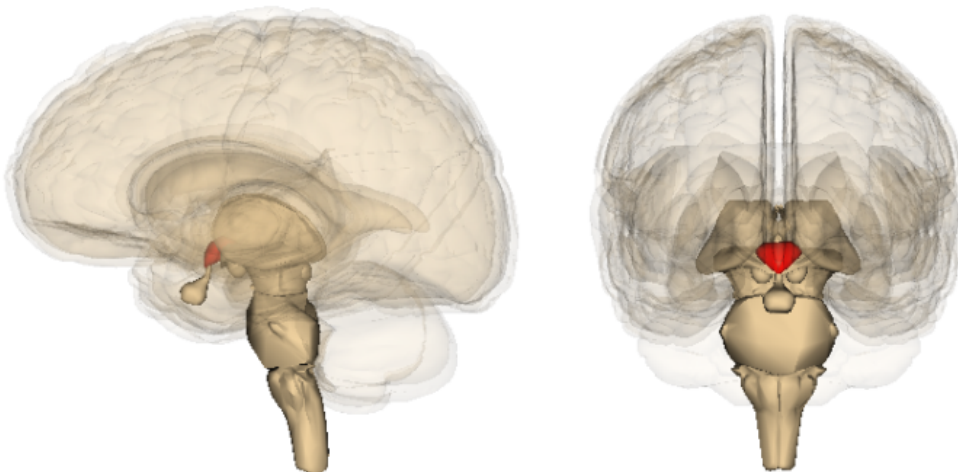


Hypothalamus Pituitary Adrenal Axis

[See online here](#)

The hormone balance of the body is often organized in feedback control systems which adjust to the respective demands of the body. The most important example of such a system is the hypothalamus pituitary axis. In the following article, the interaction with the adrenal gland and the synthesis of glucocorticoids like cortisol serve as examples for the explanation of a complete hormonally regulated system. This is especially important in order to exactly classify and understand the genesis of some important endocrine diseases.



Strain and Stress

Through the liberation of glucocorticoids, the feedback control loop between the pituitary gland, the hypothalamus and the adrenal cortex (See Adrenal Pharmacology) plays a central role in the reaction of the human body to stress. In this context, stress is primarily an unspecific reaction to a large amount of possible stressors like e.g. injuries, cold, hunger, work, but also psychological triggers like social stress.

It has been proven in experiments that the body uses the same reaction pattern if people are exposed to high levels of competition in their work environment. Specifically, it increases the level of glucocorticoids and catecholamines (e.g. adrenalin) in the blood.

Stress is a reaction of the [central nervous system](#) and is mostly mediated by the sympathetic nervous system and the endocrine pathway via the hypothalamus, the pituitary gland, and finally the adrenal cortex. Thus, this pathway is very relevant for the physiological stress reaction, but it also interacts with other areas like the immune

system and systems in charge of electrolyte balance.

Levels of Hormonally Regulated Cycles

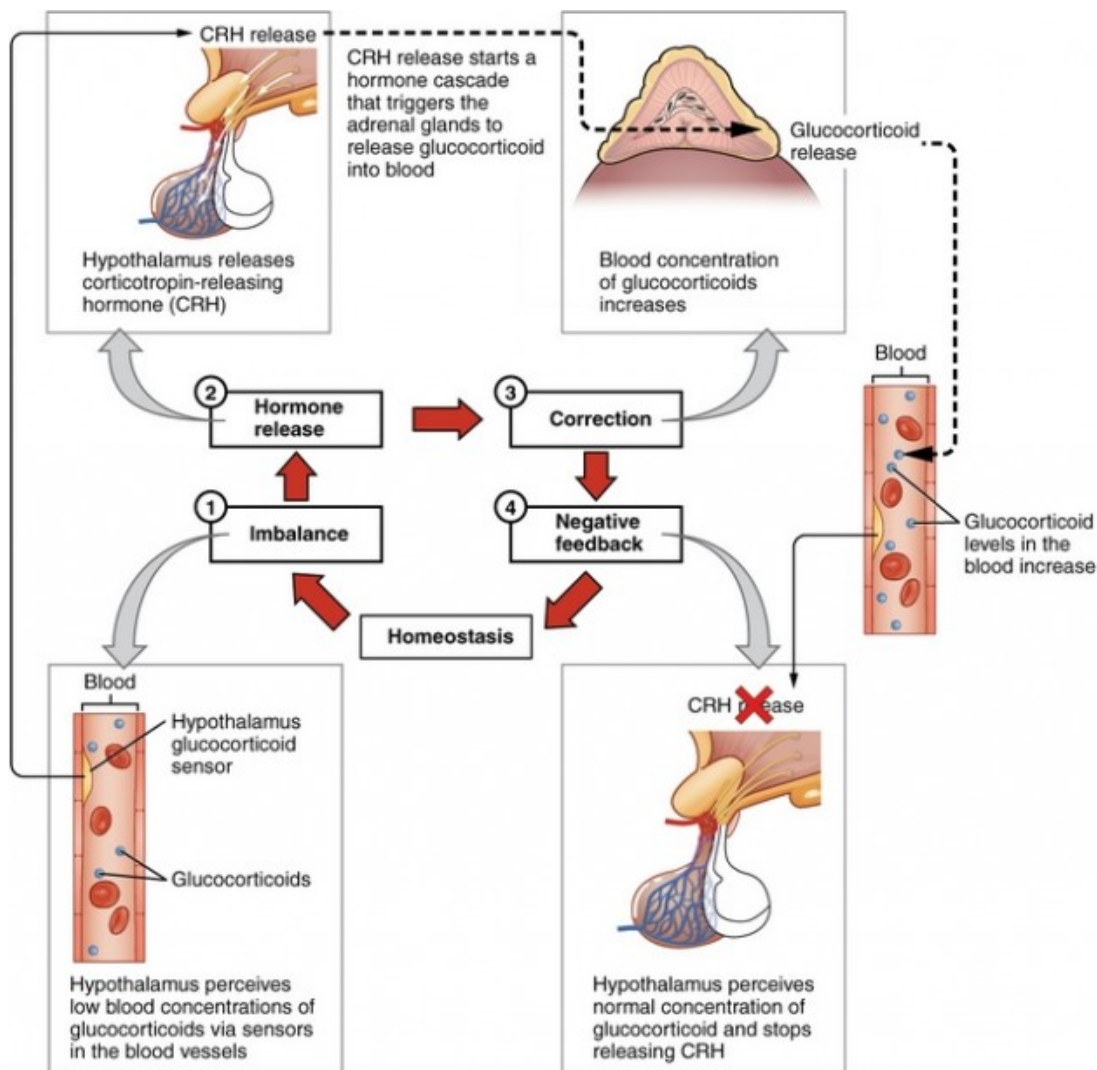


Image: "Negative Feedback Loop" by Phil Schatz. License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

The **hypothalamus pituitary adrenal axis** is - like most endocrinologically regulated cycles - organized in 3 tiers.

The **hypothalamus** is the highest-level center and connects the nervous system with the [endocrine system](#). The hormones which are released here and are transported to the pituitary gland via axons, are called **releasing hormones (RH)** or **liberines**.

The next center is the **pituitary gland**. In the **anterior lobe of the pituitary gland (adenohypophysis)**, hormones are produced, which stimulate the release of other hormones from downstream endocrine glands. The hormones released by the pituitary gland are referred to as **glandotropic hormones** or **tropines**. Hormones which do not have an effect on endocrine glands, but directly influence the target organ, are called **effector hormones**.

The **posterior lobe of the pituitary gland** secretes such effector hormones, and they are oxytocin and antidiuretic hormone (ADH). Most effector hormones originate from **endocrine glands** like the thyroid gland, the adrenal cortex, or the ovaries/testicles.

Role of the Hypothalamus

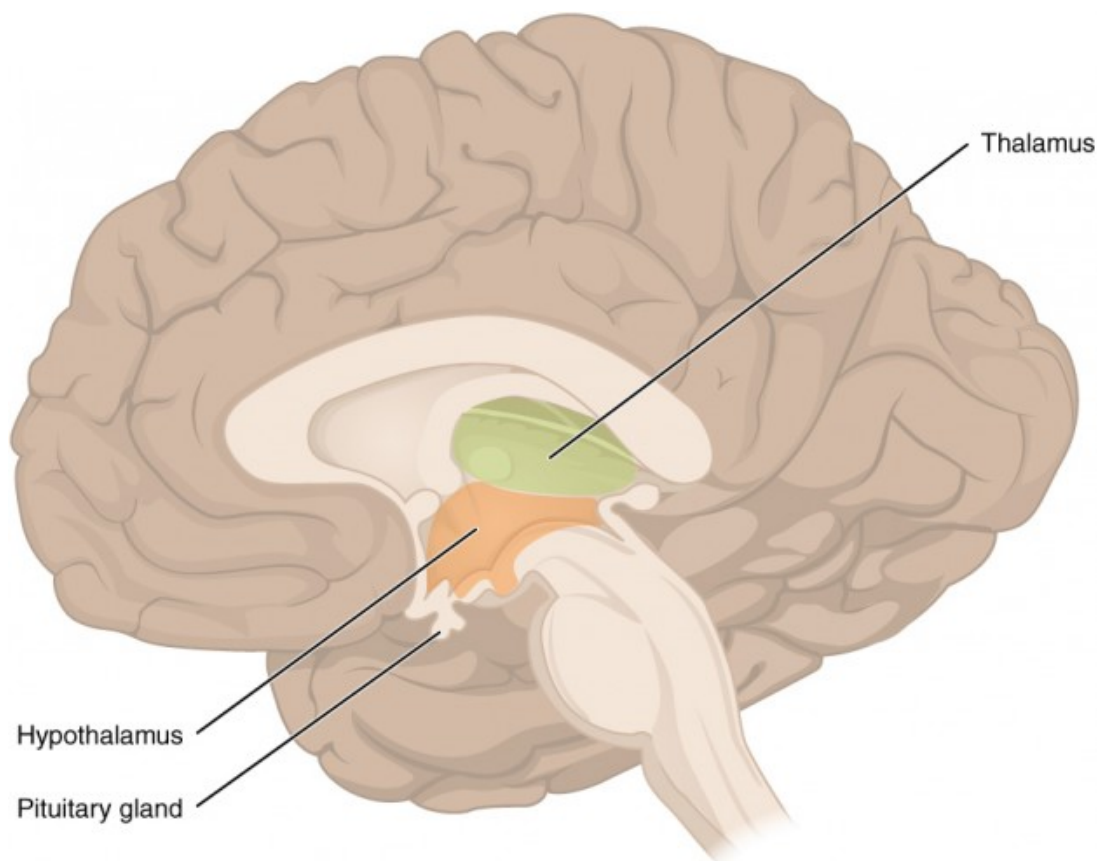


Image: "The Diencephalon" by Phil Schatz. License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

The **supreme regulating authority** of the axis is the hypothalamus. The hypothalamus is a part of the interbrain (**diencephalon**) and receives information from different centers of the **cortex**. The information is then processed to a hormonal response.

This response consists of a releasing hormone that is transported via the hypothalamic-hypophyseal portal venous system to the anterior pituitary gland and stimulates synthesis and secretion of hypophyseal hormones. In the case of the HPA axis, the responsible hormone is **corticotropin-releasing hormone (CRH)**.

At rest, the secretion of CRH occurs **in a pulsatile manner** and follows a **circadian rhythm** with the highest levels in early morning and during stress.

Role of the Pituitary Gland

The **middle regulating authority** in this cascade is the pituitary gland. If CRH reaches the **anterior lobe of the pituitary gland**, synthesis and secretion of the glandotropic hormone **ACTH** (adrenocorticotrophic hormone) is increased **via a G-protein coupled receptor**. The synthesis occurs in the pituitary gland via splitting of a precursor peptide called pro-opio-melanocortin (**POMC**), which is also used for the peptides β -endorphin, β -lipotropin, and **melanocyte-stimulating hormone (MSH)**.

The latter determines the hyperpigmentation frequently observed at insufficiency of the adrenal cortex (Addison's disease) since more POMC-peptides (and thus more MSH) is secreted at elevated ACTH-production. The liberation of ACTH follows the pulsatile

pattern of CRH and an increase of cortisol in the blood occurs only a few minutes after the secretion of ACTH.

Role of the Adrenal Cortex

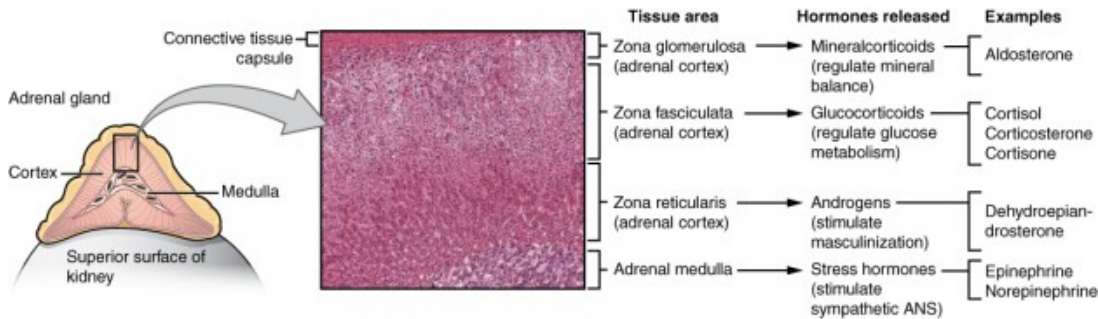


Image: "The Adrenal Glands" by Phil Schatz. License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

The **adrenal gland** is a paired purely endocrine organ which lies within the kidney capsule and directly abuts the kidney. While the **adrenal medulla** is regulated by the sympathetic nervous system and is responsible for the release of catecholamines into the blood, so-called **steroid hormones** are produced in the **adrenal cortex**.

Concerning their biosynthesis, steroid hormones originate from cholesterol and run through similar steps of synthesis. Histologically, the adrenal cortex has three different layers which mirror the locations of production of different steroid hormones:

- **Zona glomerulosa:** location of biosynthesis of **mineral corticoids** (e.g. aldosterone)
- **Zona fasciculata:** location of biosynthesis of **glucocorticoids** (e.g. cortisol)
- **Zona reticularis:** location of biosynthesis of **androgens**

Note: To remember the layers, the following mnemonics are suitable. For the histological layers from outside to inside: **G - F - R** (corresponding to the glomerular filtration rate one should be familiar with in the context of the kidneys) and for the respective steroid hormones from outside to inside: **Salt - Sugar - Sex** (corresponding to the function of the respective hormone).

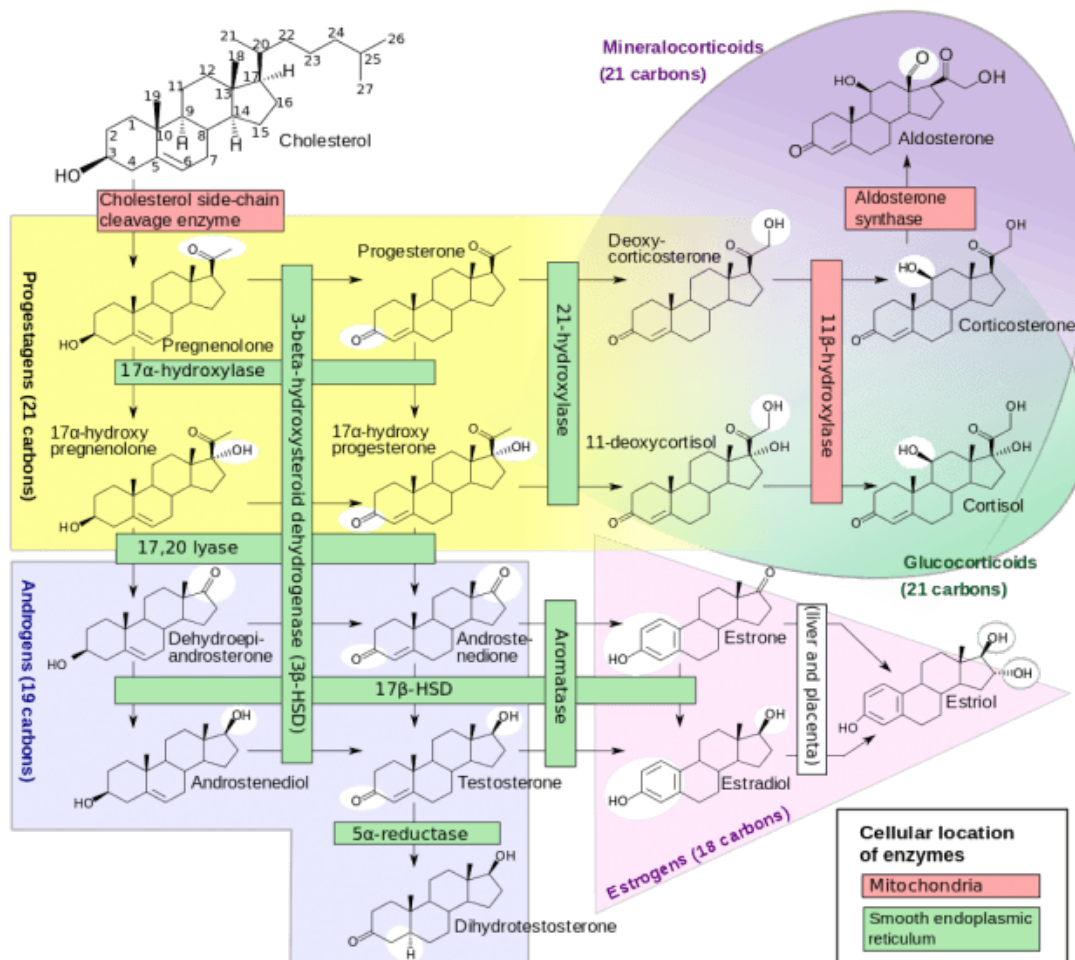


Image: "Steroidogenesis" by David Richfield and Mikael Häggström.. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Thus, **cortisol** is the final **effector hormone** and forms in the ACTH-dependent **zona fasciculata** of the adrenal cortex. Besides the effect on biosynthesis of cortisol, ACTH also makes for a **sufficient provision of NADPH**, an important cofactor of glucocorticoid synthesis, and for **an increased activity of an esterase which provides cholesterol, the original substance**.

The synthesis of cortisol begins **in the mitochondrion** with hydroxylation of cholesterol to **Pregnenolone**. This is the limiting step of cortisol synthesis, mediated by the enzyme **desmolase**. The subsequent reaction steps take place in the cytosol. Eventually, a steroid hormone with 21 C-atoms forms with a characteristic OH-group at the C11-atom.

Note: Since synthesis of the different steroid hormones is very similar, you should remember them by using an overview of all reaction steps.

Cortisol and its Function

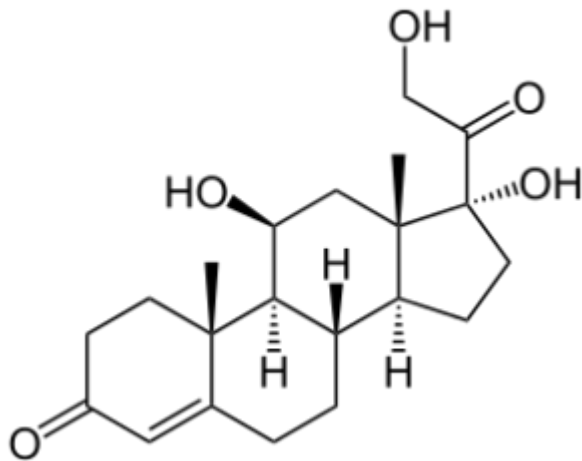


Image: "Struktur von Cortisol" by NEUROtiker. License: Public Domain

Cortisol (also: hydrocortisone) is a **steroid hormone** and one of the most important representatives of the **glucocorticoids**. Like all remaining steroid hormones, cortisol is formed from the scaffold of cholesterol. It is produced in the adrenal cortex, which is responsible for synthesis of steroid hormones. Further glucocorticoids are cortisone and corticosterone as well as synthetic compounds, which are used medically.

The effects of cortisol are numerous. Besides the effect on the **sugar-, amino acid-, and lipid-metabolism**, it especially has an influence on the immune system and the anti-inflammatory components. As a steroid hormone, cortisol is **lipophilic** and binds to an **intracellular receptor**. In the blood, it is transported by binding to a protein called **transcortin**.

When cortisone reaches the target cell as an effector hormone, it exerts its effect via regulation of gene expression on the level of **transcription** and is thus long lasting. **Cortisone does not bind to a membranous G-protein coupled receptor, but to a glucocorticoid receptor in the cytosol, which acts as a transcription factor when activated.**

Concerning metabolism, cortisone mostly has **catabolic** effects in the periphery, while centrally, that is in [the liver](#), its effects are mostly **anabolic**. While proteolysis is induced in muscle cells and lipolysis is promoted in fat tissue, increased gene expression of enzymes of gluconeogenesis and glycogen synthesis can be observed in the liver.

Glucose intake in the muscles is decreased. As a consequence, the **blood sugar level** rises, which ensures good supply of the CNS. Due to the decreased glucose intake and utilization in the periphery and increased glycogen synthesis, cortisone can be classified as an **antagonist to insulin** since it has similar effects to glucagon.

Additionally, there is an **anti-inflammatory**, that is an antiphlogistic effect of cortisone. This is due to an **inhibition of lymphocyte proliferation, an inhibition of the synthesis of interleukins, and an inhibition of cyclooxygenase-2 (COX-2).**

Concerning its influence on other organ systems, cortisol has growth-slowing effects on the bones and even causes osteoporosis, promotes alertness in the CNS, and can increase contractile force of the heart via an increase in the effect of catecholamines.

Note: In the majority of cases, the anti-inflammatory effect is the cause for the therapeutic application of glucocorticoids. Synthetic substances are e.g. **prednisolone** or **dexamethasone**.

Every day, the body produces roughly 12-30 mg of cortisol, which has a half-life period of ca. 90 minutes and is then inactivated in the liver. Glucocorticoids given for treatment lose a part of their effect at first contact with the liver, which is called the **'first pass effect'**. The metabolites are then excreted via the liver or the kidneys.

A single measurement of the cortisol level is not very meaningful since it follows a physiological **circadian rhythm**. The maximum plasma concentration of cortisol with peak values of 25 µg/dl is reached early in the morning roughly half an hour after waking up (cortisol awakening response). During the course of the day, the level drops.

Regulation of the Hypothalamus-Pituitary-Adrenal Axis

Several mechanisms ensure an appropriate response of the HPA axis and prevent an excessive release of cortisol with negative consequences for the body.

The most important of these mechanisms is the **negative feedback**. This mechanism can often be observed in endocrinology. It describes the inhibitory effect of a hormone on the production of a releasing factor to eventually inhibit its own synthesis.

In case of the glucocorticoid cascade, the increased release of cortisol has an inhibiting effect on the hypothalamus and the pituitary gland. As a consequence, less CRH and ACTH are secreted and biosynthesis of cortisol is reduced. As long as all involved organs function properly, the plasma levels of cortisol always remain within acceptable limits.

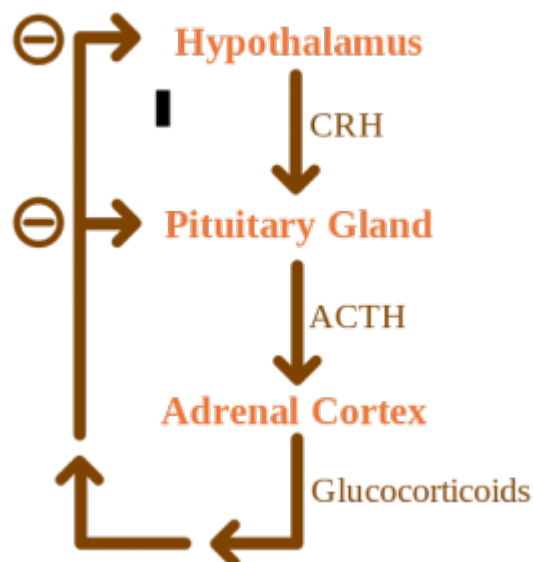


Image: "Diagram of physiologic negative feedback loop for glucocorticoids" by DRosenbach. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Note: Negative feedback is the reason why synthetic glucocorticoids inhibit endogenous production.

On the other side, there are activators of glucocorticoid synthesis that cause an increased synthesis independently of the stress reaction or the physiological circadian activity.

Catecholamines are an example of this, because they stimulate the secretion of ACTH. Also, mediators of the **immune system** like IL-1 and TNF- α have a stimulating effect.

Diseases of the Hypothalamus Pituitary Adrenal Axis

Hypercortisolism (Cushing Syndrome)

An **excessive cortisol level** is referred to as **Cushing syndrome**. The causes are complex. However, in the majority of cases it is the consequence of immunosuppressive therapy with glucocorticoids, which is called the **iatrogenic Cushing syndrome**. Thus, there is a maximal dose in the therapy guidelines, the so-called Cushing threshold, which should not be exceeded if possible.

Another frequent cause is, for example, a **tumor in the anterior lobe of the pituitary gland**, which secretes ACTH and causes abnormally increased plasma levels of cortisol. This central Cushing syndrome is also referred to as **Cushing Disease** (or Morbus Cushing).

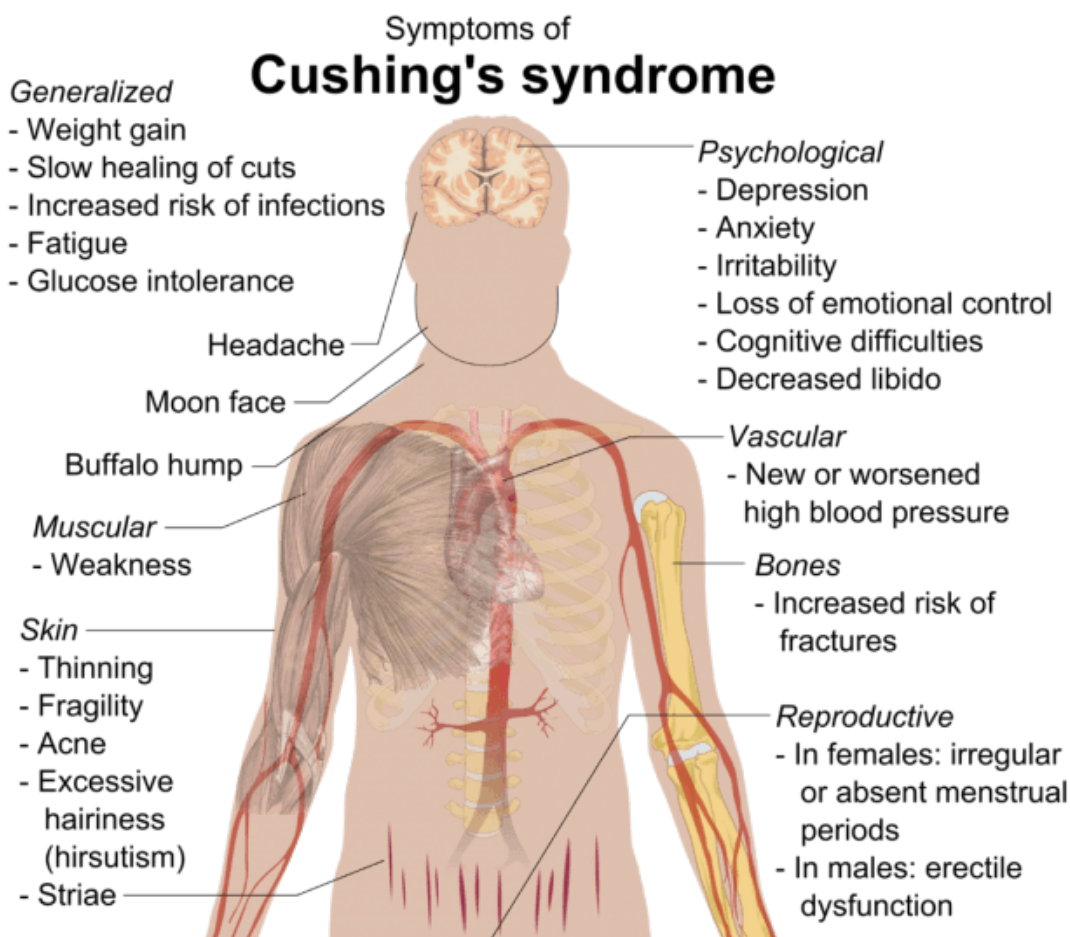


Image: "Symptoms of Cushing's syndrome" by Mikael Hågström. License: Public Domain

The symptoms of such increased glucocorticoid levels are impressive and characteristic of this disease. The **elevated blood sugar** of the patients can be explained by the effect of the hormone. This can – among others – lead to **diabetes mellitus** type II. Also, further consequences are **osteoporotic changes** and **muscle weakness** due to

proteolysis.

Concerning their outward appearance, patients often display a distinct central obesity, a so-called buffalo hump, and a moon face. Also, edemas and high blood pressure are part of the clinical picture since glucocorticoids bind to the mineralocorticoid receptor if the concentration is high enough.

Therapy (see [Diagnostic Investigation of Hypercortisolism](#)) often aims to treat the cause of the Cushing syndrome. In the case of iatrogenic Cushing syndrome, one tries to reduce the glucocorticoid amount. Adenomas of the pituitary gland are removed surgically or radiated with varying results.

Hypocortisolism (Insufficiency of the adrenal cortex)

In contrast to the clinical picture mentioned above, there is a **lack of glucocorticoids** with insufficiency of the adrenal cortex. This can manifest acutely and can even have lethal consequences if not treated appropriately. This disease is divided into a **primary** (level of the adrenal gland), **secondary** (level of the pituitary gland), and a **tertiary** form (level of the hypothalamus).

The primary insufficiency of the adrenal cortex is by far the most frequent form, which is referred to as **Addison's disease**. Several causes can lead to this disease, but in roughly 70 % of the cases, an **autoimmune disease** with antibodies against the cells of the adrenal gland is the underlying cause. Also, tumors and infections are possible causes.



[Image](#): "Classic hyperpigmentation of Addison's disease" by FlatOut. License: Public Domain

An acute and fulminant manifestation with possible circulatory shock, frequently associated with triggering factors like disease or stress, is called **Addisonian crisis** and is an endocrinological emergency.

Note: Another cause of Addison's disease is a **long-term cortisol therapy** with an ACTH drop and consequential atrophy of the zona fasciculata.

Symptoms of hypocortisolism are often of an **aspecific** nature, like general weakness and weight loss, hypotension, abdominal pain, nausea, vomiting, and distinct 'salt hunger'. **Hyperpigmentation** is typical for Addison's disease since more MSH is produced due to increased levels of ACTH as a consequence of absent cortisol feedback, as mentioned before. Thus, Addison's disease is sometimes referred to as 'bronze disease'.

Diagnostically, the primary form can be distinguished from the other forms with ACTH-diagnostics and the detection of autoantibodies. Therapy is performed with continuous substitution of gluco- and mineralocorticoids.

Review Questions

The answers can be found below the references.

1. Which statement concerning the HPA axis is not true?

- A. ACTH secreted by the pituitary gland increases biosynthesis of adrenaline.
- B. The hypothalamus liberates the hormone CRH in a pulsatile manner.
- C. Cortisol inhibits ACTH- and CRH-release.
- D. Cortisol is synthesized from cholesterol.
- E. ACTH is a glandotropic hormone.

2. Where is the hormone cortisol synthesized?

- A. In the pituitary gland.
- B. In the adrenal medulla.
- C. In the zona glomerulosa of the adrenal cortex.
- D. In the zona fasciculata of the adrenal cortex.
- E. In the hypothalamus.

3. Which is NOT a typical effect of cortisol?

- A. Increase in blood sugar level
- B. Proteolysis of muscles
- C. Excessive inflammatory reaction
- D. Induction of transcription of certain enzymes
- E. Synergism with adrenaline

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Correct answers: 1A, 2D, 3C

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