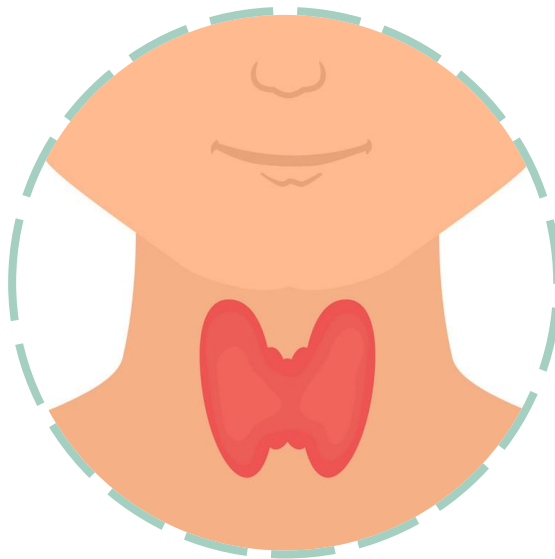


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Endocrine Block

Pharmacology team 438

Pharmacology of Corticosteroids

Objectives:

By the end of the lecture , you should know:

- Revise the synthesis of steroids
- Mechanism of action
- Pharmacokinetics of cortisol, pharmacodynamic actions and therapeutic uses
- Adverse reaction
- Steroids agonists and antagonists and their therapeutic applications.

Color index:

Black : Main content

Red : Important

Blue: Males' slides only

Purple: Females' slides only

Grey: Extra info or explanation

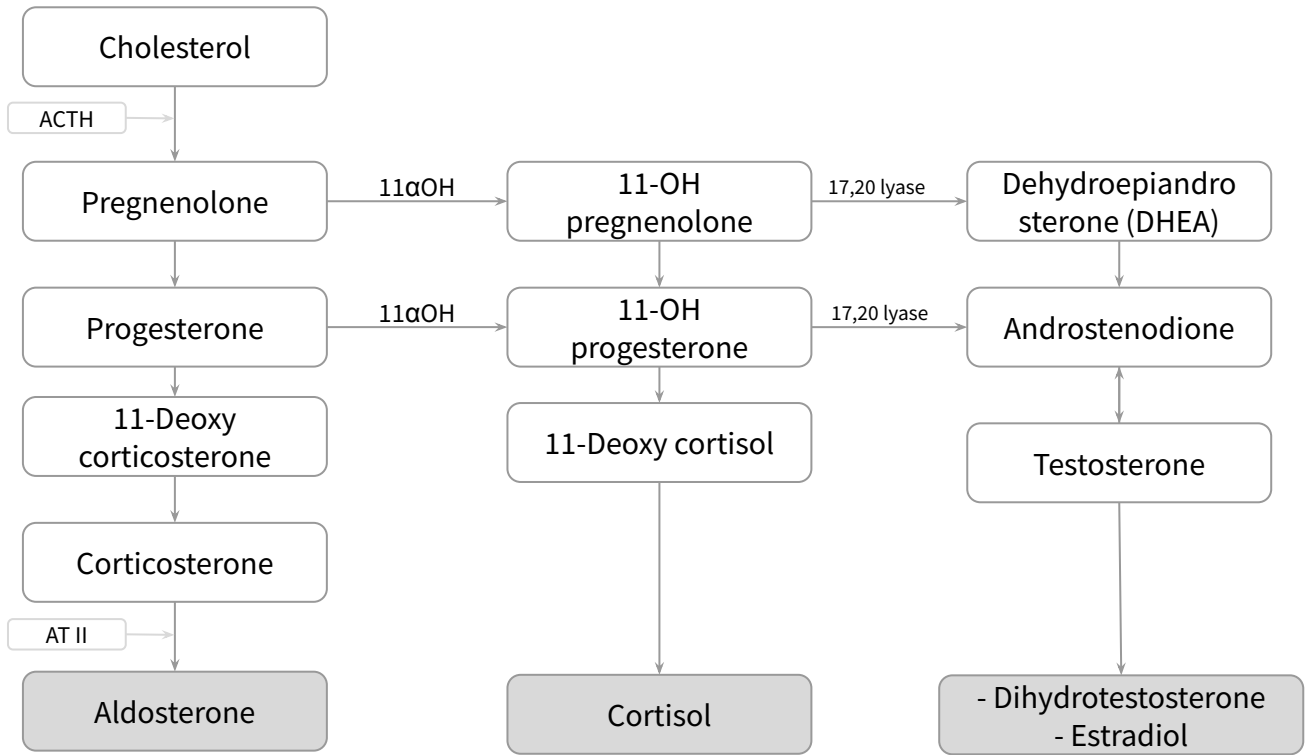
Green : Dr. notes

Biosynthesis of Adrenal Hormone¹

Mineralocorticoids

Glucocorticoids

Sex hormones



Corticosteroids

Corticosteroids are steroid hormones produced by the adrenal cortex. They consist of two groups:

They have important effects on intermediary³ metabolism, catabolism, immune responses, growth & inflammation.

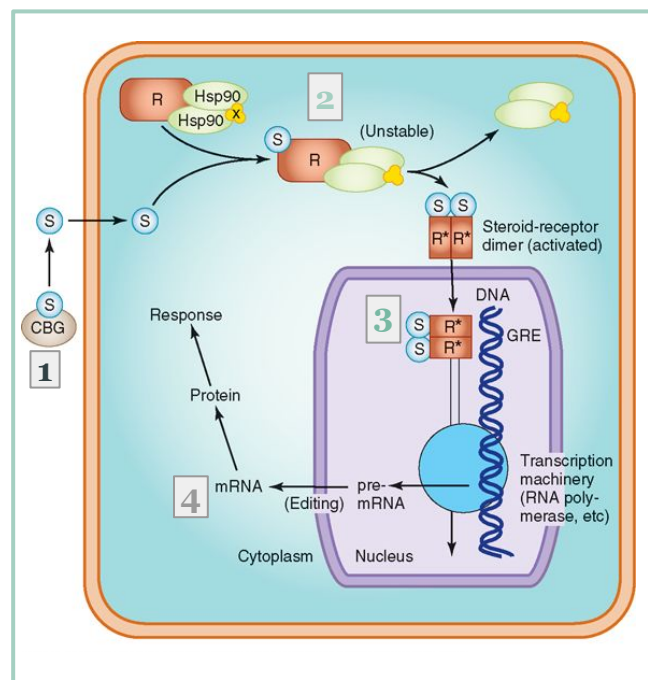
Glucocorticoids:
Cortisol (Hydrocortisone²)

Mineralocorticoids:
Aldosterone

They have **salt-retaining activity** which regulate Na & K reabsorption in the collecting tubules of the kidney

★ Mechanism of action:

- 1 Corticosteroid is present in the blood **bound to the corticosteroid binding globulin (CBG)** and enters the cell as the free molecule.
- 2 The intracellular receptor is bound to the **stabilizing proteins**, including heat shock protein 90 (Hsp90) and several others (X). **When the complex binds a molecule of steroid, the Hsp90 and associated molecules are released.**
- 3 The Steroid - receptor complex enters the nucleus as a dimer, **binds to the glucocorticoid response element (GRE)** on the gene, and regulates gene transcription by RNA polymerase 2 and associated transcription factors.
- 4 The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response.



1: all are derivatives of cholesterol
 2: synthetic/pharmaceutical form of cortisol.
 3: Are all reactions related to generation and storage of metabolic energy

Effects of Glucocorticoids:

Metabolic effects

- Glucocorticoid **stimulate gluconeogenesis**, as a result:
 - Blood glucose rises
 - Insulin secretion is stimulated→Lipolysis and lipogenesis are stimulated. With a net **increase of fat deposition in certain areas** [e.g. **the face** (moon facies), **shoulder and back** (buffalo hump)]
- ★ These effects occur when the patient is treated with **100 mg (high dose) of hydrocortisone or > for longer than 2 weeks.**

Catabolic effects

- Glucocorticoids cause **muscle protein catabolism**(↓**muscle mass/muscle wasting**).
- Lymphoid and connective tissue **fat** and skin undergo wasting.
- Catabolic effects on **bone** lead to osteoporosis
- ★ **In children growth is inhibited¹.**

Immunosuppressive effects²

- Glucocorticoids inhibit cell mediated immunologic functions, especially dependent on lymphocytes & decrease interleukins secretion.
- ★ Glucocorticoids do not interfere with the development of normal acquired³ immunity **but delay rejection reactions in patients with organ transplants.**

Anti inflammatory effect²

- Glucocorticoids have important **inhibitory effects** on the distribution, function and migration of **leukocytes.**
- **Suppressive effect** on the inflammatory **cytokines & chemokines.**
- These drugs increase neutrophils and **decrease** lymphocytes, eosinophils, basophils and monocytes.
- ★ **Inhibit phospholipase A2⁴ & Prostaglandins synthesis.**

Other effects

- **Renal:** Glucocorticoids such as cortisol are required for normal renal excretion of water loads.
- **CNS:** When given in **large doses** these drugs may cause profound behavioral changes (first insomnia & euphoria then depression).
- **GIT:** **Large doses** also **stimulate gastric acid secretion** and decrease resistance⁵ to ulcer formation.

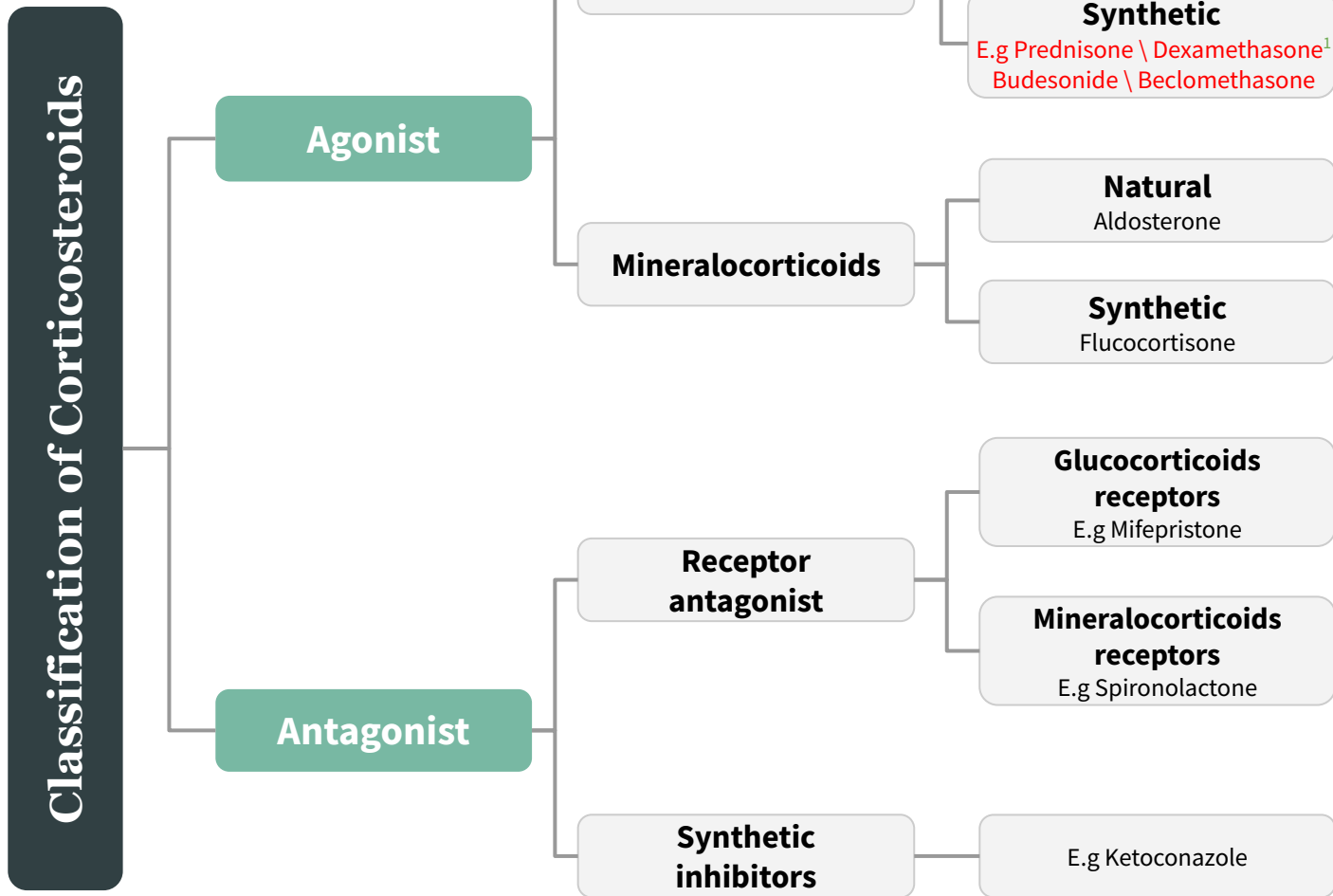
1: Steroids are contraindicated in children

2: most common therapeutic uses of steroids..

3: = Adaptive.

4: enzyme responsible for liberation of arachidonic acid (first step in the arachidonic acid pathway) which inhibit the production of all prostanoids and leukotrienes.

5: decrease prostaglandins



Glucocorticoids

	Natural cortisol (hydrocortisone)	Synthetic Glucocorticoids
Drugs	<ul style="list-style-type: none"> is the major natural glucocorticoid. The physiologic secretion of cortisol is regulated by adrenocorticotrophic (ACTH) & secretion rate varies during the day (Circadian rhythm). Peaks in the morning and trough (declines) in midnight. 	<ul style="list-style-type: none"> Prednisone and its active metabolite prednisolone Dexamethasone Budesonide Beclomethasone
P.K	<ul style="list-style-type: none"> Given orally, cortisol is well absorbed from GIT Cortisol in the plasma is 95% bound to CBG It is metabolized by the liver & has short duration of action compared with the synthetic congeners It diffuses poorly across normal skin & mucous membranes The cortisol molecule also has a small but significant mineralocorticoid effect. This is an important cause of hypertension in patients with cortisol secreting adrenal tumor or a pituitary ACTH secreting tumor (Cushing's syndrome) 	<p>★ Their properties in compared to cortisol include:</p> <ul style="list-style-type: none"> longer half life longer duration of action reduce salt retaining effect better penetration of lipid barriers for topical activity.

¹: long acting.

Glucocorticoids Cont...

Drugs	Natural cortisol (hydrocortisone)	Synthetic Glucocorticoids
Uses	<ul style="list-style-type: none"> ● Adrenal Disorder: <ol style="list-style-type: none"> 1. Addison's disease (chronic adrenocortical insufficiency) 2. Acute adrenal insufficiency associated with life threatening shock, infections or trauma 3. Congenital adrenal hyperplasia (in which synthesis of abnormal forms of corticosteroids are stimulated by ACTH). 	
	<ul style="list-style-type: none"> ● Non- adrenal Disorder: <ol style="list-style-type: none"> 1. Allergic reactions¹ (e.g. bronchial asthma, angioneurotic edema, drug reactions, urticaria, allergic rhinitis) <ol style="list-style-type: none"> a. Beclomethasone & budesonide have been developed for use in asthma and other condition in which good surface activity on mucous membrane or skin is needed and systemic effects are to be avoided. b. Rapidly penetrate the airway mucosa but have very short half lives after they enter the blood, so that systemic effects and toxicity are greatly reduced. (advantage) 2. Collagen vascular disorder² (e.g. rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, polymyositis, mixed connective tissue syndrome) 3. Organ transplants (prevention & treatment of rejection – immunosuppression) 4. GI disorders (e.g. inflammatory bowel disease) 5. Hematologic disorders³ (leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura) 6. Infections (acute respiratory distress syndrome, sepsis) 7. Neurologic disorders⁴ (to minimize cerebral edema after brain surgery, multiple sclerosis). 8. Pulmonary diseases (e.g. aspiration pneumonia, bronchial asthma, sarcoidosis) 9. Thyroid diseases (autoimmune diseases: malignant exophthalmos, subacute thyroiditis) 10. Renal disorders (nephrotic syndrome) 11. Miscellaneous (hypercalcaemia⁵ mountain sickness). 	
ADRs	<ul style="list-style-type: none"> ● Toxicity: <ol style="list-style-type: none"> 1. Cushing's syndrome (iatrogenic, by higher doses > than 100 mg hydrocortisone daily for > than 2 weeks characterized by moon shape face & buffalo hump) 2. Increased growth of fine hair on face, thighs & trunk, myopathy, muscle wasting, thinning of skin⁶, Diabetes Mellitus 3. Osteoporosis & aseptic necrosis of the hip 4. Wound healing is impaired 5. Peptic ulcer (↑GI acidity) 6. Acute psychosis, depression 7. Subcapsular cataracts (necrosis of the epithelium) 8. Growth suppression 9. Hypertension 10. Adrenal suppression⁷ 	

1: due to their immunosuppressive effect. 2: a group of disorders of connective tissues.
 3: since all are immune related cancers, we could use the immunosuppressive effects of glucocorticoids to treat.
 4: Dexamethasone is mostly used in neurological disorders due to its long duration of action and low salt-retaining activity.
 5: glucocorticoids can be used in hypercalcaemia since it helps increase calcium secretion and decrease its absorption.
 6: due to poor healing, connective tissue wasting.
 7: already high cortisol by external sources will suppress the adrenal secretion of cortisol.

Methods for minimizing corticosteroid toxicity:

1 Local application
(e.g; aerosol for asthma)

2 Alternate day therapy
(to reduce pituitary suppression)

3 Tapering¹ the dose soon after
achieving a therapeutic response.

4 To avoid adrenal insufficiency in patient
who have had long term therapy, **additional
Stress doses** may need to be given during serious
illness or before major surgery

Some commonly used natural and synthetic corticosteroids for general use

Female slide only Agents	Activity		
	Anti-inflammatory	Topical	Salt-retaining
Short to medium acting glucocorticoids			
Hydrocortisone (cortisol)	1	1	1
Cortisone	0.8	0	0.8
Prednisone	4	0	0.3
Prednisolone	5	4	0.3
Methyl- prednisolone	5	5	0.25
Meprednisone	5	-	0
Intermediate acting glucocorticoids			
Triamcinolone	5	5 ³	0
Paramethasone	10	-	0
Fluprednisolone	15	7	0
Long acting glucocorticoids			
Betamethasone	25-40	10	0
Dexamethasone	30	10	0
Mineralocorticoids			
Fludrocortisone	10	0	250

Explanation of the table:

- First, you need to understand that all the numbers compare the drugs to the physiological glucocorticoid cortisol (is why all of its numbers are 1)
- All synthetic drugs have better anti-inflammatory action than cortisol.
- Most synthetic drugs (except the ones that are indicated with 0 activity) have better topical action than cortisol (which means they penetrate lipid barriers better).
- All synthetic drugs have less salt retaining action (advantage) **EXCEPT Mineralocorticoids**.

(Dr. Alia: no need to memorize the numbers, just know the properties of each drug and memorize the names of the drugs and their duration of action)

1: = start with high dose, then when we reach the therapeutic effect decrease the dose gradually.

Mineralocorticoids

Drug	Aldosterone \ Fludrocortisone
MOA	<ul style="list-style-type: none"> • Same as that of glucocorticoids.
P.K	<ul style="list-style-type: none"> • The major natural mineralocorticoid in human. • Aldosterone is the main salt-retaining hormone, promotes Na Reabsorption, K excretion, in the distal convoluted tubule & thus it is very important in the regulation of blood volume & blood pressure • Its secretion is regulated by ACTH & by the renin-angiotensin system. • Aldosterone has short half life & little glucocorticoid activity.
Uses	<ul style="list-style-type: none"> ★ Fludrocortisone is favored for replacement therapy after adrenalectomy & in other conditions in which mineralocorticoid therapy is needed.

Corticoids Antagonist

1) Receptor Antagonist

Drugs	Spironolactone	Mifepristone
MOA	<ul style="list-style-type: none"> • mineralocorticoid antagonist & K-sparing diuretic • antagonists of aldosterone at its receptor. 	<ul style="list-style-type: none"> • A competitive inhibitor of glucocorticoid receptors
Uses	<ul style="list-style-type: none"> • Treatment of primary aldosteronism (Conn's syndrome). 	<ul style="list-style-type: none"> • Treatment of Cushing's syndrome

2) Synthetic Inhibitors

Drug	Ketoconazole (Anti Fungal ¹)
MOA	<ul style="list-style-type: none"> • It inhibits the cytochrome p450 enzymes necessary for the synthesis of all steroids
Uses	<ul style="list-style-type: none"> • Used in a number of conditions in which reduced steroid level are desirable such as: <ul style="list-style-type: none"> ○ Adrenal cancer, when surgical therapy is impractical or unsuccessful because of metastasis. ○ Hirsutism ○ Breast cancer ○ Prostate cancer

¹: act as an anti-fungal in low doses, while in high doses it blocks the synthesis of mineralocorticoids.

Quiz

MCQ

Q1- Corticosteroids are useful in the treatment of all of the following disorders except:

A- Addison disease B- Allergic rhinitis C- Cushing syndrome D- Rheumatoid arthritis

Q2- All of the following adverse effects commonly occur with glucocorticoid therapy except:

A- Peptic Ulcer. B- DM. C- Hypotension. D- Emotional disturbances.

Q3- Osteoporosis is a major adverse effect caused by the glucocorticoids. It is due to:

A- Catabolic effects on bone. B- Stimulation of the hypothalamic–pituitary–adrenal axis.
C- Decrease production of prostaglandins. D- Decrease collagen synthesis.

Q4- A child with severe asthma is being treated with high doses of inhaled corticosteroids. Which of the following adverse effects is of particular concern?

A- Hypoglycemia. B- Hirsutism. C- Growth suppression. D- Cushing syndrome. E- Cataract formation.

Q5- Which of the following drugs have a potassium sparing effect?

A- Mifepristone B- Spironolactone C- Fludrocortisone D- Budesonide

SAQ

-A 40 years old woman with rheumatoid arthritis came to the hospital with increased growth of hair on her face , abnormal fat deposition and muscle wasting. She was diagnosed to have cushing's syndrome due to prolonged use of steroids.

1- Which drug best to be used to reduce the symptoms?

2- What is the M.O.A of that drug?

3- A 56 years old male with an adrenal tumor underwent adrenalectomy.Which drug is favored as a replacement therapy?

-A 39 years old patient came to the clinic complaining of muscle cramps, headache and have high blood pressure after investigation he diagnosed with primary aldosteronsim.

4- Name a drug that can be used in her case.

5-How does the toxicity of Glucocorticoids develop?

MCQ

Q1	C
Q2	C
Q3	A
Q4	C
Q5	B

SAQ

Q1	Mifepristone
Q2	A competitive inhibitor of glucocorticoid receptors.
Q3	Fludrocortisone
Q4	Spironolactone
Q5	When taking high dose (100 mg) daily for more than 2 weeks

Answers:



*Thank you for all your
love and support.*

Good luck future doctors!

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