Corticocorticoids
• The adrenal gland consists of the cortex and the medulla.
• The medulla secretes catecholamines, whereas the
cortex secretes two types of corticosteroids (glucocorticoids and mineralocorticoids)
Corticosteroids

- The **corticosteroids** bind to specific intracellular cytoplastic 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.
- However, other glucocorticoid effects are immediate, such as the interaction with catecholamines to mediate relaxation of bronchial musculature.
A lipid-soluble steroid diffuses across the cell membrane and binds to a cytoplasmic receptor. Corticosteroid

TARGET CELL

Inactive receptor

Corticosteroid

Receptor forms a dimer.

Activated receptor complex

NUCLEUS

Glucocorticoid response element

Binding to a glucocorticosteroid response element stimulates or inhibits the activity of an adjacent promoter, which initiates or inhibits transcription of a gene.

DNA

Promoter

Gene

mRNA

Changes in amounts of specific proteins

Biologic effects

Figure 27.3
Gene regulation by glucocorticoids.
Glucocorticoids

• 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.
   - [Note: Glucocorticoid insufficiency may result in hypoglycemia (for example, during stressful periods or fasting).]

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.

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 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.

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**.

These agents influence the inflammatory response by stabilizing mast cell and basophil membranes, resulting in decreased histamine release.
• 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.

• The effects of corticosteroids on other systems are mostly associated with adverse effects of the hormones.
**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.

[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**.

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>Celestone, Diprolene, LUXIQ</td>
</tr>
<tr>
<td>Cortisone</td>
<td>Cortisone Acetate</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Decadron</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Florinef</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Medrol</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Orapred, Pediapred</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Kenalog, Nasacort, Aristospaun</td>
</tr>
</tbody>
</table>

**INHIBITORS OF ADRENOCORTICOID BIOSYNTHESIS OR FUNCTION**

<table>
<thead>
<tr>
<th>Name</th>
<th>Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eplerenone</td>
<td>Inspra</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nizoral</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldactone</td>
</tr>
</tbody>
</table>

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**Figure 27.1**
Summary of adrenal corticosteroids.
Figure 27.4
Pharmacologic effects and duration of action of some commonly used natural and synthetic corticosteroids. Activities are all relative to that of hydrocortisone, which is considered to be 1.
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** \([\text{hye-droe-}KOR-\text{tih-}sone]\), which is identical to natural cortisol, is given to correct the deficiency. Failure to do so results in death.

- 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** \([\text{floo-droe-}KOR-\text{tih-}sone]\), a potent synthetic mineralocorticoid with some glucocorticoid activity, may also be necessary to supplement mineralocorticoid deficiency.
Therapeutic Uses of the Corticosteroids

• Several semisynthetic derivatives of corticosteroids are available.
• These agents vary in anti-inflammatory potency, mineralocorticoid activity, and duration of action.
• Corticosteroids are used in replacement therapy and in the treatment of severe allergic reactions, asthma, rheumatoid arthritis, other inflammatory disorders, and some cancers.
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. [Note: Under these conditions, the synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids.]

- **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.

- Cortisol levels (urine, plasma, and saliva) and the dexamethason [dex-a-METH-a-sone] suppression test are used to diagnose Cushing syndrome.

- The synthetic glucocorticoid dexamethason 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 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.
- The choice of replacement hormone depends on the specific enzyme defect.

5. **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.
6. 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.

- 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.

- **Corticosteroids are not curative in these disorders.**

7. Treatment of allergies: Corticosteroids are beneficial in the

- **Treatment** of allergic rhinitis, as well as drug, serum, and transfusion allergic reactions. [Note: In the treatment of allergic rhinitis and asthma, **fluticasone** [flo-TIK-a-sone] and others are applied topically to the respiratory tract through inhalation from a metered dose dispenser.

- This minimizes systemic effects and allows the patient to reduce or eliminate the use of oral corticosteroids.
Figure 27.5
Routes of administration and elimination of corticosteroids.
Pharmacokinetics

- Absorption and fate: Orally administered corticosteroid preparations are readily absorbed.
- Selected compounds can also 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 cause hypothalamic–pituitary–adrenal (HPA) axis suppression.
- Greater than 90% of absorbed glucocorticoids are bound to plasma proteins, mostly corticosteroid-binding globulin or albumin.
- Corticosteroids are metabolized by the liver microsomal oxidizing enzymes.
- Prednisone [PRED-nih-sone] 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 [pred-NIH-so-lone], in the fetal liver.
- Any prednisolone formed in the mother is biotransformed to prednisone by placental enzymes.
Dosage:
• Many factors should be considered in determining the dosage of corticosteroids, including glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and time of day when the drug is administered.
• When large doses of the hormone are required for more than 2 weeks, suppression of the HPA axis occurs.
• Alternate-day administration of the corticosteroid may prevent this adverse effect by allowing the HPA axis to recover/function on days the hormone is not taken.
Adverse effects

✓ Adverse effects are often **dose related**.

• For example, in patients with 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.
Average daily dose of prednisone is the strongest predictor of serious adverse effects due to glucocorticoid therapy in patients with rheumatoid arthritis.

**Figure 27.7**
Probability of remaining free of a serious adverse event in patients with rheumatoid arthritis treated with no or different doses of prednisone.
• 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**.
• **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.
• Coadministration of medications that induce or inhibit the hepatic mixed-function oxidases may require adjustment of the glucocorticoid dose.
• **Topical therapy** can also cause **skin atrophy**, ecchymosis, and purple striae.
Figure 27.6
Some commonly observed effects of long-term corticosteroid therapy. BP = blood pressure.
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.
- The patient must be monitored carefully.
Inhibitors of adrenocorticoid biosynthesis or function

- Several substances have proven to be useful as inhibitors of the synthesis or function of adrenal steroids: *ketoconazole* spironolactone, and eplerenone

- Ketoconazole [kee-toe-KON-ah-zole] 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.
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.

• **Spironolactone** [*speer-oh-no-LAK-tone*] is also useful in the treatment of **hirsutism** in women, probably due to interference at the **androgen receptor** of the hair follicle.

• **Adverse effects** include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.
• **Eplerenone**: Eplerenone [e-PLER-ih-none]

• **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.