Adrenal Hormones

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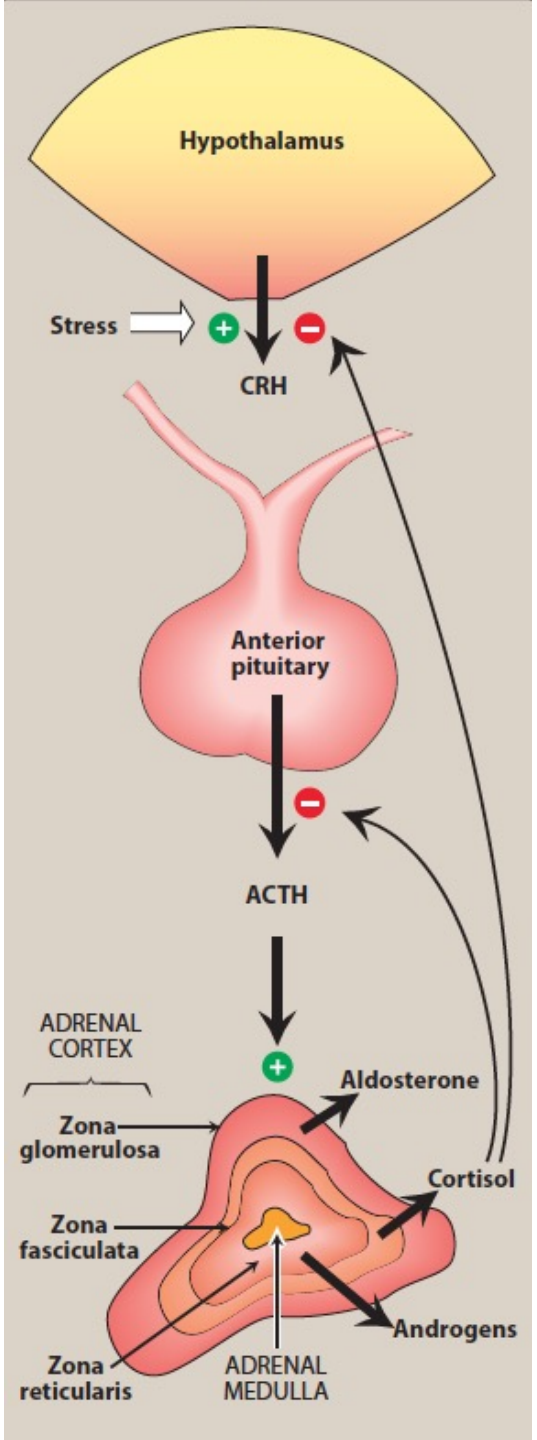


Corticosteroids (glucocorticoids and mineralocorticoids)

- **Cortisol** is the principal human glucocorticoid. Normally, its production is diurnal, with a peak early in the morning followed by a decline and then a secondary, smaller peak in the late afternoon.

- Factors such as stress and levels of the circulating steroid influence secretion. The effects of cortisol are many and diverse.

- In general, all glucocorticoids:

1. **Promote normal intermediary metabolism:** Glucocorticoids favor gluconeogenesis through increasing amino acid uptake by the liver and kidney and elevating activities of gluconeogenic enzymes. They stimulate protein catabolism (except in the liver) and lipolysis, thereby providing the building blocks and energy that are needed for glucose synthesis.

Corticosteroids

2. **Increase resistance to stress:** By raising plasma glucose levels, glucocorticoids provide the body with energy to combat stress caused by trauma, fright, infection, bleeding, or debilitating disease.

2. **Alter blood cell levels in plasma:** Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue. Glucocorticoids also increase hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes.

4. **Have anti-inflammatory action:** The most important therapeutic properties of the glucocorticoids are their potent anti-inflammatory and immunosuppressive activities.

- These therapeutic effects of glucocorticoids are the result of a number of actions. The lowering of circulating lymphocytes is known to play a role. In addition, these agents inhibit the ability of leukocytes and macrophages to respond to mitogens and antigens.

Corticosteroids

- Glucocorticoids also decrease the production and release of proinflammatory cytokines. They inhibit phospholipase A2, which blocks the release of arachidonic acid (the precursor of the prostaglandins and leukotrienes) from membrane-bound phospholipid. The decreased production of prostaglandins and leukotrienes is believed to be central to the anti-inflammatory action.

- Lastly, these agents influence the inflammatory response by stabilizing mast cell and basophil membranes, resulting in decreased histamine release.

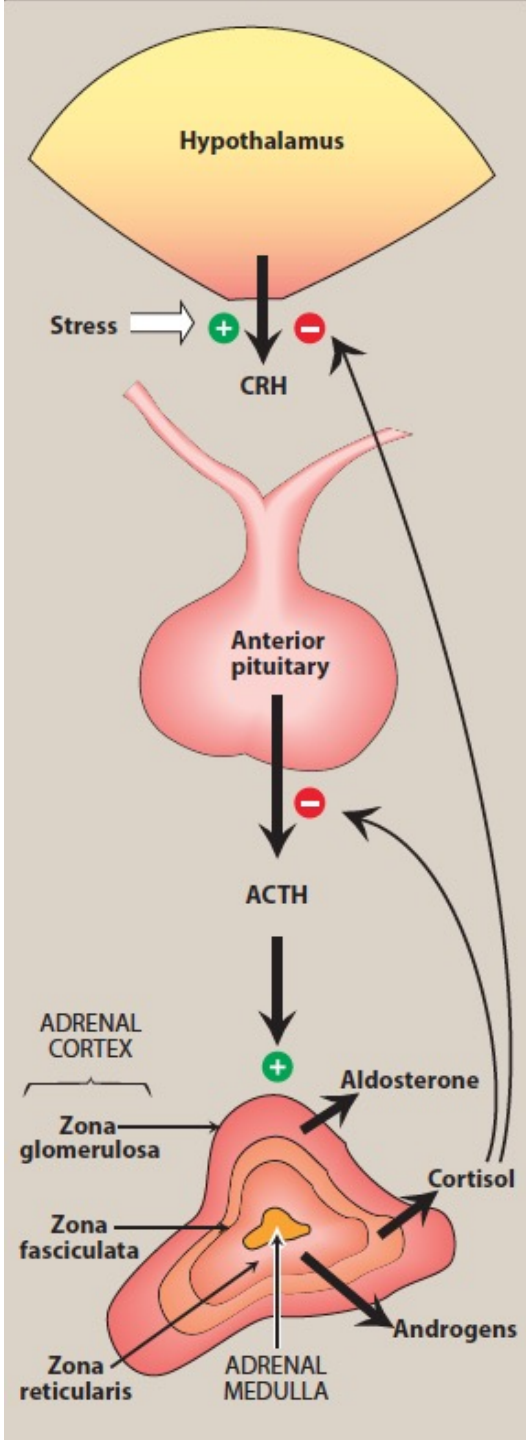
5. **Affect other systems:** High levels of glucocorticoids serve as feedback inhibitors of ACTH production and affect the endocrine system by suppressing further synthesis of glucocorticoids and thyroid-stimulating hormone.
- In addition, adequate cortisol levels are essential for normal glomerular filtration.

Mineralocorticoids

- Mineralocorticoids help to control fluid status and concentration of electrolytes, especially sodium and potassium.

- ***Aldosterone*** acts on distal tubules and collecting ducts in the kidney, causing reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which, with H^+, is then lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands.

- Target cells for aldosterone contain mineralocorticoid receptors that interact with the hormone in a manner analogous to that of glucocorticoid receptors.



Therapeutic uses of the corticosteroids

1. **Replacement therapy for primary adrenocortical insufficiency (Addison disease):** Addison disease is caused by adrenal cortex dysfunction (as diagnosed by the lack of response to ACTH administration).

- ***Hydrocortisone***, which is identical to natural cortisol, is given to correct the deficiency.

- The dosage of hydrocortisone is divided so that two-thirds of the daily dose is given in the morning and one-third is given in the afternoon.

- Administration of ***fludrocortisone***, a potent synthetic mineralocorticoid with some glucocorticoid activity, may also be necessary to supplement mineralocorticoid deficiency.

2. **Replacement therapy for secondary or tertiary adrenocortical insufficiency:** These disorders are caused by a defect in CRH production by the hypothalamus or in ACTH production by the pituitary.

- Hydrocortisone is used for treatment of these deficiencies.

Therapeutic uses of the corticosteroids

3. **Diagnosis of Cushing syndrome:** Cushing syndrome is caused by hypersecretion of glucocorticoids (hypercortisolism) that results from excessive release of ACTH by the anterior pituitary or an adrenal tumor.

- Cortisol levels (urine, plasma, and saliva) and the ***dexamethasone*** suppression test are used to diagnose Cushing syndrome. The synthetic glucocorticoid dexamethasone suppresses cortisol release in normal individuals, but not those with Cushing syndrome.

4. **Replacement therapy for congenital adrenal hyperplasia (CAH):** CAH is a group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones.

- Treatment of the condition requires administration of sufficient corticosteroids to normalize hormone levels by suppressing release of CRH and ACTH. This decreases production of adrenal androgens.

5. **Relief of inflammatory symptoms:** Corticosteroids significantly reduce the manifestations of inflammation associated with rheumatoid arthritis and inflammatory skin conditions, including redness, swelling, heat, and tenderness that may be present at the site of inflammation.

Therapeutic uses of the corticosteroids

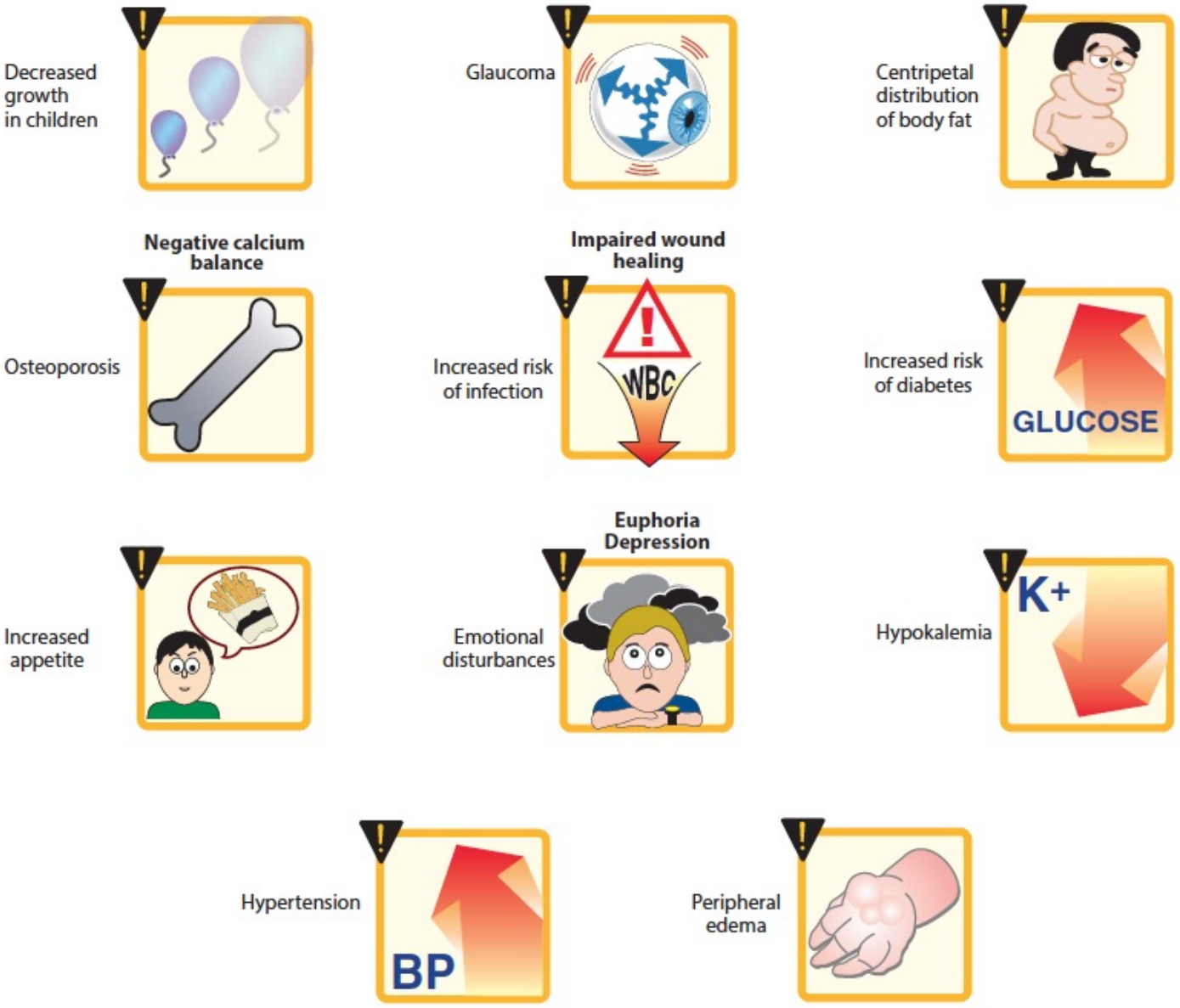
- These agents are also important for maintenance of symptom control in persistent asthma, as well as management of asthma exacerbations and active inflammatory bowel disease.

6. **Treatment of allergies:** Corticosteroids are beneficial in the treatment of allergic rhinitis, as well as drug, serum, and transfusion allergic reactions.

7. **Acceleration of lung maturation:** Respiratory distress syndrome is a problem in premature infants.

- Fetal cortisol is a regulator of lung maturation. Consequently, a regimen of betamethasone or dexamethasone administered intramuscularly to the mother within the 48 hours proceeding premature delivery can accelerate lung maturation in the fetus.

Adverse effects



- **Discontinuation:** Sudden discontinuation of these drugs can be a serious problem if the patient has suppression of the HPA axis.

- In this case, abrupt removal of corticosteroids causes acute adrenal insufficiency that can be fatal. This risk, coupled with the possibility that withdrawal might cause an exacerbation of the disease, means that the dose must be tapered slowly according to individual tolerance.

- **Inhibitors of adrenocorticoid biosynthesis or function:** Several substances have proven to be useful as inhibitors of the synthesis or function of adrenal steroids:

1. ***Ketoconazole:*** is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing syndrome.

2. ***Spironolactone:*** This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. It can also antagonize aldosterone and testosterone synthesis.

- It is effective for hyperaldosteronism and is used along with other standard therapies for the treatment of heart failure with reduced ejection fraction.

3. ***Eplerenone:*** specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the side effect of gynecomastia that is associated with the use of spironolactone.

- It is approved for the treatment of hypertension and also for heart failure with reduced ejection fraction.


Thank You!