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The Hormone Cortisol and its Biological Role in Metabolic Disorders

Abstract

Cortisol one of the steroid hormones, is synthesized by the adrenal gland under the control of the hypothalamus, under the stimulation of the ACTH hormone secreted by the anterior lobe of the pituitary gland. The paraventricular cells of the hypothalamus secrete the hormone CRH (corticitropin releasing hormone), which causes the secretion of ACTH by corticotroph cells from the anterior pituitary. ACTH is derived from the precursor POMC (proopiomelanocortin) consisting of 241 amino acids. In the pituitary, POMC is cleaved by prohormone convertase-1 into POMC ACTH and 2 polypeptides, the N-terminal peptide and beta-lipoprotein. After ACTH binds to the GPSR of the adrenal gland, intracellular signaling begins and hydrolyzes cholesterol in the cytosol. Cortisol levels are determined by a number of methods, ELISA, RIA, colorimetric and immunoassays.

Keywords: *cortizol, steroid hormones, glucocorticoids, liver, glukoneogenesis, carbohydrate metabolism*

Introduction

Hormones are present in the bloodstream at very low concentrations and exert their effects through a specific mechanism. This specific mechanism occurs via hormone-receptor binding. Although hormones released into the blood can reach all parts of the body, they exert their effects only on certain cells and tissues. Somatic cells are constantly exposed to many external signals. Most signal molecules (ligands) bind to receptors located on the cell membrane and initiate specific processes within the cell. The receptors that interact with these hormones are called protein hormone receptors. Some signal molecules (such as steroid and thyroid hormones), however, can pass through the cell membrane and bind to intracellular receptors, which may activate or suppress gene expression at the chromatin level (Chayakar, 2021). The pituitary gland weighed about 600 mg, it is an organ that carries out all endocrine processes together with the hypothalamus. The pituitary gland controls the secretion of hormones by the hormone ACTH, which it synthesizes. The hypothalamus is located just above the pituitary gland. The pituitary gland receives two different lobes, anterior and posterior, both anatomically and functionally. Hypothalamic nerve cells synthesize special secretory and inhibitory hormones. These hormones and are secreted into the portal blood-vascular system of the pituitary stem (Henley, Lightman & Carrell, 2016).

Research

ACTH (adrenocorticotropic hormone) is a peptide hormone composed of 39 amino acids, derived from proopiomelanocortin (POMC) and secreted by the anterior pituitary gland.

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ACTH, secreted from the anterior pituitary, stimulates the zona fasciculata of the adrenal cortex, leading to the secretion of cortisol. In healthy individuals, ACTH secretion is regulated by CRH (corticotropin-releasing hormone), which is secreted by the hypothalamus (Civan, Ozdamir, Gencer & Durmaz, 2018). CRH is a peptide hormone composed of 41 amino acids. The cells of the paraventricular nucleus (PVN) in the hypothalamus are responsible for CRH secretion (Figure 1). CRH release triggers the secretion of ACTH from the anterior pituitary, which in turn leads to the synthesis of cortisol from the adrenal glands. This interaction between the hypothalamus, pituitary gland, and adrenal gland is known as the hypothalamic-pituitary-adrenal (HPA) axis (Gundogdu, 2022). Cortisol, secreted from the adrenal gland, exerts a negative feedback effect on the pituitary and hypothalamus, thereby reducing the secretion of both ACTH and CRH. Arginine vasopressin (AVP), another hormone secreted from the posterior part of the pituitary gland, also stimulates ACTH secretion from the pituitary, similarly to CRH. Many stress-inducing conditions affect the HPA axis. When the body is exposed to stress, CRH secretion from the hypothalamus increases, which subsequently stimulates (Figure 1). ACTH secretion from the pituitary, leading to cortisol secretion from the adrenal gland (Lauren & Kevin, 2020).

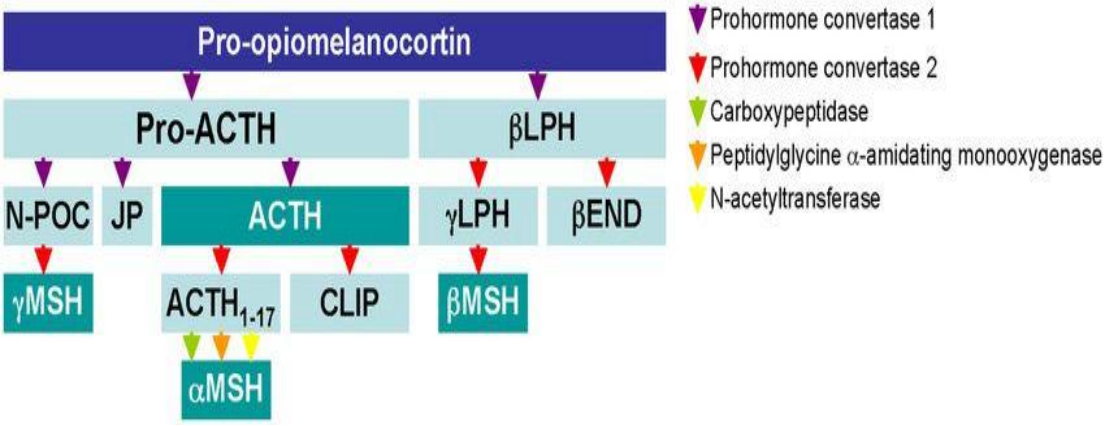

Figure 1. POMC-pro-opiomelanocortin

The first step in the cellular response to cortisol is the binding of cortisol to glucocorticoid receptors located in the cytoplasm. This binding leads to the movement of the steroid-receptor complex into the nucleus and the initiation of specific protein synthesis. Thus, a cellular response to glucocorticoids occurs. One of the target cells of glucocorticoids is peripheral mononuclear cells (MNCs), which specifically bind dexamethasone—a synthetic derivative of cortisol. Natural glucocorticoids include cortisol (hydrocortisone), cortisone, corticosterone, and 11-dehydrocorticosterone, a 21-carbon steroid. The daily secretion amount of cortisol ranges from 8 to 25 mg. In individuals with a normal sleep pattern, the secretion rate and plasma concentration of cortisol are at their highest (approximately 180 ng/ml) in the early morning hours just before waking, in accordance with the circadian rhythm (Prema, 2017, Tappy, 2008).

Cortisol exists in plasma either in free form or bound to proteins. The main plasma-binding protein is transcortin, also known as corticosteroid-binding globulin (CBG). The free fraction accounts for approximately 8% of total plasma cortisol and represents the biologically active form. Aldosterone, the most potent natural mineralocorticoid, does not have a specific transport protein; it circulates bound to albumin, with about 50% in free form. Other mineralocorticoid steroids such as corticosterone and 11-deoxycorticosterone bind to CBG. Both bound and free forms of these hormones are transported in extracellular fluid. The metabolism and clearance rate of these hormones depend on the presence or

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absence of carrier proteins. Generally, cortisol is broken down within one to two hours in target tissues, whereas aldosterone is metabolized in approximately 30 minutes. Glucocorticoids are modified and metabolized in the liver and are ultimately excreted as lipophilic steroid molecules. The conjugated metabolites of these steroids are water-soluble substances and are excreted by the kidneys. About 70% of them are eliminated in urine, 20% in feces, and 10% through sweat (skin). The protein-bound forms of these hormones are considered biologically inactive (Liu, Snidman, Leonard, Meyer & Tronick, 2016).

The major metabolite of cortisol is tetrahydrocortisol glucuronide, while for aldosterone it is tetrahydroaldosterone glucuronide (Paredes & Ribeiro, 2014). Cortisol secretion is regulated by a negative feedback mechanism. Cortisol, secreted from target organs, directly inhibits ACTH secretion. ACTH stimulates cortisol secretion from the adrenal cortex, and as plasma cortisol levels increase, ACTH secretion begins to decrease. Additionally, cortisol indirectly inhibits CRH secretion from the hypothalamus (Figure 2).

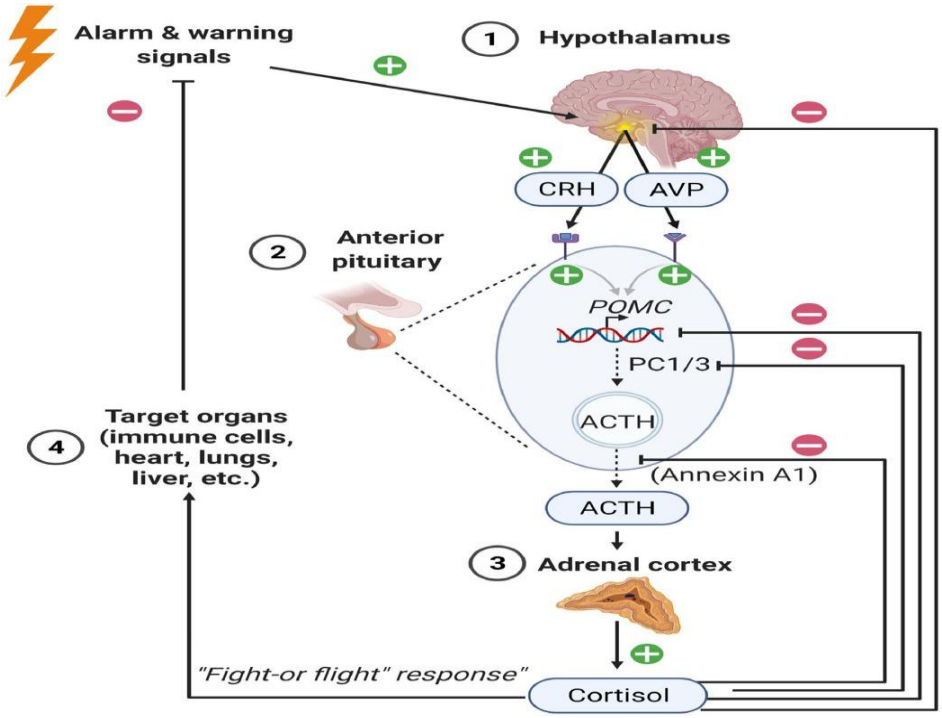

Figure 2. Regulation of cortisol synthesis

The radioimmunoassay method for measuring cortisol levels in plasma and urine is preferred for evaluating cortisol synthesis and secretion.The amount of free cortisol excreted in 24-hour urine is considered the most sensitive indicator. In a healthy person, less than 100 µg of free cortisol is excreted in urine per day. Cortisol binds to specific cytosolic receptors in target cells such as fibroblasts and hepatocytes. The hormone-receptor complex enters the nucleus and regulates the transcription of specific genes. Cortisol generally stimulates the breakdown of proteins into amino acids in skeletal muscle and promotes gluconeogenesis in the liver (Akalestou, Genser & Rutter, 2020).

Cortisol secretion is controlled by a negative feedback mechanism. Cortisol secreted from the target organ exerts a direct negative feedback effect on ACTH. ACTH increases cortisol secretion from the adrenal cortex, and when plasma cortisol levels rise, ACTH secretion begins to decline. On the other

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hand, cortisol also exerts an indirect negative feedback effect on CRH secretion from the hypothalamus (Figure3).

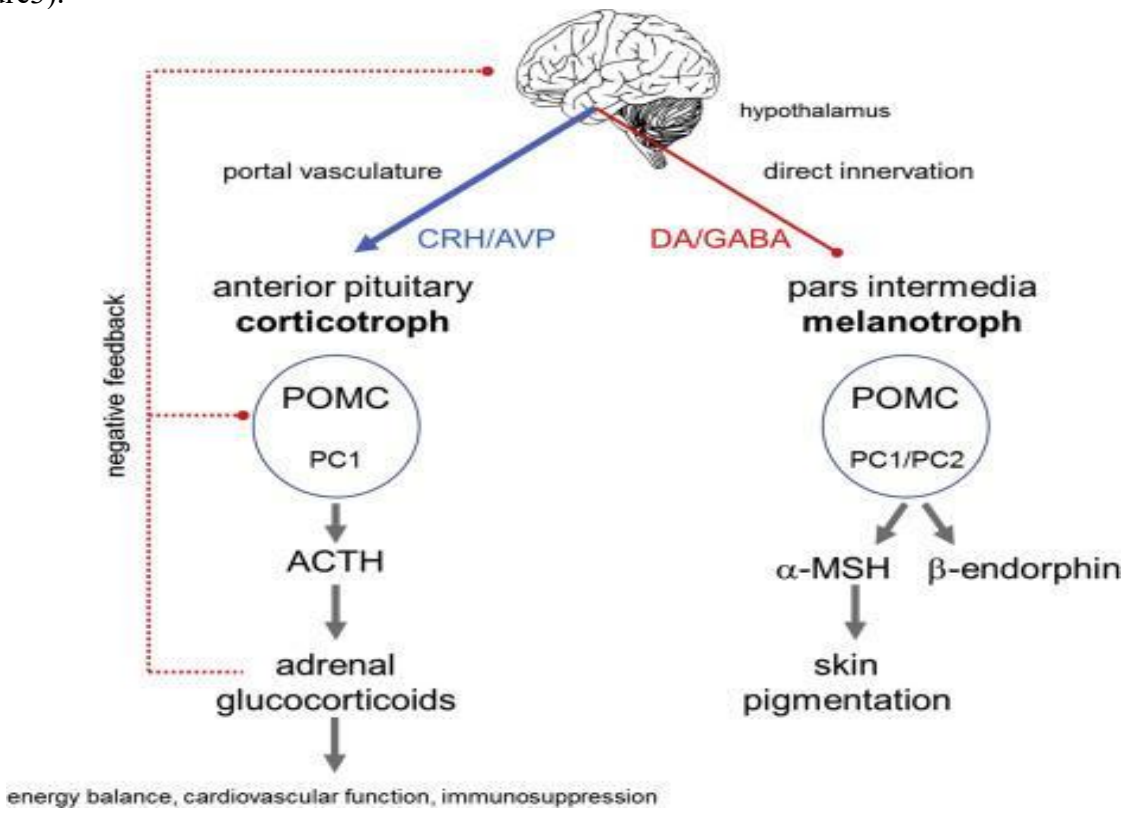

Figure 3. Synthesis of adrenal glucocorticoids by negative feedback mechanism

The excessive presence of cortisol increases blood glucose levels and enhances the process of gluconeogenesis in the liver.This increases the demand for ATP, accelerating mitochondrial activity. Electrons obtained from oxidative processes and ATP synthesis are transferred to the mitochondrial electron transport chain (ETC), but not all electrons are efficiently transferred. Due to electron and proton leakage, not all electrons can be passed to the final electron acceptor (O_2), and the energy released by transferred electrons cannot be fully used for ATP synthesis. Nevertheless, both reactive oxygen species (ROS) generated from electron leakage and uncoupling proteins (UCPs) involved in proton leakage play critical roles in cellular physiology and pathology. A high membrane potential leads to electron leakage in the electron transport chain, resulting in the production of reactive oxygen species—free radicals (Vignesh, Castro-Dominguez, James & Reis, 2024).

*Effect on carbohydrate metabolism:*The most well-known metabolic effect of cortisol and other glucocorticoids is their ability to stimulate gluconeogenesis in the liver. This is achieved by increasing all the enzymes needed to convert amino acids to glucose in liver cells, activating DNA transcription in the nuclei of liver cells, and increasing the synthesis of mRNAs for the enzymes required for gluconeogenesis. Cortisol also causes the mobilization of amino acids from extrahepatic tissues, especially muscle, meaning it facilitates the release of stored amino acids into circulation for energy production and metabolic processes. Additionally, cortisol limits glucose utilization by all body cells (Anagnostis, Athyros, Tziomalos, Karagiannis & Mikhailidis, 2009).

Effect on protein metabolism: One of the most significant effects of glucocorticoids on metabolic systems is the reduction of protein reserves in all body cells except the liver. This occurs through decreased protein synthesis and increased catabolism within cells. Both effects may be associated with

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reduced amino acid transport into extrahepatic tissues. The impact of glucocorticoids may also occur through decreased RNA synthesis in many extrahepatic tissues, particularly in muscle and lymphoid tissues (Knezevich, Nenich, Milanovich & Knezevich, 2023).

Conclusion

The cortisol synthesis pathway begins with cholesterol and proceeds through a series of steps involving specific enzymes. This hormone affects the metabolism of carbohydrates, proteins, and fats. During stressful situations, cortisol accelerates gluconeogenesis, thereby increasing blood glucose levels. At the same time, cortisol exhibits anti-inflammatory effects. There are several laboratory methods available for determining cortisol levels. Samples for cortisol measurement can be collected from saliva, sweat, blood plasma (serum), or interstitial fluid. Methods used to determine cortisol include ELISA, immunoassay, RIA (radioimmunoassay), colorimetric, bioluminescent, and other immunoassay techniques.

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