LEC. 6: ADRENAL HORMONES

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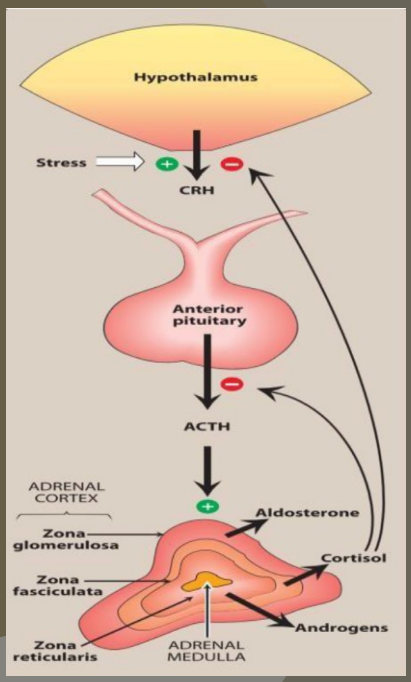
The adrenal hormones

- The adrenal cortex secretes two types of corticosteroids (glucocorticoids and mineralocorticoids) and the adrenal androgens.
- The adrenal cortex has three zones, and each zone synthesizes a different type of steroid hormone from cholesterol.
- The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone) that are responsible for regulating salt and water metabolism.
- The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol) that are involved with metabolism and response to stress.
- The inner zona reticularis secretes adrenal androgens.

Secretion by the two inner zones and, to a lesser extent, the outer zone is controlled by pituitary adrenocorticotropic hormone (ACTH; also called corticotropin), which is released in response to hypothalamic corticotropin-releasing hormone (CRH). Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion.



Corticosteroids

- Corticosteroids differ in their metabolic (glucocorticoid) and electrolyteregulating (mineralocorticoid) activity.
- The corticosteroids bind to specific intracellular cytoplasmic receptors in target tissues.
- Glucocorticoid receptors are widely distributed throughout the body, whereas mineralocorticoid receptors are confined mainly to excretory organs, such as the kidney, colon, salivary glands, and sweat glands.
- Both types of receptors are found in the brain. After dimerizing, the receptor-hormone complex recruits coactivator (or corepressor) proteins and translocate into the nucleus, where it attaches to gene promoter elements.
- There it acts as a transcription factor to turn genes on (when complexed with coactivators) or off (when complexed with corepressors), depending on the tissue.

Glucocorticoid receptors	Mineralocorticoid receptors
Intracellular cytoplasmic receptors in target tissues.	Intracellular cytoplasmic receptors in target tissues.
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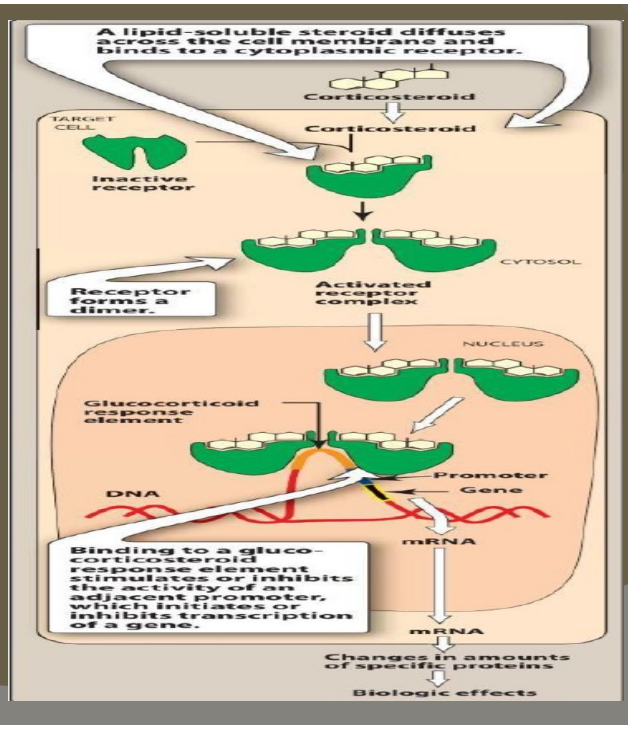
found in the brain	found in the brain



- Because of this mechanism, some effects of corticosteroids take hours to days to occur.
- This section describes normal actions and therapeutic uses of corticosteroids.
- **Glucocorticoids** :

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

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 stimulate hepatic glucose production by enhancing expression of enzymes involved in gluconeogenesis.**
- **They mobilize amino acids and stimulate lipolysis, thereby providing the building blocks and energy for glucose synthesis.**
- **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 disease. [Note: Glucocorticoid insufficiency may result in hypoglycemia (for example, during stressful periods or fasting).]**

- 3. 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 increase hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes.
- 4. Possess anti-inflammatory action:
- Potent anti-inflammatory and immunosuppressive activities are the most important therapeutic properties of glucocorticoids.
- Glucocorticoids lower circulating lymphocytes and inhibit the ability of leukocytes and macrophages to respond to mitogens and antigens.

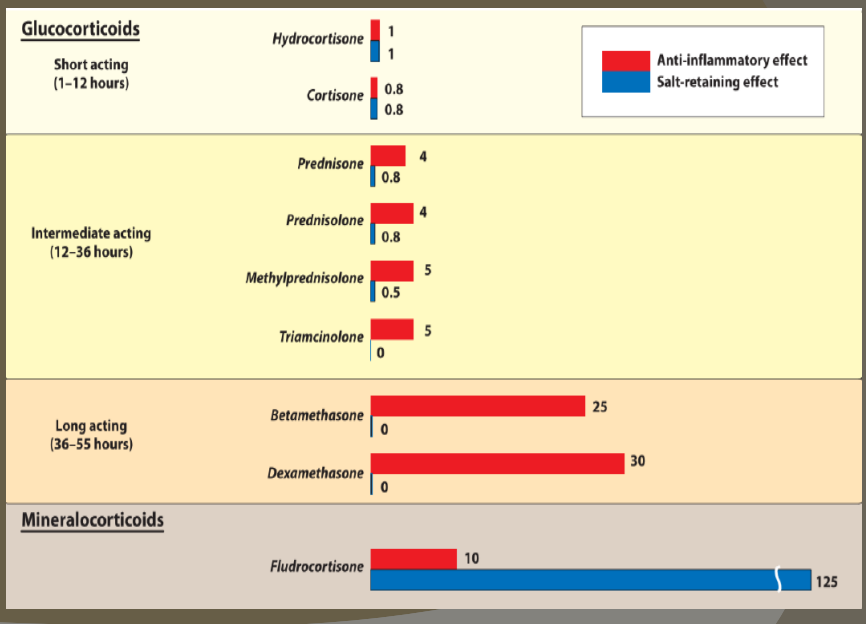
- Glucocorticoids also decrease the production and release of proinflammatory cytokines.
- They inhibit phospholipase A2, which blocks the release of arachidonic acid (the precursor of the prostaglandins and leukotriene, resulting in anti- inflammatory actions.
- Lastly, these agents influence the inflammatory response by stabilizing mast cell and basophil membranes, thereby decreasing histamine release.

- 5. Affect other systems:
- High levels of glucocorticoids provide negative feedback to reduce ACTH production and affect the endocrine system by suppressing synthesis of glucocorticoids and thyroid-stimulating hormone.
- In addition, adequate cortisol levels are essential for normal glomerular filtration.
- Corticosteroids may adversely affect other systems.

Mineralocorticoids

- Mineralocorticoids help to control fluid status and concentration of electrolytes, especially sodium and potassium.
- Aldosterone acts on mineralocorticoid receptors in the 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 lost in the urine.
- Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands.

- [Note: Elevated aldosterone levels may cause alkalosis and hypokalemia, retention of sodium and water, and increased blood volume and blood pressure. Hyperaldosteronism is treated with spironolactone.]
- **Therapeutic uses of the corticosteroids**: Semisynthetic derivatives of corticosteroids vary in anti-inflammatory potency, mineralocorticoid activity, and duration of action.
- These agents are used in replacement therapy and in the treatment of severe allergic reactions, asthma, rheumatoid arthritis, other inflammatory disorders, and some cancers.



- **1. Replacement therapy for primary adrenocortical insufficiency (Addison disease):**
- **Addison disease is caused by adrenal cortex dysfunction (diagnosed by lack of response to ACTH administration).**
- **Hydrocortisone, which is identical to natural cortisol, is given to correct the deficiency. Failure to do so results in death.**
- **Two-thirds of the daily dosage of hydrocortisone is administered in the morning and one-third in the afternoon, mimicking the normal diurnal variation in cortisol levels.**
- **Administration of fludrocortisone, a potent synthetic mineralocorticoid, may also be necessary to correct 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.**

- 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.
- [Note: Chronic treatment with high doses of glucocorticoids is a frequent cause of iatrogenic Cushing syndrome.]
- 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.
- CAH may lead to virilization in females due to overproduction of adrenal androgens.
- Treatment requires administration of sufficient corticosteroids to suppress release of CRH and ACTH and normalize hormone levels.
- This decreases production of adrenal androgens. The choice of replacement hormone depends on the specific enzyme defect.

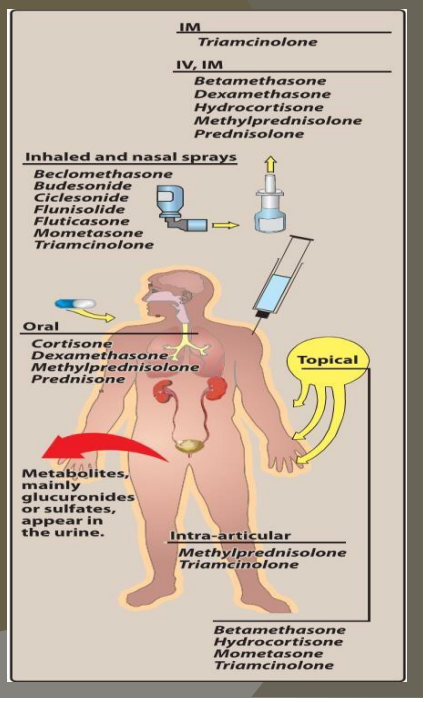
- 5. Relief of inflammatory symptoms:
- Corticosteroids significantly reduce inflammation associated with rheumatoid arthritis and inflammatory skin conditions, including redness, swelling, heat, and tenderness.
- These agents are important for symptom control in persistent asthma, as well as treatment of exacerbations of asthma and inflammatory bowel disease.
- In osteoarthritis, intraarticular corticosteroids may be used for treatment of a disease flare. Corticosteroids are not curative in these disorders.

- 6. Treatment of allergies:
- Corticosteroids are beneficial in the treatment of allergic rhinitis, as well as drug, serum, and transfusion allergic reactions.
- In the treatment of allergic rhinitis and asthma, fluticasone and others are inhaled into the respiratory tract from a metered dose dispenser. This minimizes systemic effects, reducing or eliminating the use of oral corticosteroids.
- 7. Acceleration of lung maturation:
- Fetal cortisol is a regulator of lung maturation. Consequently, a regimen of betamethasone or dexamethasone administered intramuscularly to the mother within 48 hours proceeding premature delivery can accelerate lung maturation in the fetus and prevent respiratory distress syndrome.

- Pharmacokinetics:
- 1- Absorption and fate: Corticosteroids are readily absorbed after oral administration. Selected compounds may be administered intravenously, intramuscularly, intra-articularly, topically, or via inhalation or intranasal delivery.
- All topical and inhaled glucocorticoids are absorbed to some extent and, therefore, have the potential to suppress the hypothalamic-pituitaryadrenal (HPA) axis.

After absorption, glucocorticoids are greater than 90% bound to plasma proteins, mostly corticosteroid-binding globulin or albumin.

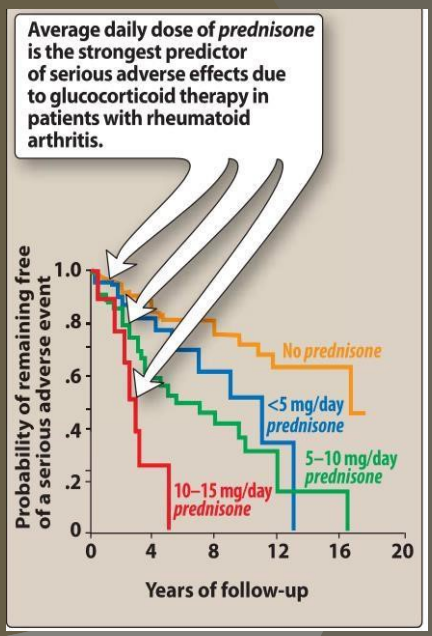
Corticosteroids are metabolized by the liver microsomal oxidizing enzymes. The metabolites are conjugated to glucuronic acid or sulfate and excreted by the kidney.



- [Note: The half-life of corticosteroids may increase substantially in hepatic dysfunction.]
- Prednisone is preferred in pregnancy because it minimizes steroid effects on the fetus.
- It is a prodrug that is not converted to the active compound, prednisolone, in the fetal liver.
- Any prednisolone formed in the mother is biotransformed to prednisone by placental enzymes.

- 2. Dosage:
- Factors that should be considered in determining the dosage of corticosteroids include: glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and time of day when the drug is administered.
- When large doses of corticosteroids are required for more than 2 weeks, suppression of the HPA axis occurs.
- Alternate-day administration of corticosteroids may prevent this adverse effect by allowing the HPA axis to recover/function on days the hormone is not taken.

- **Adverse effects:** Common adverse effects of long-term corticosteroid therapy are often dose related. For example, in rheumatoid arthritis, the daily dose of prednisone was the strongest predictor of occurrence of adverse effects.



- Osteoporosis is the most common adverse effect due to the ability of glucocorticoids to suppress intestinal Ca2 + absorption, inhibit bone formation, and decrease sex hormone synthesis. Patients are advised to take calcium and vitamin D supplements.
- Bisphosphonates may also be useful in the treatment of glucocorticoid-induced osteoporosis.
- [Note: Increased appetite is not necessarily an adverse effect. In fact, it is one of the reasons for the use of prednisone in cancer chemotherapy.]
- The classic Cushing-like syndrome (redistribution of body fat, puffy face, hirsutism, and increased appetite) is observed in excess corticosteroid replacement.
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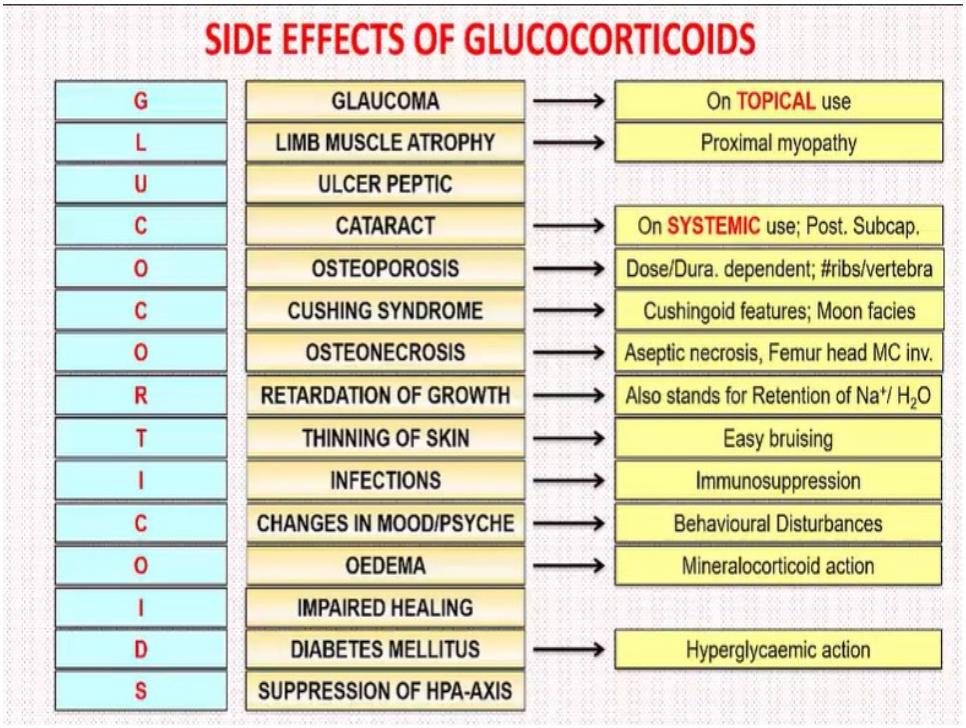
- Cataracts may also occur with long-term corticosteroid therapy.
- Hyperglycemia may develop and lead to diabetes mellitus. Diabetic patients should monitor blood glucose and adjust medications accordingly if taking corticosteroids.
- Topical therapy can cause skin atrophy, ecchymosis, and purple striae.
- Other possible adverse effects of glucocorticosteroid include:
- Decrease growth in children, glaucoma, centripetal distribution of body fat, increase risk of infection, increase risk of diabetes, emotional disturbances, hypokalemia, hypertension and peripheral edema.



Discontinuation

- Sudden discontinuation of these drugs can cause serious consequences 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 could exacerbate the disease, means that the dose must be tapered slowly according to individual tolerance. The patient must be monitored carefully.

Inhibitors of adrenocorticoid biosynthesis or function

- Several substances are therapeutically useful as inhibitors of the synthesis or function of adrenal steroids: ketoconazole, spironolactone, and eplerenone.
- 1. Ketoconazole:
- 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. Spironolactone also antagonizes aldosterone and testosterone synthesis.
- It is effective for hyperaldosteronism and hepatic cirrhosis, and is used with other standard therapies for treatment of heart failure with reduced ejection fraction. It is also useful in the management of hirsutism in women, probably due to antiandrogen activity on the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

- 3. Eplerenone:
- Eplerenone specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist.
- This specificity avoids the adverse effect of gynecomastia that is associated with spironolactone.
- It is approved for the treatment of hypertension and for heart failure with reduced ejection fraction.