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Cortisol and its Role in the Development of Diseases

Abstract

Oxidative stress arises from excessive accumulation of free radicals in the body, imbalanced synthesis of reactive oxygen species (ROS) and disruption of antioxidant defense mechanisms. ROS mainly include oxygen ions (superoxide anion), free radicals, and peroxides derived from mitochondria or NADPH oxidase. Accumulated ROS react with lipids, proteins and DNA, leading to apoptosis and disruption of protein synthesis. Among ROS superoxide anion and hydrogen peroxide, which act as critical messengers initiating changes in cellular signaling, are key mediators in diseases such as atherosclerosis, diabetes, and neurodegenerative disorders.

Keywords: *free radicals, oxidative stress, carbohydrate metabolism, superoxide anion, neurodegenerative diseases*

Introduction

Oxidative stress occurs due to the excessive accumulation of free radicals and disruption of antioxidant defense mechanisms. Contributing factors include environmental pollution, unhealthy diet, radiation, and chronic stress. Free radicals are unstable atoms or molecules with an incomplete outer electron shell, making them highly reactive and capable of capturing electrons from other molecules to stabilize themselves. This imbalance can cause severe cellular problems. Due to their reactivity, free radicals can damage cell membrane structures (Anagnostis, Athyros, Karagiannis & Mikhailidis, 2009), leading to cellular dysfunction and death. Superoxide anion and hydrogen peroxide, acting as key messengers among ROS, are major contributors to diseases like atherosclerosis, diabetes, and neurodegeneration. Additionally, ROS causes oxidation within cells and reduces antioxidant defenses. Through their various effects, reactive oxygen species play a significant role in human pathophysiology by promoting cell proliferation, tumor development and cell death in degenerative disorders of the central nervous system (Knezevich, Nenich & Milanovich, 2023).

Research

Cortisol is chemically classified as a pregnene-triol-dione. By specifying the positions of substituents on the molecule and the carbon atoms they bind to, cortisol can be defined as delta4-pregnene-11beta,17alpha,21-triol-3,20-dione. In the side chain and ring carbons, there is no alpha or beta orientation for the keto groups (Figure 1).

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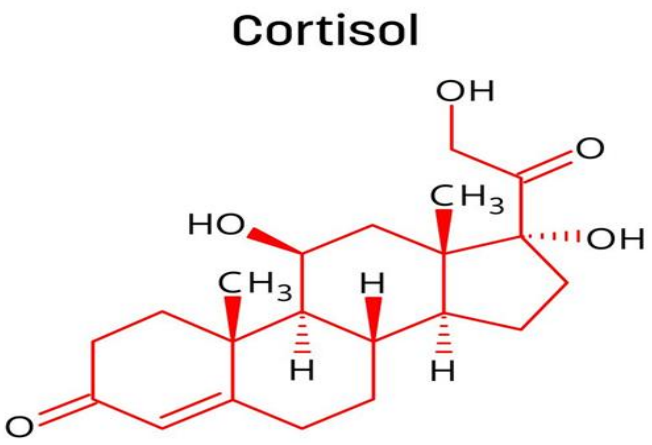

Figure 1. Biochemical structure of cortisol

Cortisol has two main functions: promoting the breakdown of proteins and fats to provide metabolites convertible to glucose in the liver, and activating antistress and anti-inflammatory pathways. By increasing gluconeogenesis and inhibiting glucose uptake in tissues other than the central nervous system, cortisol helps maintain blood glucose levels (Akalestou, Genser & Rutter, 2020). Thus, oxidative stress can lead to acute and chronic diseases.

Cancer: Cancer refers to the abnormal proliferation of cells forming new tissues in organs or tissues. Oxidative stress can directly damage various molecules in the body, including DNA. Persistent oxidative stress leads to DNA damage, potentially resulting in uncontrolled cell growth. Major cancer types caused by oxidative stress include breast and prostate cancers.

Cardiovascular diseases: Oxidative stress promotes the formation of cholesterol plaques in blood vessels, which can lead to cardiovascular diseases and atherosclerosis over time. Chronic stress increases blood pressure, and blood returns to the heart with higher force, affecting the heart muscle wall. Over time, this causes thickening of the heart muscle, known as left ventricular hypertrophy, which leads to irregular heartbeats. In general, chronic stress elevates blood pressure and damages specific areas of arteries. Immune cells targeting inflammation focus on these damaged areas (Chayakar, 2021).

Diabetes mellitus: Diabetes develops when the pancreas fails to produce enough insulin or when insulin is not effectively used. Oxidative stress can damage the pancreas, leading to insufficient or ineffective insulin function.

Inflammatory processes: Oxidative stress can lead to inflammation of joints and surrounding tissues, contributing to the development of rheumatoid arthritis.

Neurodegenerative disorders: Prolonged oxidative stress may damage the central nervous system, leading to disorders such as Alzheimer's, Parkinson's disease, amyotrophic lateral sclerosis (ALS), memory loss, and depression. These diseases are linked to elevated cortisol production during stress, which accelerates aging and disease onset. Numerous studies show a relationship between chronic stress, poor health outcomes, and risk factors such as cardiovascular diseases and impaired immune function. However, the exact mechanisms by which stress exerts these effects, particularly whether it accelerates aging at the cellular level and how this translates into organismal aging, remain unclear. Recent research indicates that telomeres and telomerase play a crucial role in cellular aging and potentially in disease development. Telomeres are DNA-protein complexes that ensure chromosome stability. During cell division, due to limitations in DNA polymerase activity, telomeres are not fully replicated, leading to shortening with each replication. In vitro, once telomeres shorten sufficiently, the cell enters senescence. In humans, telomeres shorten with age in all studied proliferative somatic cells, including fibroblasts and leukocytes. The cellular environment plays a significant role in regulating telomere length and telomerase activity. Importantly, oxidative stress can shorten telomeres in vitro, while antioxidants may slow this shortening (Zhang, Lai, Chen, Zhang & Liu, 2023). Stress has been associated with oxidative DNA

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damage in leukocytes in women. Considering these findings, chronic psychological stress may lead to telomere shortening, decreased telomerase activity in peripheral blood mononuclear cells, and increased oxidative stress (Henley, Lightman & Carrell, 2016). Alongside other glucocorticoids, cortisol is known to exert potent anti-inflammatory effects at pharmacological levels. Therefore, glucocorticoid drugs are currently used in the treatment of many inflammatory diseases. They are commonly prescribed to patients with lymphoid cancers such as lymphomas, leukemia, and myelomas (Lauren & Kevin, 2020).

Effects on protein metabolism: Cortisol has primarily catabolic effects, inhibiting DNA synthesis, increasing protein breakdown, and promoting nitrogen excretion. Cortisol deficiency does not significantly enhance protein synthesis, but excess cortisol leads to progressive protein loss in muscles, muscle weakness, and atrophy. Cortisol also limits glucose utilization in all body cells (Figure 2).

Effects on fat metabolism: Hormones that mobilize lipids increase cellular lipase activity, regulating fatty acid metabolism. Cortisol accelerates the release of fatty acids into the bloodstream from tissues, increasing their plasma concentration and utilization as an energy source. This effect is linked to reduced glucose transport into adipocytes, which require glucose-derived α-glycerophosphate for triglyceride storage. In its absence, fatty acids begin to be released from adipose tissue (Vignesh, Castro-Dominguez, James, Gamble-Turner, Lightman & Reis, 2024).

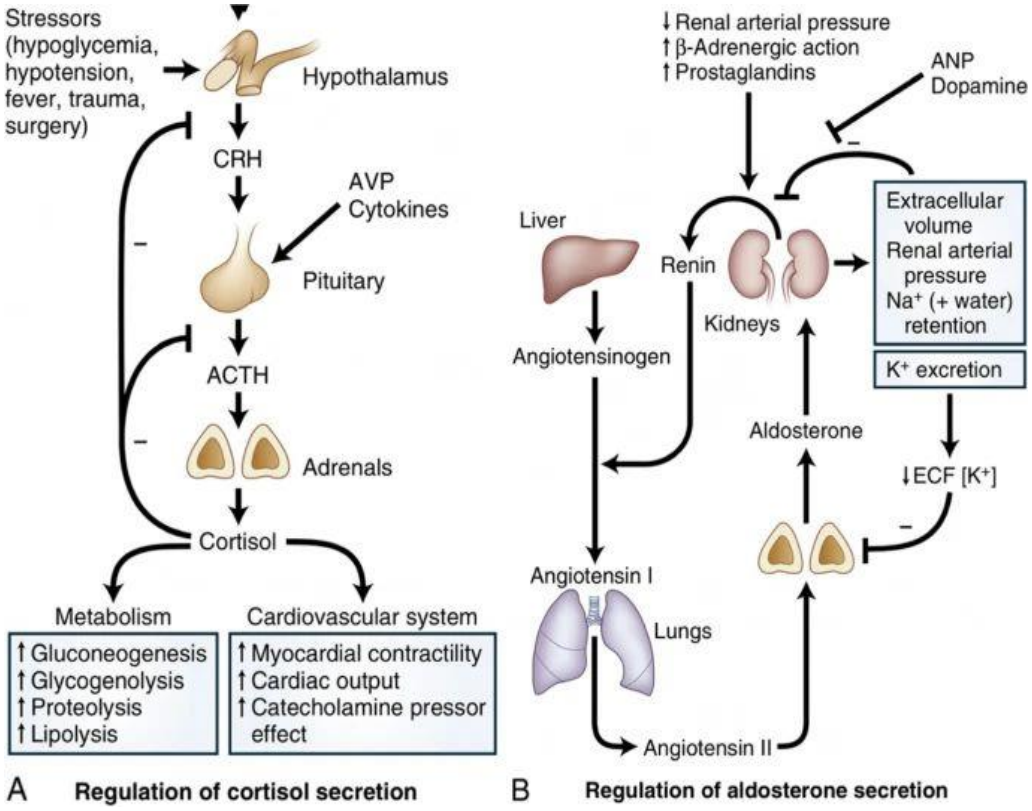

Figure 2. Synthesis, regulation of synthesis, and biochemical effects of glucocorticoids

Conclusion

At the cellular level, glucocorticoids inhibit the synthesis and action of inflammatory cytokines. At high doses, they can suppress immune system functions by reducing cell-mediated immune responses and immunoglobulin synthesis and activity. However, high-dose glucocorticoids have serious side effects. Oxidative stress negatively impacts human health, with symptoms including chronic fatigue, premature skin aging, circulatory disorders and insomnia. Oxidative stress can contribute to both acute and chronic diseases.

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