The natural adrenocortical hormones are steroid molecules produced and released by the adrenal cortex. Both natural and synthetic corticosteroids are used for the diagnosis and treatment of disorders of adrenal function. They are also used more often and in much larger doses for treatment of a variety of inflammatory and immunologic disorders.

The adrenal cortex releases a large number of steroids into the circulation. Some have minimal biologic activity and function primarily as precursors, and there are some for which no function has been established. The hormonal steroids may be classified as those having important effects on intermediary metabolism and immune function (glucocorticoids), those having principally salt-retaining activity (mineralocorticoids), and those having androgenic or estrogenic activity.

In humans, the major glucocorticoid is cortisol and the most important mineralocorticoid is aldosterone. Quantitatively, dehydroepiandrosterone (DHEA) in its sulfated form (DHEAS) is the major adrenal androgen.

Secretion of adrenocortical steroids is controlled by the pituitary release of corticotropin (ACTH). Secretion of the salt-retaining hormone aldosterone is primarily under the influence of angiotensin.

A. Glucocorticoids

A. Mechanism of Action

Most of the known effects of the glucocorticoids are mediated by widely distributed glucocorticoid receptors (intracellular cytoplasmic receptors in target tissues). These receptors interact with the promoters of—and regulate the transcription of—target genes. In the absence of the hormonal ligand, glucocorticoid receptors are primarily cytoplasmic, in oligomeric complexes with chaperone heat-shock proteins (hsp). Free hormone from the plasma and interstitial fluid enters the cell and binds to the receptor, inducing
conformational changes that allow it to dissociate from the heat shock proteins. The dimeric ligand-bound receptor complex then is actively transported into the nucleus, where it interacts with DNA and nuclear proteins. It binds to glucocorticoid receptor elements (GREs) in the promoters of responsive genes. In addition to binding to GREs, the ligand-bound receptor also forms complexes with and influences the function of other transcription factors, such as AP1 and nuclear factor kappa-B (NF-κB), which act on non-GRE-containing promoters, to contribute to the regulation of transcription of their responsive genes. These transcription factors have broad actions on the regulation of growth factors, proinflammatory cytokines, and to a great extent mediate the anti-growth, antiinflammatory, and immunosuppressive effects of glucocorticoids.

**Actions**

In general, all glucocorticoids

1. **Metabolic Effects:** The glucocorticoids have important dose-related effects on carbohydrate, protein, and fat metabolism. Glucocorticoids stimulate and are required for gluconeogenesis and glycogen synthesis in the fasting state. Glucocorticoids increase serum glucose levels and thus stimulate insulin release and inhibit the uptake of glucose by muscle cells, while they stimulate hormone sensitive lipase and thus lipolysis.

2. **Catabolic and Antianabolic Effects:** Although glucocorticoids stimulate RNA and protein synthesis in the liver, they have catabolic and antianabolic effects in lymphoid and connective tissue, muscle, peripheral fat, and skin. Supraphysiologic amounts of glucocorticoids lead to decreased muscle mass and weakness and thinning of the skin. Catabolic and antianabolic effects on bone are the cause of osteoporosis in Cushing’s syndrome and impose a major limitation in the longterm therapeutic use of glucocorticoids.

3. **Anti-Inflammatory and Immunosuppressive Effects:** Glucocorticoids dramatically reduce the manifestations of inflammation. This is due to their profound effects on the concentration, distribution, and function of peripheral leukocytes and to their suppressive effects on the
inflammatory cytokines and chemokines and on other mediators of inflammation. After a single dose of a short-acting glucocorticoid, the concentration of neutrophils in the circulation increases while the lymphocytes (T and B cells), monocytes, eosinophils, and basophils decrease. Glucocorticoids also inhibit the functions of tissue macrophages and other antigen-presenting cells. The ability of these cells to respond to antigens is reduced. The effect on macrophages is particularly marked and limits their ability to phagocytose and kill microorganisms and to produce tumor necrosis factor-α, interleukin-1, metalloproteinases, and plasminogen activator. In addition to their effects on leukocyte function, glucocorticoids influence the inflammatory response by reducing the prostaglandin, leukotriene, and platelet-activating factor synthesis that results from activation of phospholipase A2. Finally, glucocorticoids reduce expression of cyclooxygenase-2, the inducible form of this enzyme, in inflammatory cells, thus reducing the amount of enzyme available to produce prostaglandins. Glucocorticoids cause vasoconstriction when applied directly to the skin, possibly by suppressing mast cell degranulation. They also decrease capillary permeability by reducing the amount of histamine released by basophils and mast cells.

4. Other Effects Increased amounts of glucocorticoids often produce behavioral disturbances in humans: initially insomnia and euphoria and subsequently depression. Large doses of glucocorticoids may increase intracranial pressure (pseudotumor cerebri). Glucocorticoids given chronically suppress the pituitary release of ACTH, growth hormone, thyroid-stimulating hormone, and luteinizing hormone. Large doses of glucocorticoids have been associated with the development of peptic ulcer, possibly by suppressing the local. They also promote fat redistribution in the body, with increase of visceral, facial, nuchal, and supraclavicular fat, and they appear to antagonize the effect of vitamin D on calcium absorption.
Pharmacokinetics

A. Source

- Pharmaceutical steroids are usually synthesized from cholic acid obtained from cattle or steroid sapogenins found in plants. Further modifications of these steroids have led to the marketing of a large group of synthetic steroids with special characteristics that are pharmacologically and therapeutically important.

- Orally administered corticosteroid preparations are readily absorbed.
- Selected compounds can also be administered intravenously, intramuscularly (Betamethasone, Dexamethasone, Hydrocortisone, Methylprednisolone, Triamcinolone), intra-articularly (for example, into arthritic joints), topically, or via inhalation or intranasal delivery (Beclomethasone, Budesonide, Fluticasone, Mometasone, Triamcinolone).
- 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. The metabolites are conjugated to glucuronic acid or sulfate, and the products are 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.

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.

**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 Figure above. Corticosteroids 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 (as diagnosed by the lack of response to ACTH administration). Hydrocortison, 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.
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. 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.

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. 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. In noninflammatory disorders such as osteoarthritis, intra-articular 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.

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.
Toxicity

1. When glucocorticoids are used for short periods (< 2 weeks), it is unusual to see serious adverse effects even with moderately large doses. However, insomnia, behavioral changes (primarily hypomania), and acute peptic ulcers
2. Most patients who are given daily doses of 100 mg of hydrocortisone or more (or the equivalent amount of synthetic steroid) for longer than 2 weeks undergo a series of changes that have been termed iatrogenic Cushing’s syndrome (redistribution of body fat, puffy face, hirsutism, and increased appetite)
3. The continuing breakdown of protein and diversion of amino acids to glucose production increase the need for insulin and over time result in weight gain; visceral fat deposition; myopathy and muscle wasting; thinning of the skin, with striae and bruising; hyperglycemia; and eventually osteoporosis, diabetes, and aseptic necrosis of the hip
4. Impaired wound healing
5. peptic ulcers
6. The clinical findings associated with certain disorders, particularly bacterial and mycotic infections, may be masked by the corticosteroids
7. Hypomania or acute psychosis may occur, particularly in patients receiving very large doses of corticosteroids
8. Increased intraocular pressure is common, and glaucoma may be induced

Adrenal Suppression

When corticosteroids are administered for more than 2 weeks, adrenal suppression may occur. If treatment extends over weeks to months, the patient should be given appropriate supplementary therapy at times of minor stress (twofold dosage increases for 24–48 hours) or severe stress (up to tenfold dosage increases for 48–72 hours) such as accidental trauma or major surgery. If corticosteroid dosage is to be reduced, it should be tapered slowly. If therapy is to be stopped, the reduction process should be quite slow when the dose reaches replacement levels. It may
take 2-12 months for the hypothalamic-pituitary-adrenal axis to function acceptably, and cortisol levels may not return to normal for another 6-9 months.

**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.

**Contraindications**

Glucocorticoids must be used with great caution in patients with peptic ulcer, heart disease or hypertension with heart failure, certain infectious illnesses such as varicella and tuberculosis, psychoses, diabetes, osteoporosis, or glaucoma.

**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.*