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Cortisol as a Mediator of Oxidative Stress in Human Body Cells

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Abstract: Cortisol and oxidative stress are key components in the pathophysiology of numerous chronic diseases. Cortisol, known as the "stress hormone," is released by the adrenal gland in response to stressors, regulating metabolism, immune response, and hemodynamic balance. However, its overproduction in chronic stress situations can lead to detrimental effects, including an increase in reactive oxygen species (ROS), which are responsible for oxidative stress. This review article explores the relationship between cortisol, oxidative stress, and their impact on health, with an emphasis on conditions such as work-related stress, cellular aging, and chronic diseases. Additionally, intervention strategies aimed at mitigating the effects of this physiopathological interplay are analyzed.

The following work was carried out based on theoretical methods, where the objective of the research or phenomenon under study is divided into sections to obtain a more concrete perspective. In this case, oxidative stress caused by elevated cortisol levels serves as a determinant for structuring this review article. The bibliographic databases consulted were PubMed and the Google Scholar search engine. The objective of this article is to compile descriptive information from various bibliographic sources to highlight the relationship between elevated cortisol levels, oxidative stress, and, consequently, aging and work-related stress.

Keywords: *Burnout, Stress, Cortisol, Cellular Oxidation.*

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I. INTRODUCTION

Cortisol and oxidative stress play fundamental roles in regulating physiological processes and the body's response to stressors. Cortisol is a steroid hormone produced by the adrenal cortex, whose secretion is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. This mechanism is activated in stressful situations, ensuring an appropriate adaptive response through energy mobilization, immune modulation, and cardiovascular regulation. However, prolonged exposure to elevated cortisol levels, common in chronic stress, can induce harmful effects, including metabolic alterations, immunosuppression, and oxidative imbalances.

Oxidative stress, on the other hand, occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant capacity. This phenomenon causes cellular damage, promoting the onset of chronic diseases such as diabetes, atherosclerosis, cancer, and neurodegenerative disorders. Recent studies have highlighted a close relationship between elevated cortisol and increased oxidative stress, emphasizing its role in the pathophysiology of conditions associated with chronic stress, such as work-related stress and metabolic syndrome.

The aim of this review article is to analyze the interaction between cortisol and oxidative stress, exploring the underlying mechanisms, their clinical implications, and potential therapeutic strategies aimed at mitigating their adverse effects on health.

II. METODOLOGY

The following work was carried out based on theoretical methods, where the objective of the research or phenomenon under study is divided into sections to obtain a more concrete perspective. In this case, oxidative stress caused by elevated cortisol levels serves as a determinant for structuring this

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review article. The bibliographic databases consulted were PubMed and the Google Scholar search engine. The objective of this article is to compile descriptive information from various bibliographic sources to highlight the relationship between elevated cortisol levels, oxidative stress, and consequently aging and work-related stress.

III. RESULTS AND DISCUSSION

Cortisol is a steroid hormone produced by the adrenal gland, specifically in the zona fasciculata of the adrenal cortex. It is known as the "stress hormone" due to its crucial role in the stress response. However, it also regulates other essential functions in the body.

It is involved in functions such as: Regulation of metabolism: It stimulates gluconeogenesis, promotes lipolysis, and decreases glucose uptake by cells, ensuring sufficient energy during stress situations. Inflammatory response: It has anti-inflammatory and immunosuppressive effects, modulating the immune system's response. Regulation of blood pressure: It influences the balance of sodium and water, helping to maintain blood pressure. Sleep-wake cycle: Cortisol levels are highest at dawn and decrease towards the evening, following a circadian rhythm.

The term "stress" was coined by Hans Selye in 1936, who, based on results from his laboratory work, observed a "general adaptation syndrome" in experimental animals as a response to a threatening situation. The physiological, psychological, and behavioral adjustments of an individual triggered by mild or excessive adversity represent the response to what we call stress. This refers to the condition determined by experiences or factors that disrupt the emotional and/or physical stability of the individual. The response that our body experiences to a condition recognized as stressful can be described in three stages: Alarm or alert phase, where the activation of the HPA axis and increased sympathetic division function occur. (1)

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant capacity to neutralize them. ROS, such as free radicals, are byproducts of cellular metabolism, but in excess, they can damage lipids, proteins, and DNA.

The stress defined by Selye is a general adaptation syndrome where the neuroendocrine system mechanism is activated to prepare the body for fight or flight. Stress induces diseases that depend on substances such as catecholamines, cortisol, and immune system impairment; all of these mediators impact the spread and metastasis of cancer and DNA repair mechanisms. (2)

Cortisol is related to cellular oxidative stress, and the following relationships can be observed:

- *Impact of Cortisol on Oxidative Stress:*

In situations of chronic stress, elevated cortisol levels stimulate the production of ROS in cells. Excess cortisol and antioxidant systems: Excess cortisol can inhibit the activity of antioxidant systems such as glutathione, which exacerbates oxidative damage. Oxidative stress and adrenal function: Oxidative damage at the level of the adrenal glands can alter cortisol synthesis and release. Prolonged oxidative stress and HPA dysfunction: Prolonged oxidative stress contributes to hypothalamic-pituitary-adrenal (HPA) dysfunction, perpetuating a vicious cycle of chronic stress, elevated cortisol, and cellular damage. Clinical implications: In diseases such as metabolic syndrome, there is an interaction between high cortisol levels, oxidative stress, and tissue damage. Neurodegenerative diseases: Conditions like Alzheimer’s and Parkinson’s show alterations in the regulation of the HPA axis and an increase in oxidative stress.

Cortisol, an essential glucocorticoid hormone produced by the adrenal glands, plays a fundamental role in various physiological processes. Its release is finely orchestrated by the suprachiasmatic nucleus, which governs the circadian rhythm and activates the intricate hypothalamic-pituitary-adrenal (HPA) axis, a vital neuroendocrine system responsible for the stress response and maintenance of homeostasis. Alterations in cortisol regulation due to chronic stress, disease, and aging have profound implications for multiple body systems. (3)

The way elevated cortisol levels in the body are related to work-related stress, which can affect any professional responsible for specific personnel, can be exhausting over the years.

- *Initial Response:*

Work-related stress activates the hypothalamic-pituitary-adrenal (HPA) axis, stimulating the release of cortisol as an adaptive response to stress. This helps mobilize energy, increase focus, and manage pressure.

- *Chronic Stress:*

If work-related stress is constant and prolonged, cortisol levels may remain elevated (hypercortisolism), which can trigger a series of negative effects such as insomnia, hypertension, decreased immunity, and metabolic disorders.

- *Burnout Syndrome:*

One of the most common conditions associated with work stress, burnout syndrome can be defined as a syndrome characterized by feelings of exhaustion (EE), depersonalization (DP), and a decrease in personal accomplishment (PA), as a result of prolonged exposure to work-related stress. (4)

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➢ *Disruptions in the Circadian Rhythm:*

Chronic work-related stress can disrupt the circadian rhythm of cortisol, leading to low levels in the morning and elevated levels at night, contributing to exhaustion and sleep problems.

Work-related stress, according to the European Commission for Safety and Health at Work, is defined as "the harmful physical and emotional reactions that occur when the demands of work do not match the worker's capabilities, resources, or needs." In general, and following the Karasek model and the Karasek and Theorell model, the balance between demand and the level of control will determine the degree of stress at a given moment. The absence of a recovery process after a period of continuous stress, as well as the cumulative nature of stress itself, can lead to chronic stress. (5)

Cortisol is also commonly known as the stress hormone because it is released in higher doses under stressful conditions. In response to essentially all stressors, two types of hormones are released: catecholamines and glucocorticoids, and the speed and magnitude of both depend on the specific stressor. (6)

Blood cortisol studies are essential for correlating the levels of this hormone with biomarkers of oxidative stress, such as malondialdehyde (MDA) or superoxide dismutase (SOD) activity. In the context of work-related stress, cortisol levels measured at different times of the day can help identify dysfunctional patterns associated with chronic stress.

The hypothalamic-pituitary-adrenal axis is critical for the adaptation and survival of vertebrates. Briefly, it can be said that its activation is primarily driven by adrenocorticotropic hormone (ACTH) secreted at the pituitary level as a result of stimulation by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) at the central level, ultimately leading to cortisol secretion in the adrenal gland. (7)

In a study aimed at determining cortisol levels in pregnant women, comparing umbilical cord blood cortisol values in patients with induced and spontaneous labor, the following results were obtained. The study included 73 pregnant women who attended Sanatorio Allende from July 1 to October 30, 1999. Most were primigravidas, primiparas, with a gestational age of 39 ± 1 weeks, and an average age of 27.3 ± 5.2 years. All had normal pregnancies. The study considered labor hours, medication, induction (considering the dose of misoprostol administered), frequency and duration of contractions, labor complications, gender, Apgar score, and the newborn's birth time. The control group included pregnant women with spontaneous labor, and the experimental group included those with induced labor, comparing fetal blood cortisol levels. (8)

In another descriptive study, where the goal was to consider cortisol as a potential biomarker for stress, the following results were obtained.

It was found that stress causes physiological changes impacting several systems (hypothalamic-pituitary-adrenal, sympathetic-adreno-medullary, and immune systems), which justifies the use of biomarkers for its objective measurement. One of these biomarkers is cortisol in hair, as it is a non-invasive sample and not sensitive to changes in the circadian rhythm, among other advantages. This approach to quantifying cortisol is increasingly used to identify the effects of stress in a variety of situations, due to its ability to provide a useful tool. It is considered a potential biomarker, which also offers a strategy for assessment over time and provides an interesting perspective for future research. (9)

Another similar review study yielded the following bibliographic results.

The physiological changes associated with stress would justify the use of biomarkers as a tool for objective measurement, particularly in conditions of chronic stress, as it has been described that the hypothalamic-pituitary-adrenal axis becomes depleted after prolonged exposure to the same stressor, leading to alterations in levels of substances such as pro-inflammatory cytokines. Adverse working conditions have been mentioned as triggers for chronic stress, which is why medical residents are considered a vulnerable population; with variations depending on the hours dedicated to theoretical and practical activities, rest hours, and the type of specialty in which they receive training. (10)

A cross-sectional field study in which samples were collected from patients aged 20 to 40 years in a city in Ecuador revealed the following results related to Burnout syndrome and cortisol.

A descriptive cross-sectional study was conducted on patients attending the "Celilab" Clinical Laboratory. The results of risk factors based on the Maslach test showed that 67% had a high emotional level, 63.4% had high depersonalization, 77.7% had low personal achievement, and based on the Maslach test, 69.64% suffered from Burnout syndrome. Alterations in cortisol levels were observed throughout the workday, while the remaining 30.35% did not show alterations in cortisol levels. The chi-square test, with a p-value <0.005, indicated a relationship between elevated cortisol levels and the risk of developing Burnout syndrome. (11)

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IV. CONCLUSIONS

Cortisol and oxidative stress are key factors in the stress response and the development of numerous chronic pathologies. Although cortisol plays essential roles in adapting to acute stress, its prolonged overproduction contributes to oxidative imbalance, promoting cellular damage and organ dysfunction. This relationship is particularly relevant in contexts of chronic stress, such as work-related stress, where a negative feedback loop between elevated cortisol levels and increased oxidative stress is observed. Strategies such as stress reduction, the promotion of healthy habits, and the use of antioxidants could be effective in counteracting these effects. A deep understanding of this interaction is crucial for developing more effective interventions in stress management and the prevention of associated diseases.

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