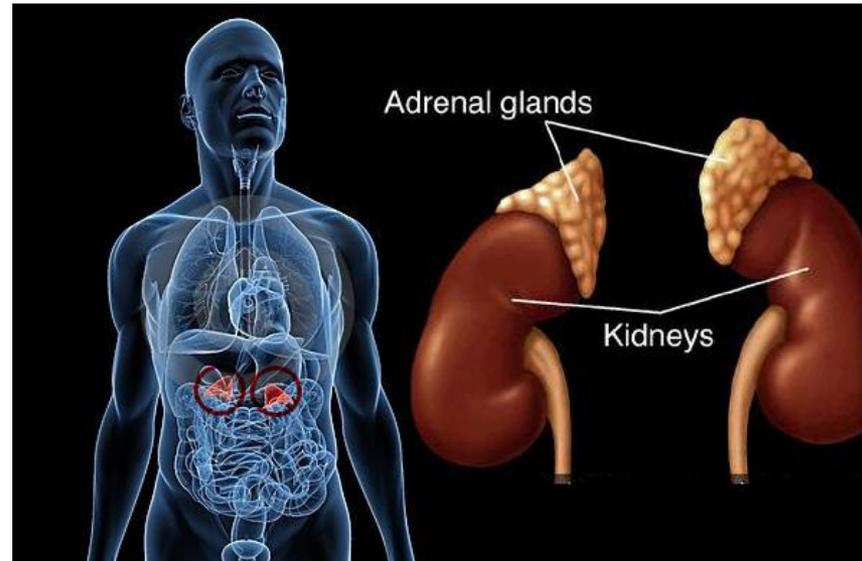




Adrenal Pharmacology



Pharmacology Team

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Steroidal hormones

- A **steroid hormone** (abbreviated as **sterone**) is a steroid that acts as a hormone
- Steroid hormones can be grouped into five groups by the receptors to which they bind:
 - Estrogens
 - Progestogens
 - Androgens
 - **Glucocorticoids**
 - **Mineralocorticoids**

Steroidogenesis

Steroidogenesis

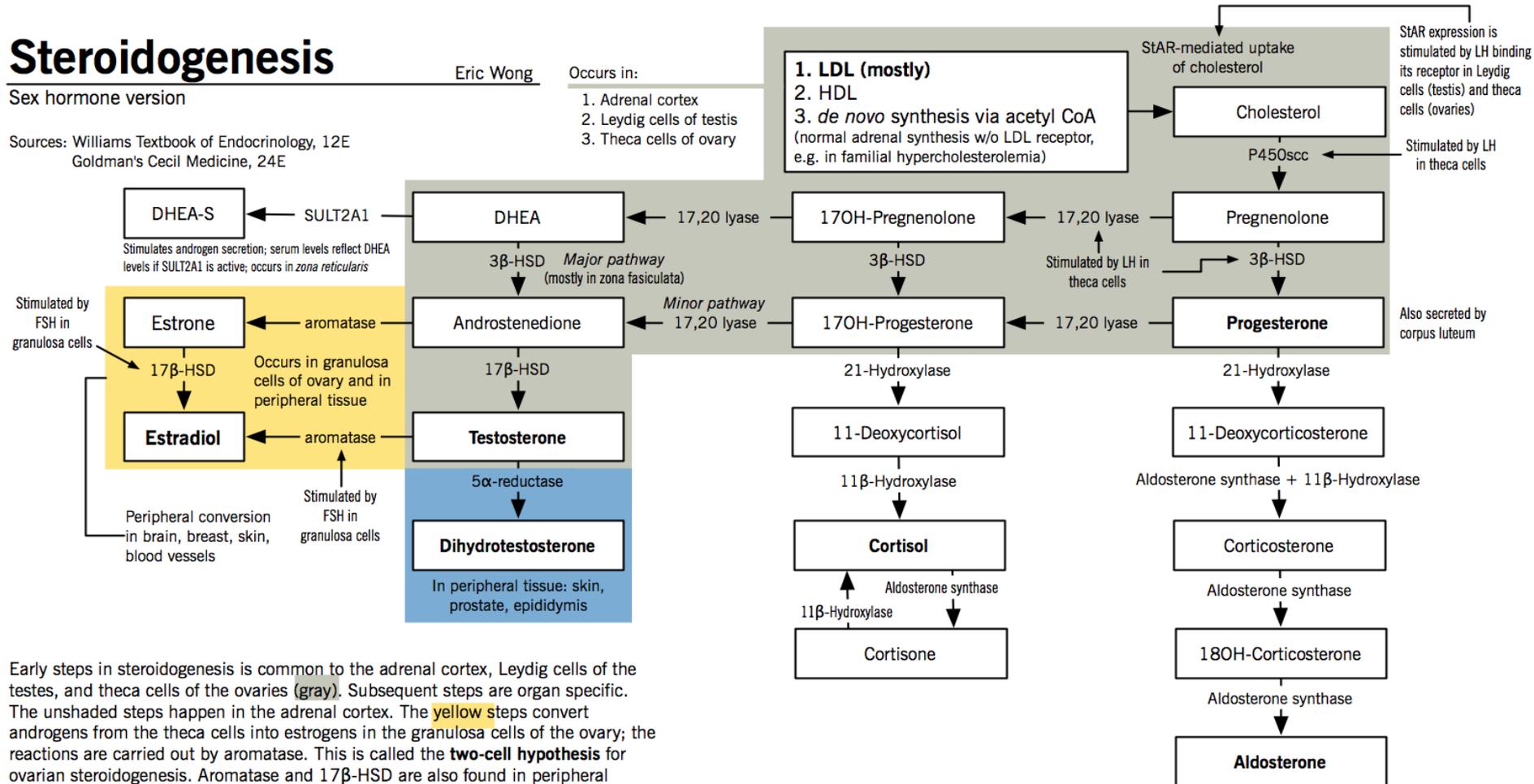
Sex hormone version

Sources: Williams Textbook of Endocrinology, 12E
Goldman's Cecil Medicine, 24E

Eric Wong

Occurs in:

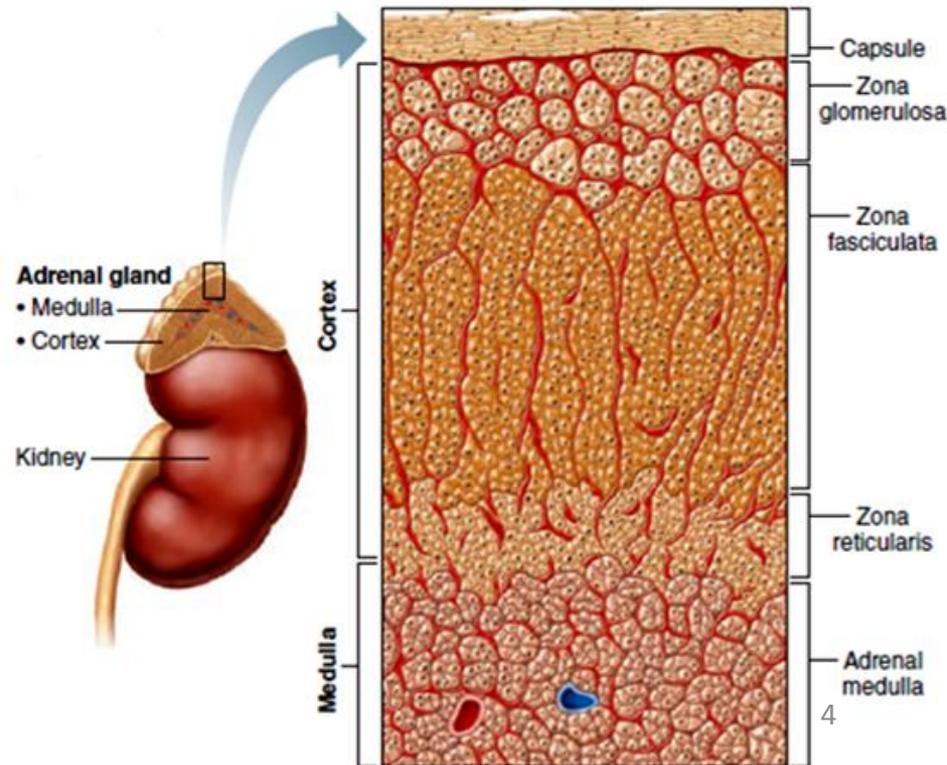
1. Adrenal cortex
2. Leydig cells of testis
3. Theca cells of ovary



Early steps in steroidogenesis is common to the adrenal cortex, Leydig cells of the testes, and theca cells of the ovaries (gray). Subsequent steps are organ specific. The unshaded steps happen in the adrenal cortex. The yellow steps convert androgens from the theca cells into estrogens in the granulosa cells of the ovary; the reactions are carried out by aromatase. This is called the **two-cell hypothesis** for ovarian steroidogenesis. Aromatase and 17β-HSD are also found in peripheral tissues. Finally, the blue step happens in peripheral tissues such as skin, prostate, and epididymis, where testosterone is converted into the more potent DHT.

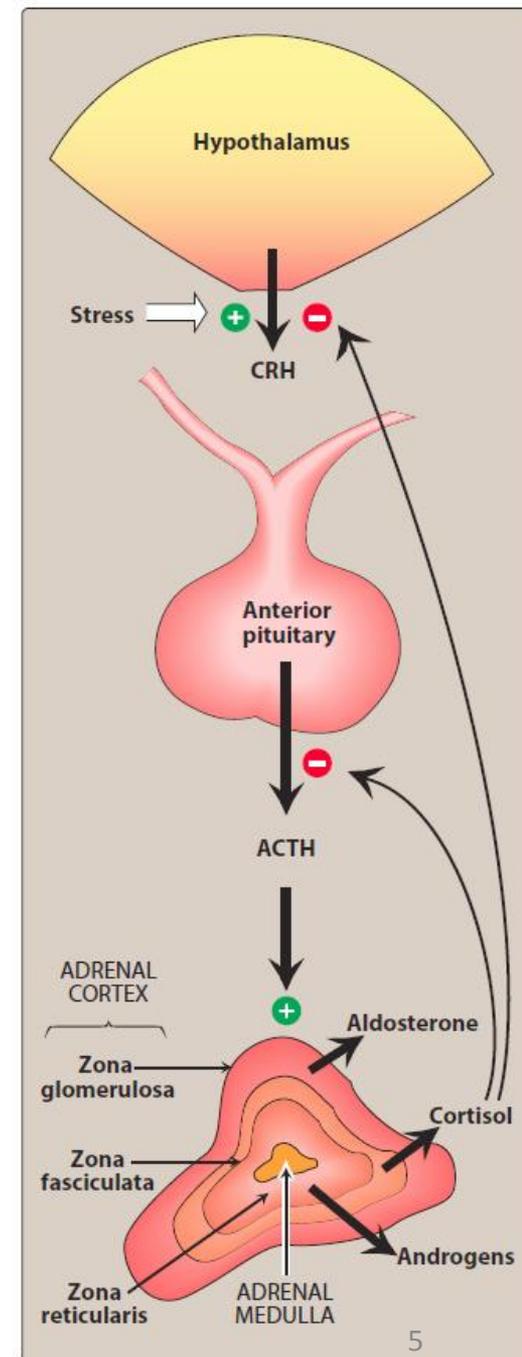
Hypothalamic-pituitary-adrenal axis (HPA)

- The adrenal gland consists of the cortex and the medulla.
- The medulla secretes catecholamines, whereas the cortex secretes glucocorticoids, mineralocorticoids and adrenal androgens.
- The adrenal cortex has three zones
- Each zone synthesizes a different type of steroid hormone from cholesterol.



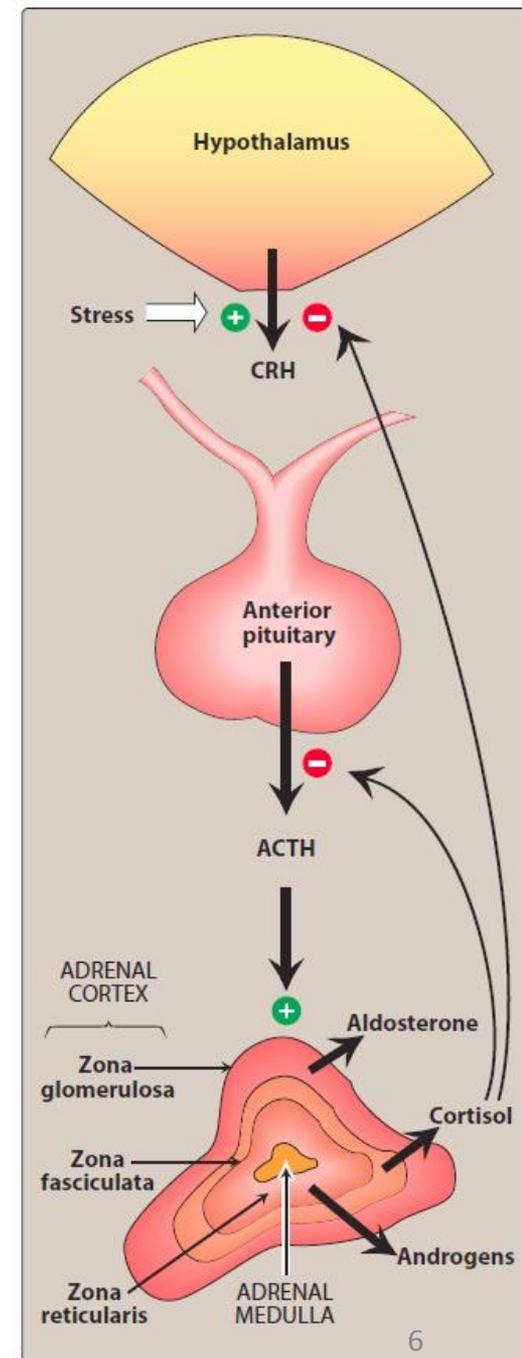
Hypothalamic-pituitary-adrenal axis (HPA)

- **The outer zona glomerulosa:**
 - Produces mineralocorticoids (aldosterone)
 - Regulates salt and water metabolism.
 - Production of aldosterone is regulated primarily by the renin–angiotensin system.
- **The middle zona fasciculata:**
 - Synthesizes glucocorticoids (cortisol)
 - Involved with metabolism and response to stress.



Hypothalamic-pituitary-adrenal axis (HPA)

- **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 ACTH.
- ACTH is released in response to hypothalamic CRH.
- Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion

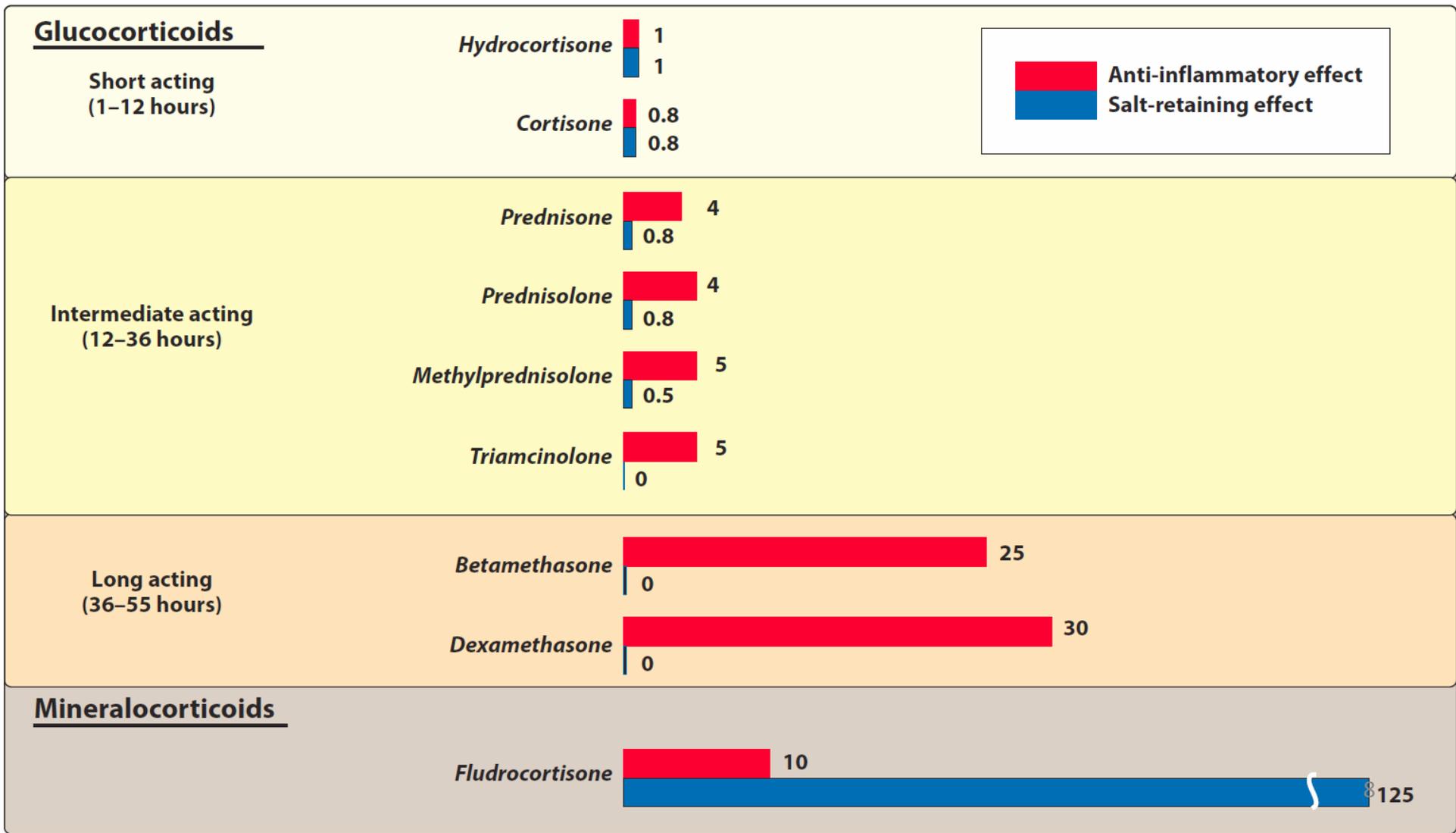


Corticosteroids

- The effects of mineralocorticoids and glucocorticoids are mediated by two separate and specific intracellular receptors, the MR (mineralocorticoid receptor) and GR (glucocorticoid receptor)
- Glucocorticoids can be administered: IM, SC, topical (skin, ophthalmic, otic, rectal..etc), inhalation
- **Agents with the longest half-life tend to be the most potent:**
 - Short-acting agents such as cortisol are active for 1–12 hours
 - Intermediate-acting agents such as prednisolone are active for 12–36 hours
 - Long-acting agents such as dexamethasone are active for 36–55 hours

- **Synthetic adrenocortical steroids:**

- A wide array of steroid compounds with various ratios of mineralocorticoid to glucocorticoid properties has been synthesized



Oral corticosteroids

Agent	Equivalent Dose (mg)	Metabolic Potency	Anti-Inflammatory Potency	Sodium-retaining Potency
Oral Glucocorticoids				
Cortisol	20	20	1	1
Cortisone	25	20	1	1
Prednisone	5	5	4	0.5
Prednisolone	5	5	4	0.5
Dexamethasone	0.75	1	30	0.05
Betamethasone	0.6	1.0–1.5	25–40	0.05
Triamcinolone	4	4	5	0.1
Aldosterone		0.3		3,000
Fludrocortisone	0.01	0.1		125–250

Topical corticosteroids

Topical Glucocorticoids

Betamethasone	Highest potency
Clobetasol	Highest potency
Halobetasol	Highest potency
Amcinonide	High potency
Fluocinonide	High potency
Triamcinolone	High potency
Beclomethasone	Medium potency
Fluticasone	Medium potency
Hydrocortisone	Medium potency
Dexamethasone	Low potency
Desonide	Low potency

Corticosteroids

- **Drug administration attempts to pattern the circadian rhythm:** A double dose is given in the morning, and a single dose is given in the afternoon
- **Alternate-day therapy** relieves clinical manifestations of the disease state while causing less severe suppression of the adrenal-hypothalamic-pituitary axis.
- In this therapy, large doses of short-acting or intermediate-acting glucocorticoids are administered every other day
- Patients removed from long-term glucocorticoid therapy must be weaned off the drug over several days, using progressively lower doses to allow recovery of adrenal responsiveness

Physiologic effects of Glucocorticoids

- Increased protein breakdown, leading to a negative nitrogen balance
- Increase blood glucose levels by stimulation of gluconeogenesis
- Increase the synthesis of several key enzymes involved in glucose and amino acid metabolism
- Increase plasma fatty acids and ketone body formation via increased lipolysis and decreased glucose uptake into fat cells and redistribution of body fat

Physiologic effects of Glucocorticoids

- Increase kaliuresis
- Decrease intestinal absorption of calcium and inhibit osteoblasts
- Promote Na⁺ and water retention

Physiologic effects of Glucocorticoids

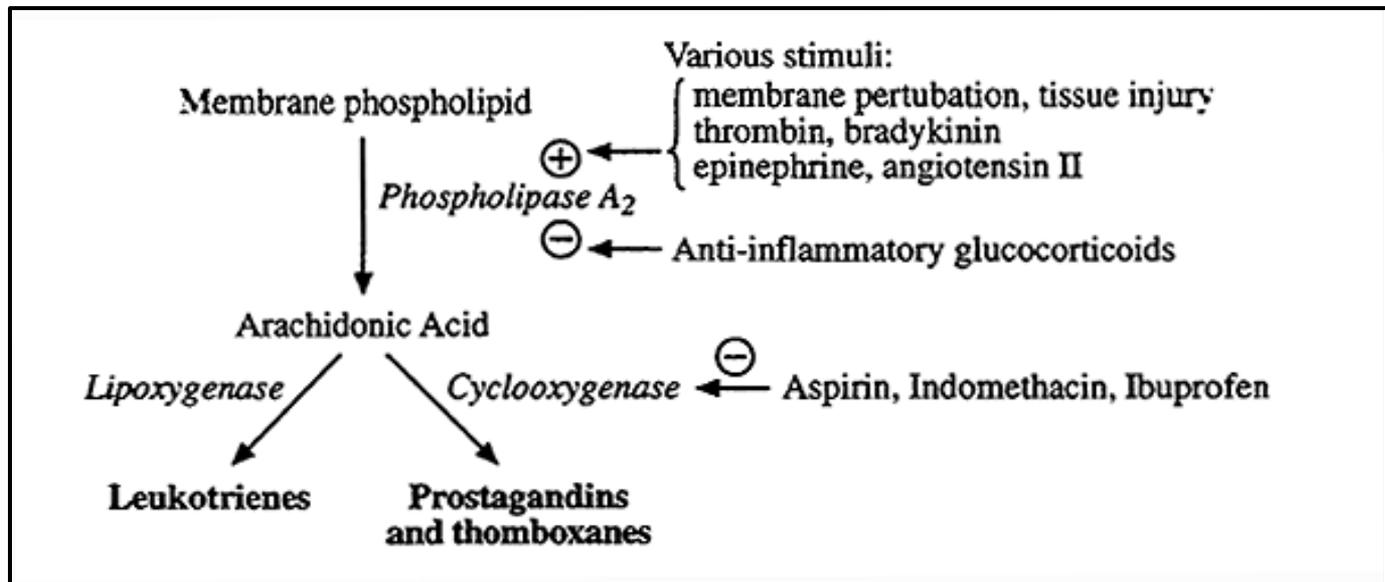
- **Anti-inflammatory effects:**

- Inhibits all of the classic signs of inflammation (erythema, swelling, pain, and heat). **Specific effects include:**

- Inhibition of the antigenic response of macrophages and leukocytes
 - Inhibition of vascular permeability by reduction of histamine release
 - Glucocorticoids decrease circulating WBC
 - Long-term therapy results in the inhibition of plasma ACTH and involution and atrophy of all lymphoid tissues

Physiologic effects of Glucocorticoids

- **Anti-inflammatory effects:**
 - Inhibition of cytokine production, including IL-1, IL-2, IL-3, IL-6, tumor necrosis factor- α , and granulocyte-macrophage colony-stimulating factor
 - Inhibition of arachidonic acid and prostaglandin production by inhibition of phospholipase A₂ and the cyclooxygenases



Physiologic effects of Glucocorticoids

- **Other effects**
 - Inhibition of fibroblast growth and collagen synthesis
 - Stimulation of acid and pepsin secretion in the stomach
 - Altered CNS responses, influencing mood and sleep patterns
 - Induction of surfactant production in the fetal lung at term

Therapeutic effects of Glucocorticoids

- **Replacement therapy:**
 - Glucocorticoids are used in for primary or secondary insufficiency (**Addison disease**); this therapy usually requires the use of **both** a mineralocorticoid and a glucocorticoid
- **Inflammation and immunosuppression**
 - Autoimmune diseases: nephrotic syndrome, membranous nephropathy, ulcerative colitis, rheumatoid arthritis, acute rheumatic fever, myasthenia gravis, bursitis, lupus erythematosus, asthma
 - Hypersensitivity and allergic reactions
 - Organ or graft rejection

Therapeutic effects of Glucocorticoids

- Dermatologic disorders: Eczema, Psoriasis..etc
- Idiopathic nephrosis of children
- Neuromuscular disorders, such as Bell's palsy
- Shock
- Adrenocortical hyperplasia
- Stimulation of surfactant production and acceleration of lung maturation in a preterm fetus
- Neoplastic diseases, including adult and childhood leukemias

Therapeutic effects of Glucocorticoids

- **Diagnosis of Cushing syndrome: (dexamethasone suppression test)**
 - This test measures the suppression of plasma cortisol following the administration of dexamethasone which normally binds to GR in the pituitary and inhibits ACTH production.
 - Failure to suppress cortisol may indicate primary Cushing syndrome or ectopic ACTH production

Some definitions

- **Addison disease:** chronic adrenal insufficiency
 - A rare, chronic endocrine system disorder in which the adrenal glands do not produce sufficient steroid hormones (glucocorticoids and often mineralocorticoids)
 - Characterized by a number of relatively nonspecific symptoms, such as abdominal pain and weakness
 - Under certain circumstances, these may progress to Addisonian crisis, a severe illness which may include very low blood pressure and coma

Some definitions

- **Rheumatoid arthritis**
 - Rheumatoid arthritis (RA) is an autoimmune disease that results in a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible (synovial) joints
- **Bursitis**
 - The inflammation of one or more bursae (small sacs) of synovial fluid in the body

Some definitions

- **lupus erythematosus**
 - Lupus erythematosus is a name given to a collection of autoimmune diseases in which the human immune system becomes hyperactive and attacks normal, healthy tissues
 - Symptoms of these diseases can affect many different body systems, including joints, skin, kidneys, blood cells, heart, and lungs



Some definitions

- **Nephrotic syndrome:**
 - Nephrotic syndrome is a nonspecific kidney disorder characterized by a number of signs: proteinuria, hypoalbuminemia and edema
- **Ulcerative colitis:**
 - A form of inflammatory bowel disease (IBD)

Adverse effects of glucocorticoids

- Most are exaggerated physiologic effects leading to a state of iatrogenic Cushing disease.
- Certain glucocorticoids have mineralocorticoid activity, potentially causing
 - Sodium retention
 - Potassium loss (hypokalemia)

Adverse effects of glucocorticoids

- Adrenal suppression
- Hyperglycemia and steroid-induced diabetes mellitus
- Weight gain
- Osteoporosis
- Peptic ulcer

Adverse effects of glucocorticoids

- Cataracts and increased intraocular pressure leading to glaucoma
- Edema
- Hypertension
- Increased susceptibility to infection and poor wound healing
- Muscle weakness and tissue loss

Adverse effects of glucocorticoids



Mineralocorticoids

- **Actions**
 - Primarily affect the kidney, regulating salt and water balance and increasing sodium retention and potassium loss.
 - **Fludrocortisone** is the agent of choice for long-term mineralocorticoid replacement
- **Adverse effects**
 - Include sodium retention and hypokalemia, edema, and hypertension
- **Therapeutic uses.**
 - Mineralocorticoids are used in replacement therapy to maintain electrolyte and fluid balance in hypoadrenalism

Drugs used for Obesity

Drugs used for Obesity

- The term obesity is given to individuals with a body mass index (BMI) of 30 kg/m² or greater.
- An individual whose BMI is greater than 30 or greater than 27 with at least two comorbidities (e.g. hypertension and diabetes) is considered a potential candidate for pharmacological treatment of obesity
- Drugs for obesity are considered effective if they demonstrate at least a 5% greater reduction in body weight as compared to placebo

Lipase inhibitor (Orlistat)

- **Mechanism of action:** Orlistat inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat
- Adverse gastrointestinal effects associated with the drug may also contribute to an overall decreased intake of food
- Administration of orlistat decreases fat absorption by about 30%.

Pharmacokinetics of Orlistat

- Orlistat is administered orally with each meal that contains fat.
- It has minimal systemic absorption and is mainly excreted in the feces.

Adverse effects of Orlistat

- GIT symptoms (most common): oily spotting, flatulence, fecal urgency, and increased defecation.
- These effects may be minimized through a low-fat diet and the use of concomitant cholestyramine.
- Orlistat is contraindicated in pregnancy and in patients with chronic malabsorption syndrome or cholestasis.

Adverse effects of Orlistat

- Orlistat interferes with the absorption of fat-soluble vitamins and β -carotene.
- Patients should be advised to take supplements of vitamins A, D, E, and K and also β -carotene.
- The vitamin supplement should not be taken within 2 hours of orlistat
- Orlistat can also interfere with the absorption of other medications