A Review of Cortisol: The "Stress Hormone"

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Abstract

Cortisol, also known as hydrocortisone, is a steroid hormone produced by the adrenal cortex in the adrenal gland of mammals. The zona fasciculata is the tissue that produces this glucocorticoid in response to stimulation by Adrenocorticotropic Hormone (ACTH). Cortisol is classified as a glucocorticoid, which aids in metabolism of fats, proteins, and carbohydrates. Cortisol is commonly referred to as the stress hormone because it is involved in the body's natural response to stress. Most cells in the body contain receptors for cortisol, allowing it to have many functions within the body [5].

In normal cortisol release, its actions restore homeostasis after stress. Cortisol is responsible for controlling the body's blood sugar levels, regulating metabolism. It acts as an anti-inflammatory and can promote the breakdown of glycogen, lipids, and proteins which reduces protein levels in most body cells. Cortisol influences memory formation, controls salt and water balance, and helps development of the fetus [1]. Cortisol is responsible for triggering key processes during parturition in many species.

Cortisol is produced by specific enzymes known as the P450 enzymes, which are located on chromosome ten, region CYP17. 11-beta HSD1 and 11-beta HSD2 are the enzymes associated with the metabolism of cortisol [8].

The over or underproduction of cortisol can produce diseases within the body. Primary Hypercortisolism occurs when excessive levels of cortisol are present in the blood resulting in Cushing's syndrome. Hypocortisolism or adrenal insufficiency results when the adrenal glands do not produce enough cortisol for the body. Addison's disease refers to primary adrenal insufficiency, where the adrenal glands malfunction [1].

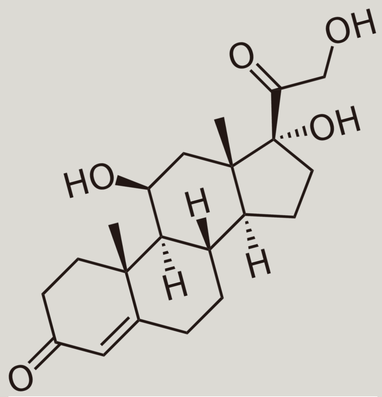


Figure 1: The chemical structure of cortisol (PubChem, 2017)

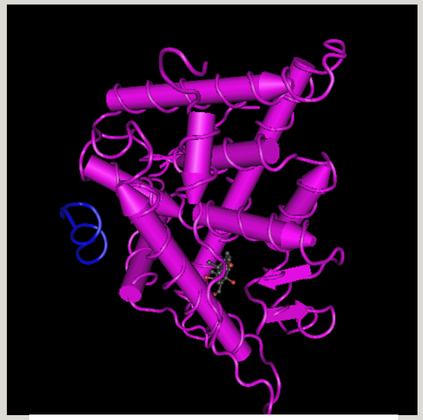


Figure 2: Crystal Structure of Cortisol-bound Glucocorticoid Receptor Ligand Binding Domain *(Zhang, 2014)*

Mode of Action [2]

G-protein stimulates **adenylate cyclase**: ATP converts to cAMP

→ **cAMP** activates Protein Kinase A (**PKA**) by inducing a **conformational change**, releasing catalytic subunits

→ This unit travels to the **mitochondrial membrane**

→ A protein called **steroidogenic acute regulatory protein** (**StAR**) is "switched on" by **phosphorylation**

→ **StAR** imports **cholesterol** into mitochondrion

→ Cholesterol is converted to **17-OH-pregnenolone** by enzymes

→ This is sent to the **endoplasmic reticulum**, where it is converted to **11-deoxycortisol**

→ **11-deoxycortisol** is sent back into the mitochondrion where it is finally transformed into **cortisol**

→ **Cortisol** can freely cross the cell membrane & is transported into the **bloodstream**

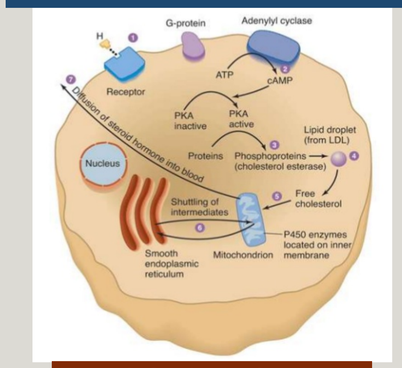


Figure 3: Synthesis of cortisol within the cell (Ridley, 2017)

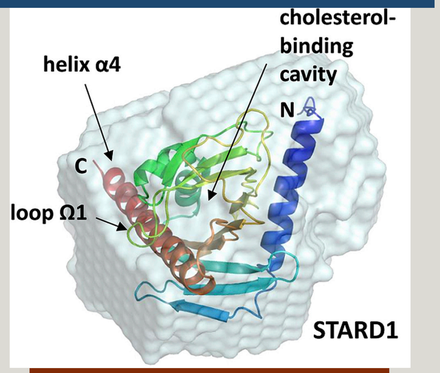


Figure 4: The StAR protein binding complex (Sluchanko, 2017)

Normal Physiologic Effects of Cortisol

Cortisol restores homeostatic mechanisms after the body is exposed to stress. Cortisol's primary targets are metabolic, but it also influences other pathways including ion transport or even the immune response [2].

Cortisol stimulates gluconeogenesis, the process that synthesizes glucose from oxaloacetate, to increase blood sugar, countering the effects of insulin. However, to counteract the increase in blood glucose, cortisol stimulates the synthesis of glycogen within in the liver, carefully regulating the amount of glucose traveling throughout the blood.

Cortisol's effect on metabolism is essential, illustrated by how it maintains a steady supply of glucose during a state of the body fasting. When the body goes through a fasting period, the blood glucose is greatly decreased, but that is regulated by cortisol stimulating the process of gluconeogenesis.

In addition, cortisol is key in the regulation of certain ions, including sodium and potassium, which helps the body to regulate physiologic pH after a stress-inducing event. Sodium is prevented from leaving the cell, while potassium is readily excreted, otherwise known as the regulation of the sodium-potassium pump. Because of this regulation, it has been theorized that cortisol may have evolved as a sodium transporter [7].

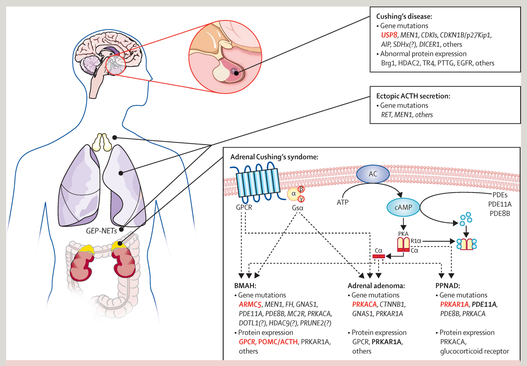


Figure 5: Gene mutations associated with Cushing's disease (Randall, 2011)

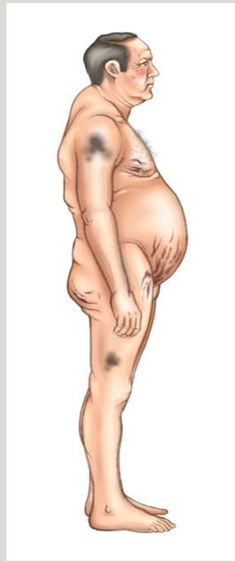
Cushing's Syndrome

Causes:

Cushing's syndrome is caused by prolonged exposure to high levels of cortisol within the body. Cushing's syndrome may be caused by exogenous glucocorticoids or overproduction of cortisol. Exogenous glucocorticoids are steroid hormones that are created to be chemically similar to natural cortisol. People take exogenous glucocorticoids, like prednisone, for asthma, lupus, rheumatoid arthritis and other inflammatory diseases. Glucocorticoids may also be used to suppress the immune system after transplant surgery in order for the body to not reject the new organ. Overproduction of cortisol in the body is a result of a pituitary ACTH-producing tumor, or a primary adrenal tumor.

Women may often exhibit excess hair growth on the face, neck, chest, abdomen, and thighs. Their menstrual cycle may become irregular or eventually stop. Men may exhibit decreased fertility, decreased sex drive, and impotence [3].

Round, red, full face
Acne or skin infections
Thin skin, easily bruised
Increase in adipose tissue
Upper body obesity with thin limbs



Type II Diabetes
"Buffalo back"
High blood pressure
Weak muscles
Bone pain or tenderness
Thinning of bones: spine and rib fractures

Figure 6: Physical symptoms of Cushing's syndrome (UCLA Health, 2017)

Current Treatments:

Treatments for Cushing's syndrome vary depending on the cause. If a glandular tumor is present, the tumor must be surgically removed. Sometimes the pituitary or adrenal glands are removed entirely so the hormone is no longer produced. If surgery is unsuccessful or not feasible, pharmacological therapy is used in which drugs inhibit the hormone itself. Many of the FDA-approved medications to treat Cushing's syndrome work by the processes of competitive and non-competitive inhibition.

A common drug used to treat Cushing's syndrome is knowns as Ketoconazole. It interferes with adrenal steroidogenesis (i.e. the synthesis of cortisol) in the adrenal gland by inhibiting cytochrome P450-dependent enzymes [2]. This is an example of a mixture of competitive and non-competitive inhibition.

Another popular drug to treat Cushing's syndrome is called Metyrapone, which is a selective inhibitor of glucocorticoid synthesis by inhibiting the 11-beta hydroxylation, which is the final step in the glucocorticoid pathway [4].

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