic data with clinical findings, this paper emphasizes the potential for using cortisol-related biomarkers in the early diagnosis of hypertension and proposes new directions for therapeutic intervention. Ultimately, understanding cortisol's contribution to blood pressure regulation is crucial not only for managing endocrine disorders but also for addressing one of the most prevalent cardiovascular risk factors worldwide.

Keywords: Cortisol, Blood Pressure, Cushing's Syndrome, Hormonal Stress, Hormonal Regulation.

الملخص
يُعد الكورتيزول الهرمون القشري السكري الأساسي في الجسم، عنصراً حيوياً في الاستجابة للتوتر، ويلعب دوراً محورياً في الحفاظ على التوازن الداخلي (الاستتباب). خلال فترات التوتر الجسدي أو النفسي، يزداد إفراز الكورتيزول نتيجة تنشيط محور الوطاء-النخامة-الكظر(HPA) ، وهو ما يؤثر بشكل مباشر في وظائف القلب والأوعية الدموية، لا سيما في تنظيم ضغط الدم. وتشمل آليات تأثير الكورتيزول على ضغط الدم تنظيم نغمة الأوعية الدموية، وزيادة احتباس السوائل، والتفاعل مع نظام الرينين-أنجيوتنسين-ألدوستيرون .(RAAS) وقد أظهرت الأدلة المتزايدة أن ارتفاع مستويات الكورتيزول بشكل مستمر، سواء بسبب التوتر المزمن أو اضطرابات في محور HPA أو حالات مرضية مثل متلازمة كوشينغ، يرتبط بشكل وثيق بظهور ارتفاع ضغط الدم. تستعرض هذه المراجعة العلاقة المعقدة بين الكورتيزول وضغط الدم من خلال دمج نتائج الأبحاث السريرية والنماذج التجريبية مع مفاهيم علم الغدد الصماء. كما تسلط الضوء على دور الإنزيمات مثل 11-βهيدروكسي ستيرويد ديهيدروجيناز (11β-HSD)التي تنظم النشاط داخل الخلايا للكورتيزول، وكذلك حساسية مستقبلات القشرانيات المعدنية (MR) في أعضاء رئيسية مثل الكلى، باعتبارها عناصر أساسية في تأثير الكورتيزول الرافع للضغط. وتُبرز الورقة أيضاً الثغرات الحالية في الفهم العلمي، بما في ذلك التباين الفردي

في الاستجابات الهرمونية، والاستعدادات الجينية، والصعوبة في التمييز بين الارتفاع الفسيولوجي والمرضي في مستويات الكورتيزول. من خلال دمج البيانات الآلية مع النتائج السريرية، تؤكد المراجعة على أهمية استخدام مؤشرات حيوية مرتبطة بالكورتيزول في التشخيص المبكر لارتفاع ضغط الدم، وتقترح مسارات جديدة للتدخل العلاجي. في الختام، فإن فهم مساهمة الكورتيزول في تنظيم ضغط الدم يُعد أمراً بالغ الأهمية ليس فقط في إدارة اضطرابات الغدد الصماء، ولكن أيضاً في التصدي لأحد أكثر عوامل الخطر القلبية الوعائية شيوعاً على مستوى العالم.

الكلمات المفتاحية: الكورتيزول، ضغط الدم، ارتفاع ضغط الدم، متلازمة كوشينغ، الإجهاد الهرموني، التنظيم الهرموني.

Introduction

Hypertension remains a leading risk factor for cardiovascular morbidity and mortality worldwide. While lifestyle and genetic factors have been extensively studied, the role of endocrine pathways particularly cortisol has gained increasing attention in recent years. Cortisol influences vascular tone, sodium retention, and fluid balance, which are all critical to BP regulation. This review aims to synthesize existing literature on the connection between increased cortisol levels and elevated blood pressure, identifying biochemical pathways and clinical implications.

Physiology of Cortisol and Blood Pressure Regulation

Cortisol, a critical steroid hormone, is synthesized and secreted by the adrenal cortex and is under tight regulatory control by the hypothalamic-pituitary-adrenal (HPA) axis. This system operates as the body's central command for hormonal stress response. When the brain perceives a stressor, whether physical, emotional, or environmental, the hypothalamus releases corticotropin-releasing hormone (CRH). This hormone then signals the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH), which travels through the bloodstream to stimulate the adrenal glands, resulting in the synthesis and release of cortisol [1].

Once in circulation, cortisol acts on virtually every tissue in the body. It plays a central role in orchestrating the physiological adaptations required to maintain homeostasis during stress. These effects include increasing blood glucose availability by promoting gluconeogenesis, suppressing immune function to prevent overactivation of inflammatory pathways, and, notably, modulating cardiovascular function to ensure adequate perfusion of vital organs during stress.

Cortisol contributes to the regulation of blood pressure through multiple interrelated mechanisms that reflect its influence on vascular tone and fluid balance. First, cortisol enhances the sensitivity of blood vessels to catecholamines such as norepinephrine and epinephrine, making vascular smooth muscle more responsive to vasoconstrictive signals. Second, cortisol can activate mineralocorticoid receptors, especially when its levels are elevated, mimicking the action of aldosterone [2]. This leads to increased reabsorption of sodium and water in the kidneys, expanding blood volume and, consequently, raising blood pressure. Third, cortisol inhibits the production and bioavailability of nitric oxide (NO), a potent vasodilator produced by endothelial cells. The suppression of NO results in vasoconstriction, further contributing to increased vascular resistance and elevated blood pressure.

Cortisol-Induced Hypertension: Mechanisms

11β-HSD Enzymes

Two key enzymes, 11β-HSD1 and 11β-HSD2, control local cortisol activity. 11β-HSD2 converts active cortisol to inactive cortisone in mineralocorticoid target tissues (e.g., kidneys), protecting mineralocorticoid receptors (MR) from cortisol. Dysfunction in this enzyme system allows cortisol to stimulate MR, mimicking aldosterone effects.

Studies have shown that reduced 11β-HSD2 activity leads to sodium retention and hypertension [3], [4].

HPA Axis Dysregulation

Chronic stress can cause sustained HPA axis activation, leading to persistent cortisol elevation. This has been observed in individuals with depressive disorders, shift workers, and those with PTSD, all associated with higher BP [5], [6].

Vascular and Renal Effects

Cortisol increases expression of angiotensinogen in the liver and enhances angiotensin II receptor sensitivity, contributing to vasoconstriction and elevated systemic vascular resistance [7]. In the kidneys, cortisol affects glomerular filtration rate and sodium reabsorption, key elements in BP maintenance.

Clinical Evidence Linking Cortisol and Blood Pressure

Cushing's Syndrome

Cushing's syndrome is the prototypical example of cortisol-induced hypertension, with 75–85% of patients developing elevated BP [8]. Treatment of cortisol excess in these patients typically results in BP normalization.

Pseudo-Cushing States and Subclinical Hypercortisolism

Even modest cortisol elevation, as seen in subclinical hypercortisolism, has been associated with increased cardiovascular risk. A study by Di Dalmazi et al. found a higher incidence of hypertension in patients with adrenal incidentalomas and mild cortisol excess [9].

Population Studies

Several population-based studies have demonstrated associations between cortisol levels and BP. For example, the Whitehall II study reported that higher diurnal cortisol slopes were linked to increased systolic BP [10].

Cortisol as a Biomarker for Stress-Related Hypertension

Cortisol measurement (serum, saliva, or urine) has been proposed as a biomarker for stress-induced hypertension. Salivary cortisol, especially the diurnal slope and morning levels, has shown promise in identifying individuals at risk [11].

However, challenges remain due to diurnal variation, assay variability, and the need for standardized thresholds.

Therapeutic Implications

Understanding the cortisol-BP connection opens avenues for targeted therapies:

- Metyrapone and Ketoconazole: Inhibitors of cortisol synthesis used in Cushing's syndrome may reduce BP [12].
- Mineralocorticoid Receptor Antagonists: Drugs like spironolactone and eplerenone can counteract cortisol's MR activation effects [4].
- Lifestyle Interventions: Stress reduction via mindfulness, cognitive behavioral therapy, and exercise may indirectly lower BP by dampening HPA activity [13].

Gaps and Future Directions

- Longitudinal Studies: There is a need for prospective cohort studies examining cortisol-BP relationships over time.
- Genetic Studies: Variations in genes encoding 11β-HSD or MR sensitivity may explain individual susceptibility.
- Integrative Approaches: Combining endocrinology, cardiology, and psychoneuroimmunology may improve risk stratification.

Table 1: Mechanisms by Which Cortisol Increases Blood Pressure.

Mechanism	Physiological Effect	References
↑ Vascular Sensitivity to Catecholamines	Increased vasoconstriction and total peripheral resistance	[1], [2]
Mineralocorticoid Receptor Activation	↑ Na^+ and H_2O retention, ↑ blood volume	[3], [4]
Inhibition of Nitric Oxide (NO)	↓ Vasodilation, ↑ vascular tone	[2]
↑ Angiotensinogen Expression	↑ Angiotensin II effect → vasoconstriction	[7]

Table 1 summarizes the four main mechanisms through which elevated cortisol levels contribute to increased blood pressure. These include increased vascular reactivity to catecholamines, activation of mineralocorticoid receptors, suppression of nitric oxide production, and upregulation of components of the renin-angiotensin system. Each mechanism contributes to vasoconstriction, volume expansion, or bothkey drivers of hypertension.

Conclusion

Cortisol's influence on blood pressure is both profound and multifaceted. While pathological states like Cushing's syndrome clearly demonstrate the hypertensive effects of cortisol, subclinical elevations and chronic stress also pose cardiovascular risks. Understanding the biochemical and physiological underpinnings of cortisol-induced hypertension can enhance diagnosis, prevention, and treatment strategies in clinical practice.

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