Adrenocorticosteroids & Adrenocortical Antagonists

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Week 13 / Lecture 16

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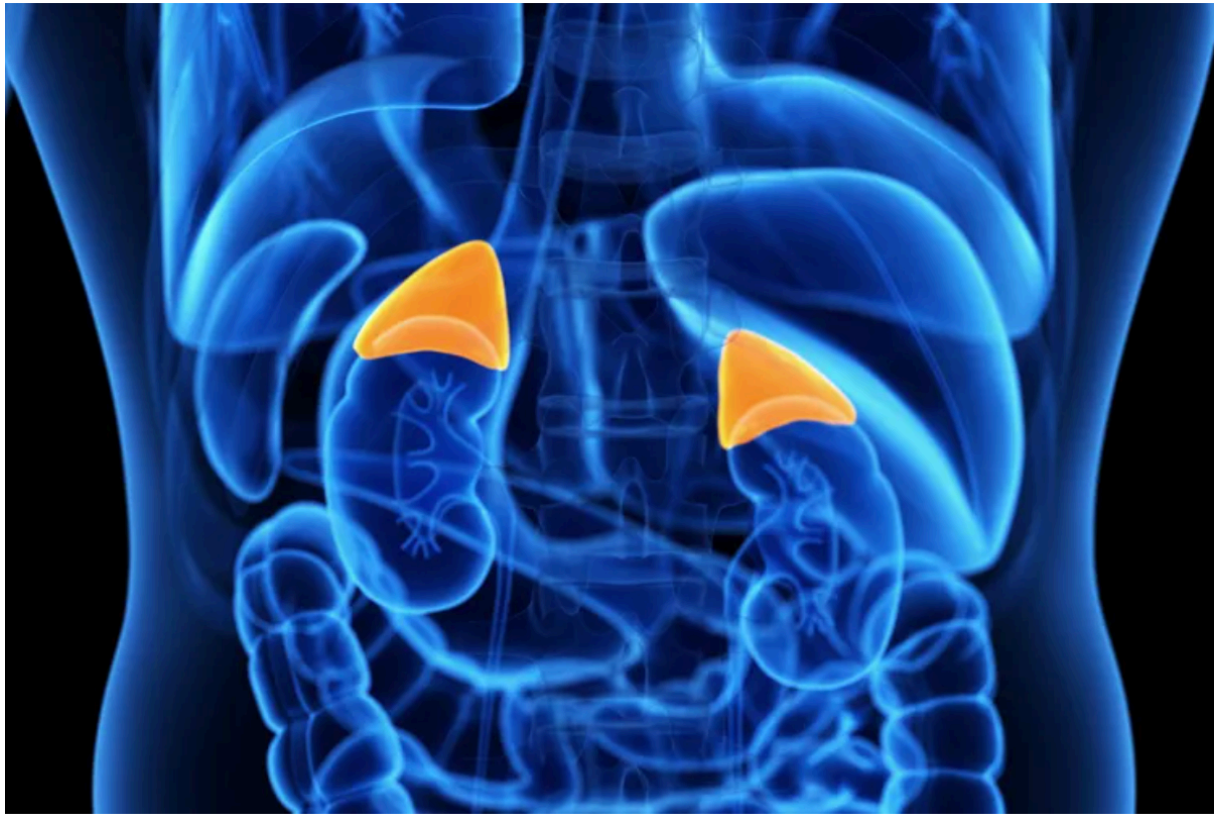
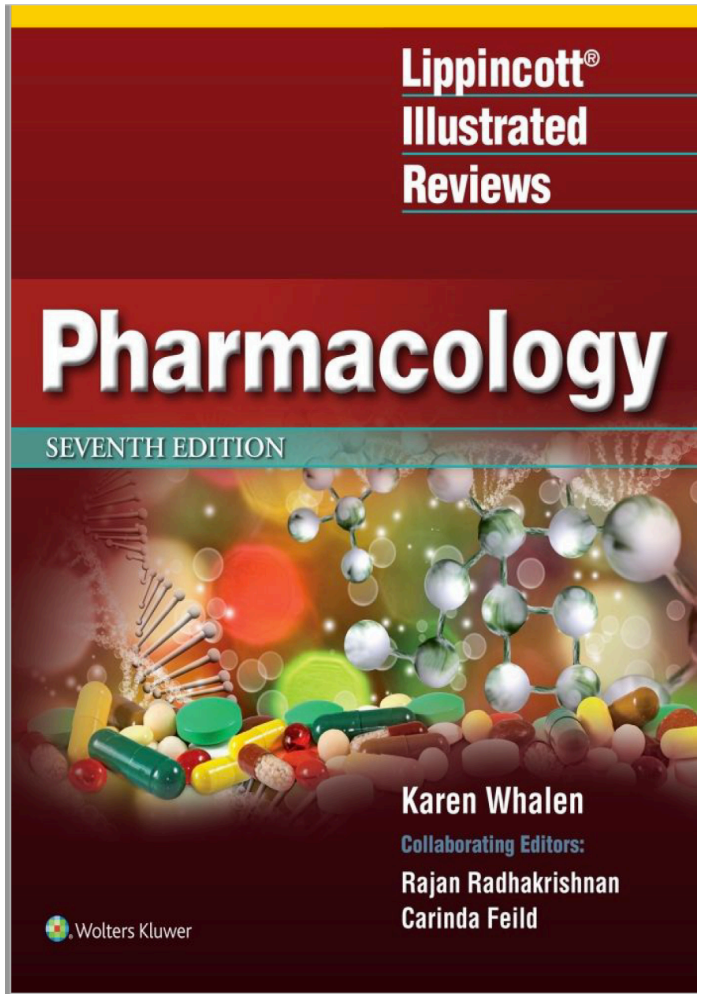
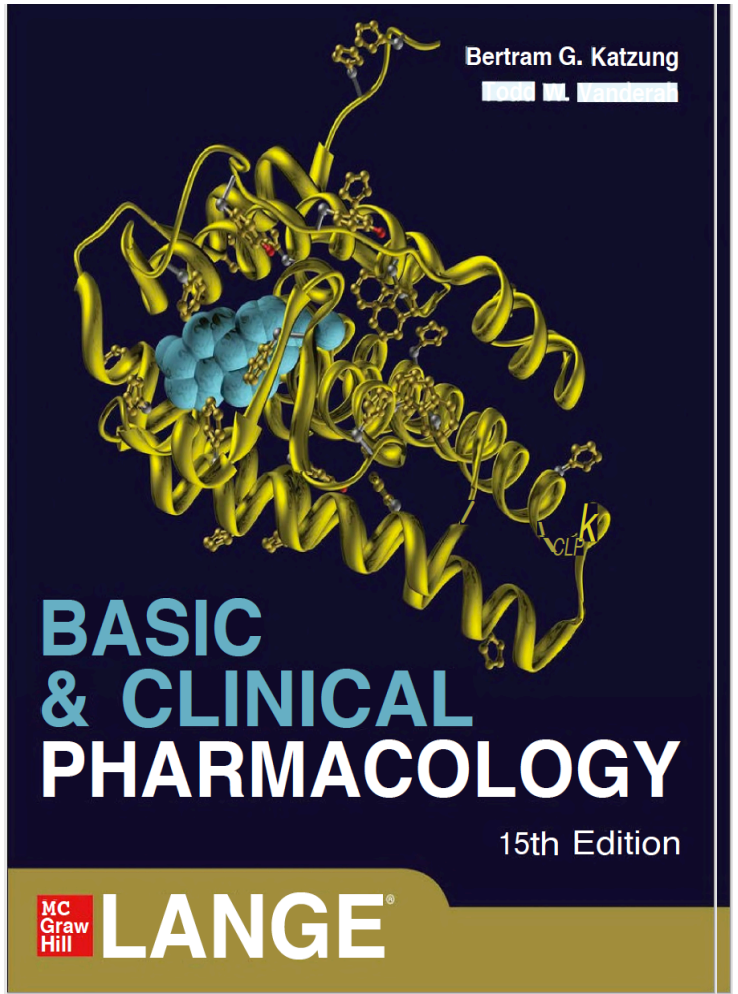
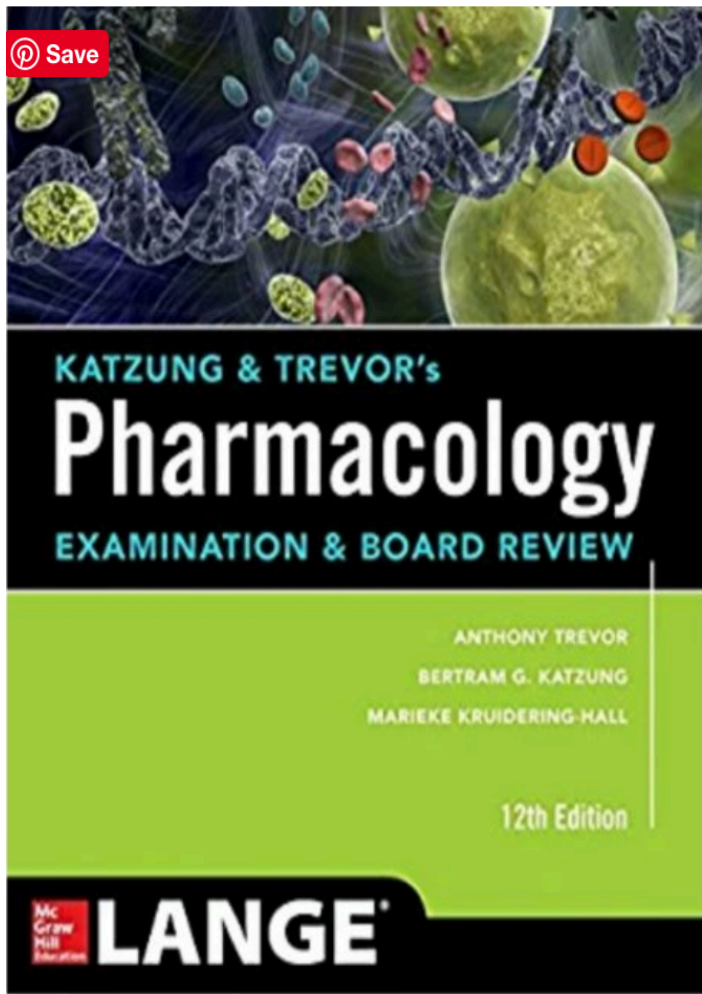


Recommended Text Books





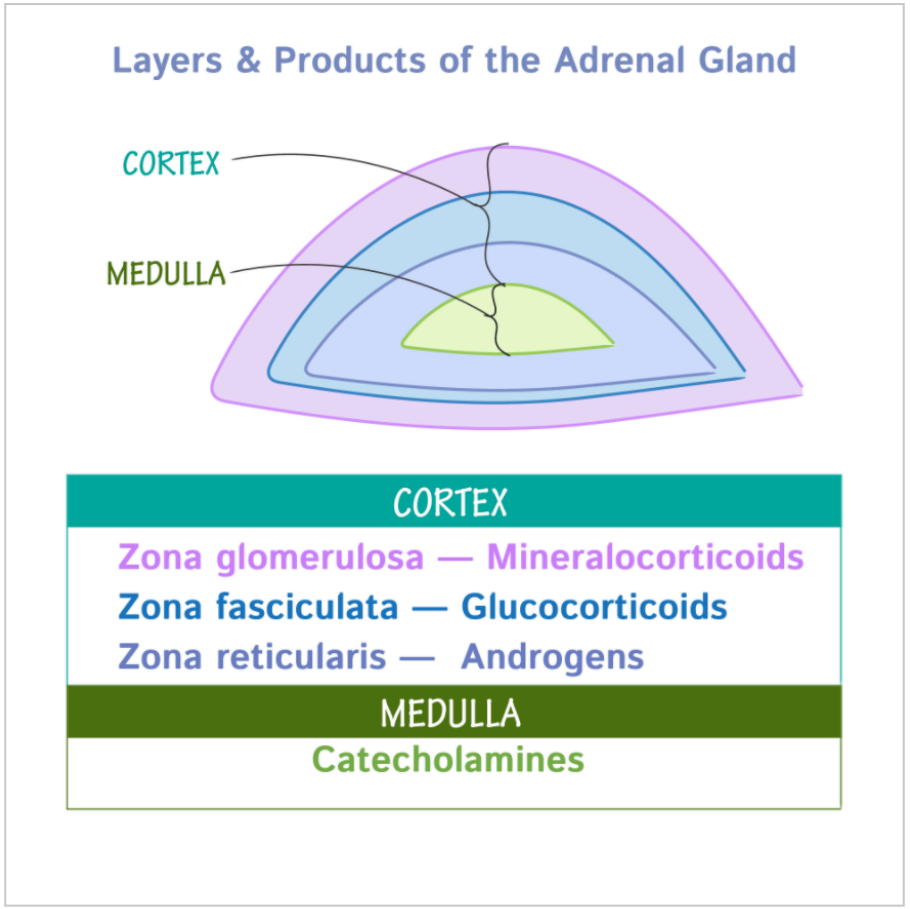


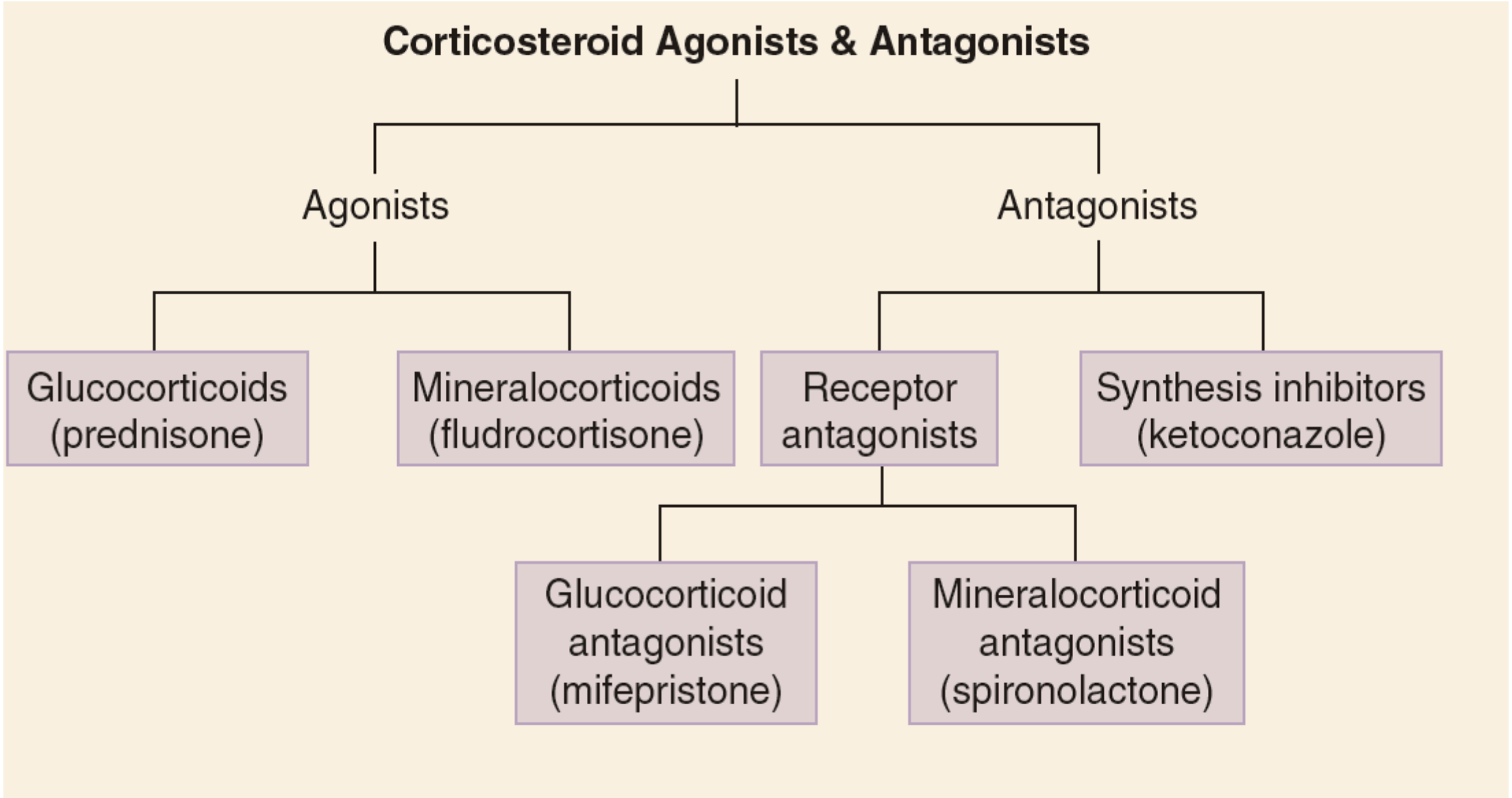
Subject Outline

- Introduction
- The Naturally Occurring Glucocorticoids
- Pharmacodynamics
- Organ and Tissue Effects
- Important Glucocorticoids
- Clinical Uses
- Toxicity
- Mineralocorticoids
- Corticosteroid Antagonists

The adrenal cortex releases a large number of steroids into the circulation:

1. The major glucocorticoid is cortisol
2. The most mineralocorticoid is aldosterone
3. Dehydroepi-androsterone (DHEA) in its sulfated form DHEAS is the major adrenal androgen.




Corticosteroid Agonists & Antagonists
Agonists
Antagonists
Glucocorticoids (prednisone)
Mineralocorticoids (fludrocortisone)
Receptor antagonists
Synthesis inhibitors (ketoconazole)
Glucocorticoid antagonists (mifepristone)
Mineralocorticoid antagonists (spironolactone)

The Naturally Occurring Glucocorticoids

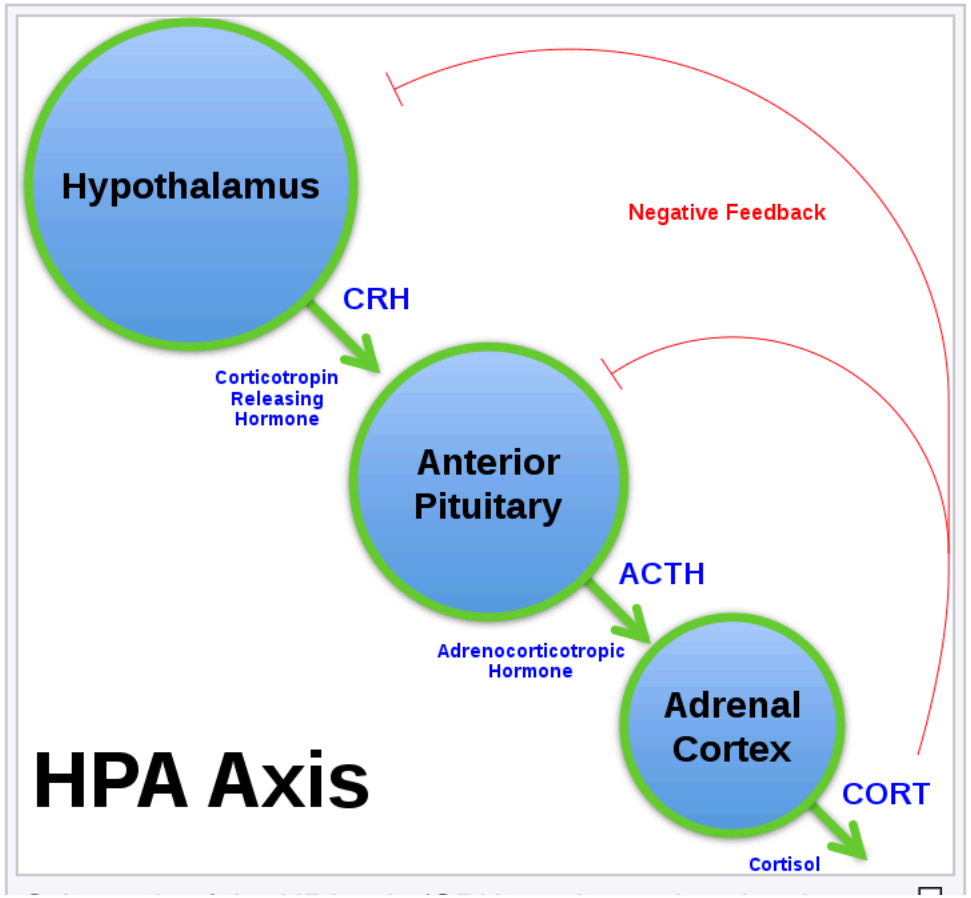
Cortisol also called hydrocortisone

exerts a wide range of physiologic effects, including:

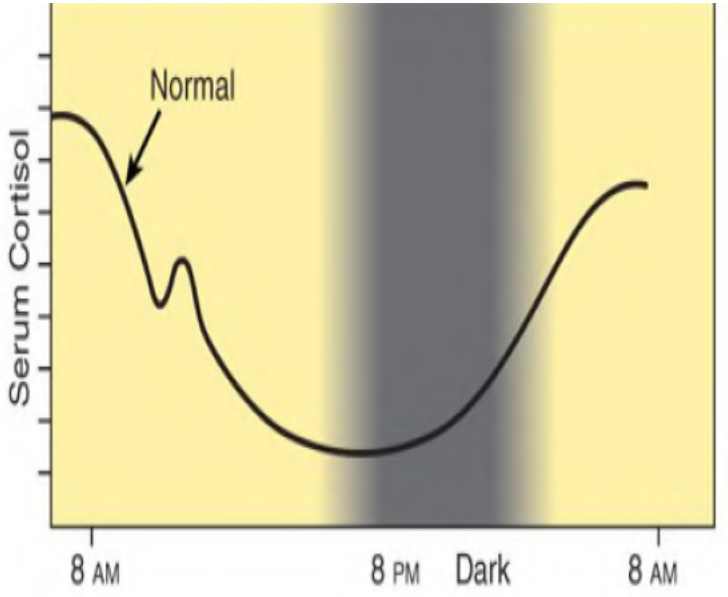
- **Regulation of intermediary metabolism,**
- **Cardiovascular function,**
- **Growth, and immunity.**

Cortisol is synthesized from cholesterol

Its synthesis and secretion are tightly regulated by the CNS,
which is very sensitive to negative feedback by the circulating cortisol and exogenous (synthetic) glucocorticoids.



The rate of secretion follows a circadian rhythm governed by pulses of ACTH that peak in the early morning hours and after meals.



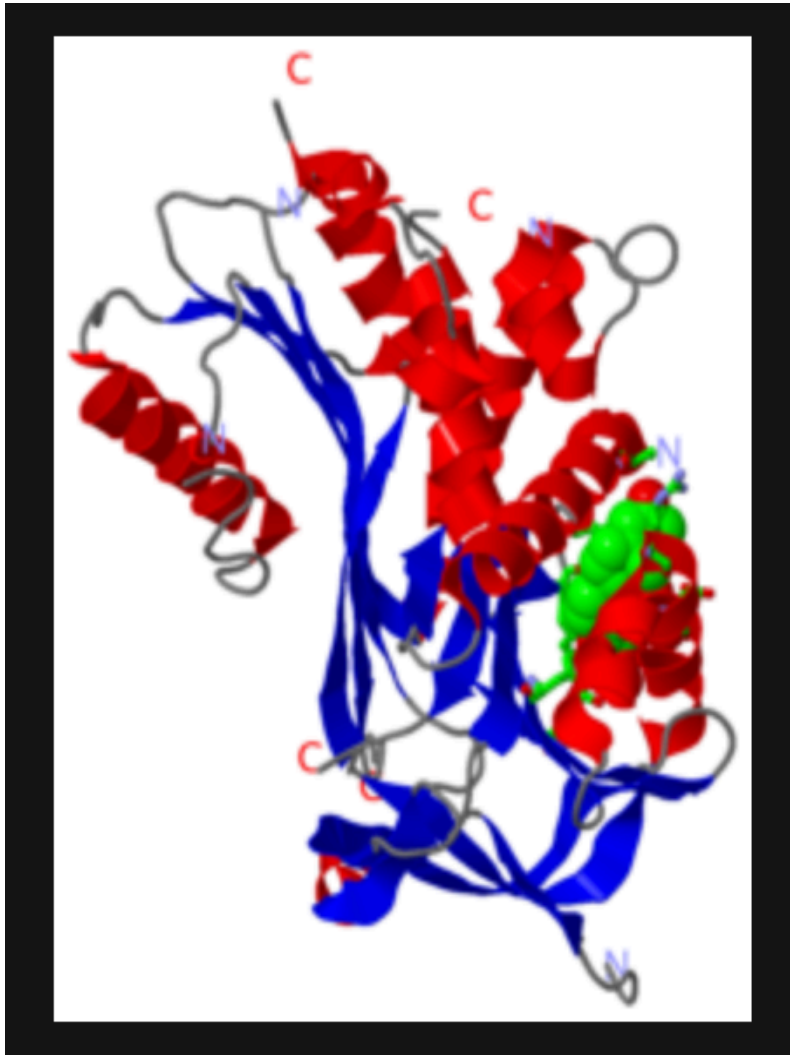
Circadian variation in plasma cortisol throughout the 24-hour day

In plasma,

- Cortisol is bound to circulating proteins.

- Corticosteroid-binding globulin (CBG) , an α2 globulin synthesized by the liver, binds about 90% of the circulating hormone under normal circumstances.

- The remainder is free (about 5–10%) or loosely bound to albumin (about 5%) and is available to exert its effect on target cells.



Corticosteroid-binding globulin

When plasma cortisol levels exceed 20–30 mcg/dL, CBG is saturated, and the concentration of free cortisol rises rapidly.

CBG is increased in:

- **Pregnancy**
- **Estrogen administration**
- **Hyperthyroidism**

CBG is decreased in:

- **Hypothyroidism,**
- **Genetic defects in synthesis**
- **Protein deficiency states**

- **Synthetic corticosteroids such as dexamethasone are largely bound to albumin rather than CBG.**

- **The half-life of cortisol in the circulation is normally about 60–90 minutes, it may be increased when hydrocortisone is administered in large amounts or when stress, hypothyroidism, or liver disease is present.**

Pharmacodynamics

Mechanism of Action

- Their effects are mediated by intracellular glucocorticoid receptors.
- Which are members of Nuclear receptors that 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).**

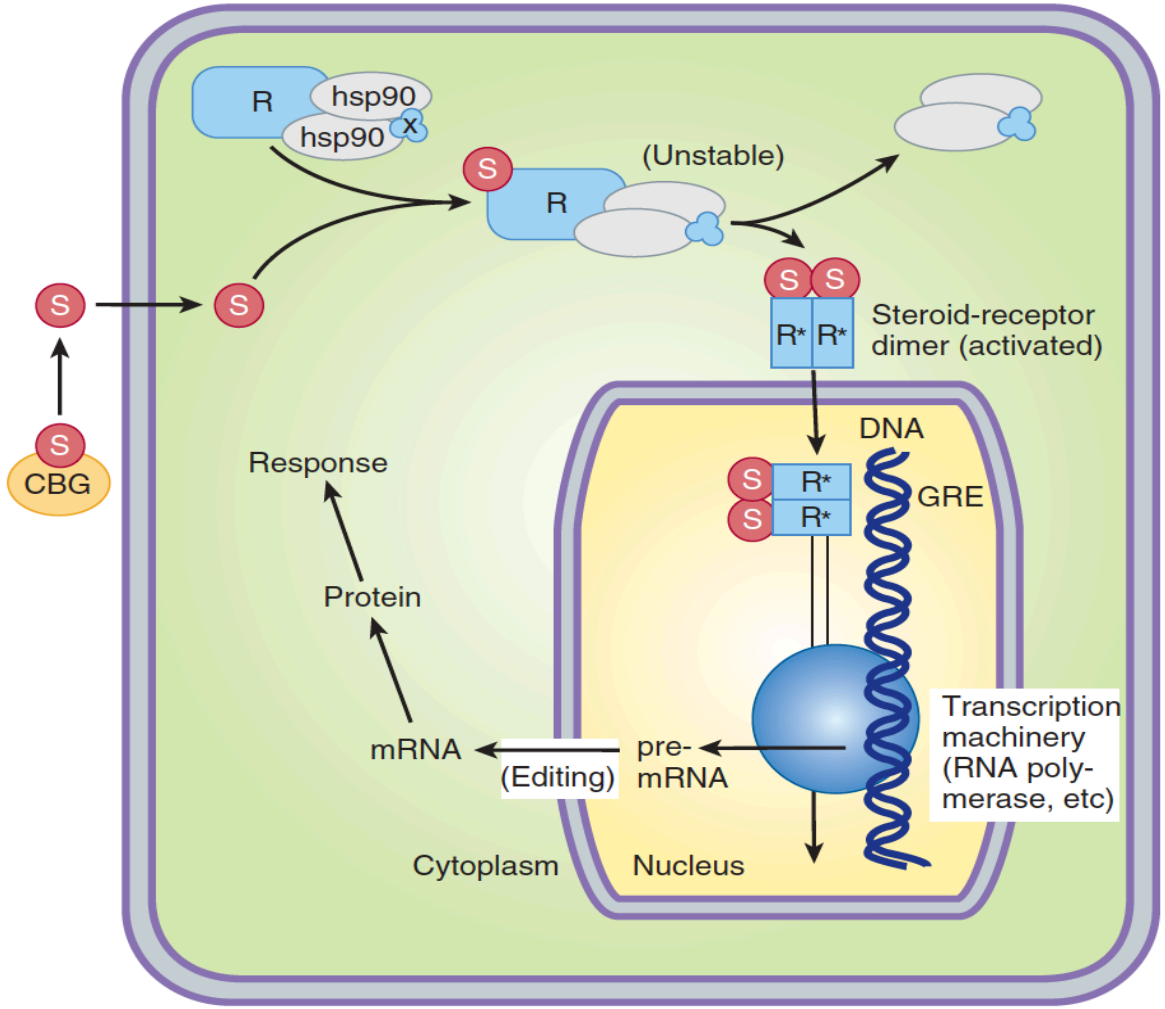
➢ **The most important of these are two molecules of hsp90**

- **Free hormone 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.**



A model of the interaction of a steroid (S)and its receptor (R), and the subsequent events in a target cell. The steroid is present in the blood in bound form on the CBG but enters the cell as the free molecule

- **In addition to binding to GREs, the ligand-bound receptor also forms complexes with and influences the function of other transcription factors.**
- **These transcription factors have broad actions on the regulation of growth factors, proinflammatory cytokines and etc.**

- **Two genes for the corticoid receptor have been identified:**
- **One encoding the classic glucocorticoid receptor GR and the other encoding the mineralocorticoid receptor MR.**

Organ and Tissue Effects

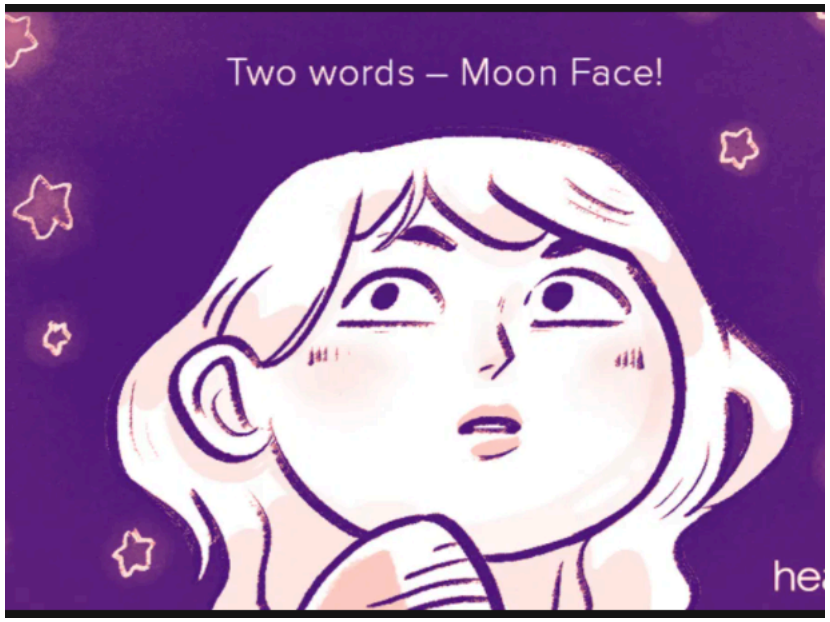
1. Metabolic Effects

Glucocorticoids stimulate gluconeogenesis.

blood glucose rises,

muscle protein is catabolized, and

insulin secretion is stimulated.



Both lipolysis and lipogenesis are stimulated, with a net increase of fat deposition in certain areas (face ,shoulders and back).

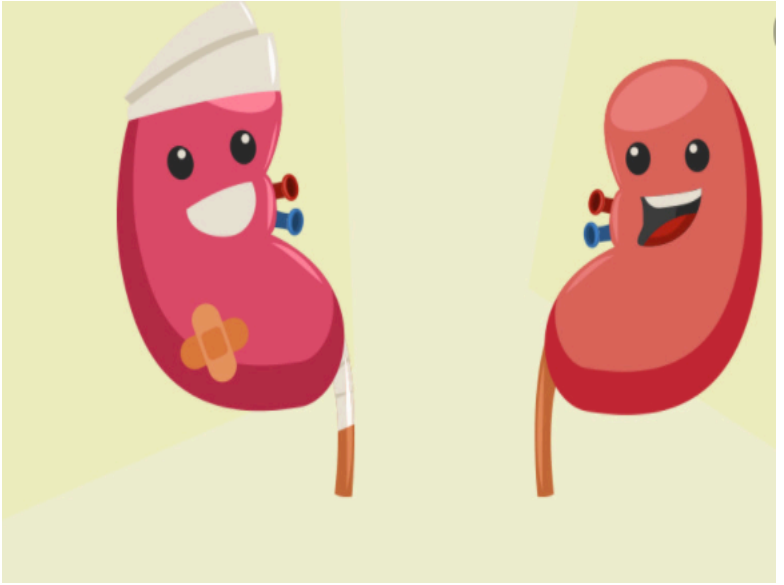
2. Catabolic and Antianabolic Effects

- they have catabolic and antianabolic effects in lymphoid and connective tissue, muscle, peripheral fat & skin.
- Supra-physiologic amounts of glucocorticoids lead to decreased muscle mass, weakness and thinning of the skin.

- Catabolic and anti-anabolic effects on bone are the cause of osteoporosis in Cushing's syndrome and impose a major limitation in the long-term therapeutic use of glucocorticoids.
- In children, glucocorticoids reduce growth.

3. Immunosuppressive Effects

- Glucocorticoids inhibit cell-mediated immunologic functions, especially those dependent on lymphocytes.
- They are actively lympho-toxic, are important in the treatment of hematologic cancers.
- The drugs do not interfere with the development of normal acquired immunity but delay rejection reactions in patients with organ transplants.



4. Anti-inflammatory Effects

- These drugs increase neutrophils and decrease lymphocytes, eosinophils, basophils, and monocytes.
- The migration of leukocytes is also inhibited.

5. Other Effects

- Large doses of glucocorticoids have been associated with the development of peptic ulcer
- They promote fat redistribution in the body, with increase of visceral, facial and supraclavicular fat
- They appear to antagonize the effect of vitamin D on calcium absorption.

Important Glucocorticoids

1. Natural Glucocorticoid / Cortisol

- The physiological secretion of cortisol is regulated by ACTH and varies during the day (circadian rhythm);
- the peak occurs in the morning & the trough occurs about midnight.
- In the plasma, cortisol is 95% bound to CBG.

Glucocorticoids Duration of Action

1. Short to medium acting glucocorticoids

Hydrocrotisone , cortisone , prednisone, prednisolone

2. Intermediate acting glucocorticoids (15-24 hrs)

Triamicinolone

3. Long acting glucocorticoids (24-36hrs)

Betamethasone, Dexamethasone

Mineralocorticoid

Fludrocortisone **8-12hrs**

2. Synthetic Glucocorticoids

- **Prednisone (and its active metabolite prednisolone) dexamethasone, triamcinolone**
- **Their properties (compared with cortisol) include:**

➢ **longer half-life and duration of action,**

➢ **reduced salt-retaining effect,**

➢ **better penetration of lipid barriers for topical activity**

Clinical Uses

1. Adrenal Disorders

- **Chronic adrenal cortical insufficiency (Addison's disease)**
- **Acute adrenal insufficiency**
- **Congenital Adrenal Hyperplasia (defect in the synthesis of cortisol)**
- **Cushing Syndrome (**Associated with the chronic presence of excessive glucocorticoids**)**.

➢This disorder is treated by surgical removal of the tumor producing ACTH or cortisol.

➢These patients must receive large doses of cortisol during and after the surgical procedure

2. Nonadrenal Disorders

- Many disorders respond to corticosteroid therapy.
- Some of these are inflammatory or immunologic in nature (asthma, organ transplant rejection, collagen diseases, rheumatic disorders).

- The treatment of hematopoietic cancers, neurologic disorders, chemotherapy-induced vomiting & hypercalcemia.

- Glucocorticoids have important effects on the development of the fetal lungs.
- The structural and functional changes in the lungs near term, including the production of pulmonary surface-active material required for air breathing (surfactant), are stimulated by glucocorticoids.
- **Betamethasone**, a glucocorticoid with a low degree of protein binding, is given to pregnant women in premature labor to hasten maturation of the fetal lungs.

Toxicity

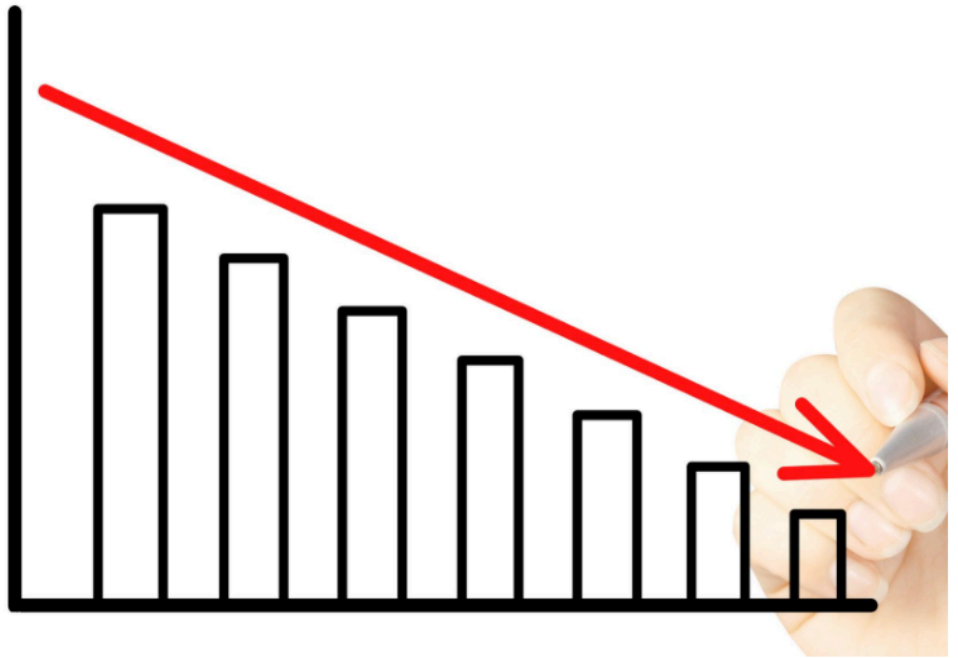
- Short-term (<2 weeks) therapy is well tolerated.
- Longer courses can cause serious toxicity.
- **Some of toxicity are life threatening and include**:

metabolic effects (growth inhibition, diabetes, muscle wasting, osteoporosis), salt retention, reduced wound healing, and psychosis.

Methods for minimizing these toxicities include:

- Local application (aerosols for asthma),
- Alternate-day therapy (to reduce pituitary suppression),
- Tapering the dose soon after achieving a therapeutic response.

Patients who are being withdrawn from glucocorticoids after prolonged use should have their doses tapered slowly, over the course of several months, to allow recovery of normal adrenal function.



Special Precautions

- Patients receiving glucocorticoids must be monitored carefully for the development of hyperglycemia, glycosuria, sodium retention with edema or hypertension, hypokalemia, peptic ulcer, osteoporosis, and hidden infections.

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.

Mineralocorticoids

A. Aldosterone

- The secretion of aldosterone is regulated by ACTH and by the RAS

B. Other Mineralocorticoids

- Fludrocortisone is favored for replacement therapy after adrenalectomy

Corticosteroid Antagonists

A. Receptor Antagonists

- **Spironolactone** and **eplerenone,** Antagonists of aldosterone at its receptor
- **Mifepristone** is a competitive inhibitor of glucocorticoid receptors as well as progesterone receptors and has been used in the treatment of Cushing's syndrome.

B. Synthesis Inhibitors

Ketoconazole

- Inhibits the CYP450 enzymes necessary for the synthesis of all steroids

Aminoglutethimide

- Aromatase Inhibitor
- Blocks the conversion of cholesterol to pregnenolone
- inhibits synthesis of all hormonally active steroids

Metyrapone

- Inhibits the normal synthesis of cortisol but not that of cortisol precursors

Etomidate

- Inhibits 11β-hydroxylase and can be used in Cushing's syndrome