Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Steroids

Color index:
Important
Note
Extra
Dr. Alias presentation notes

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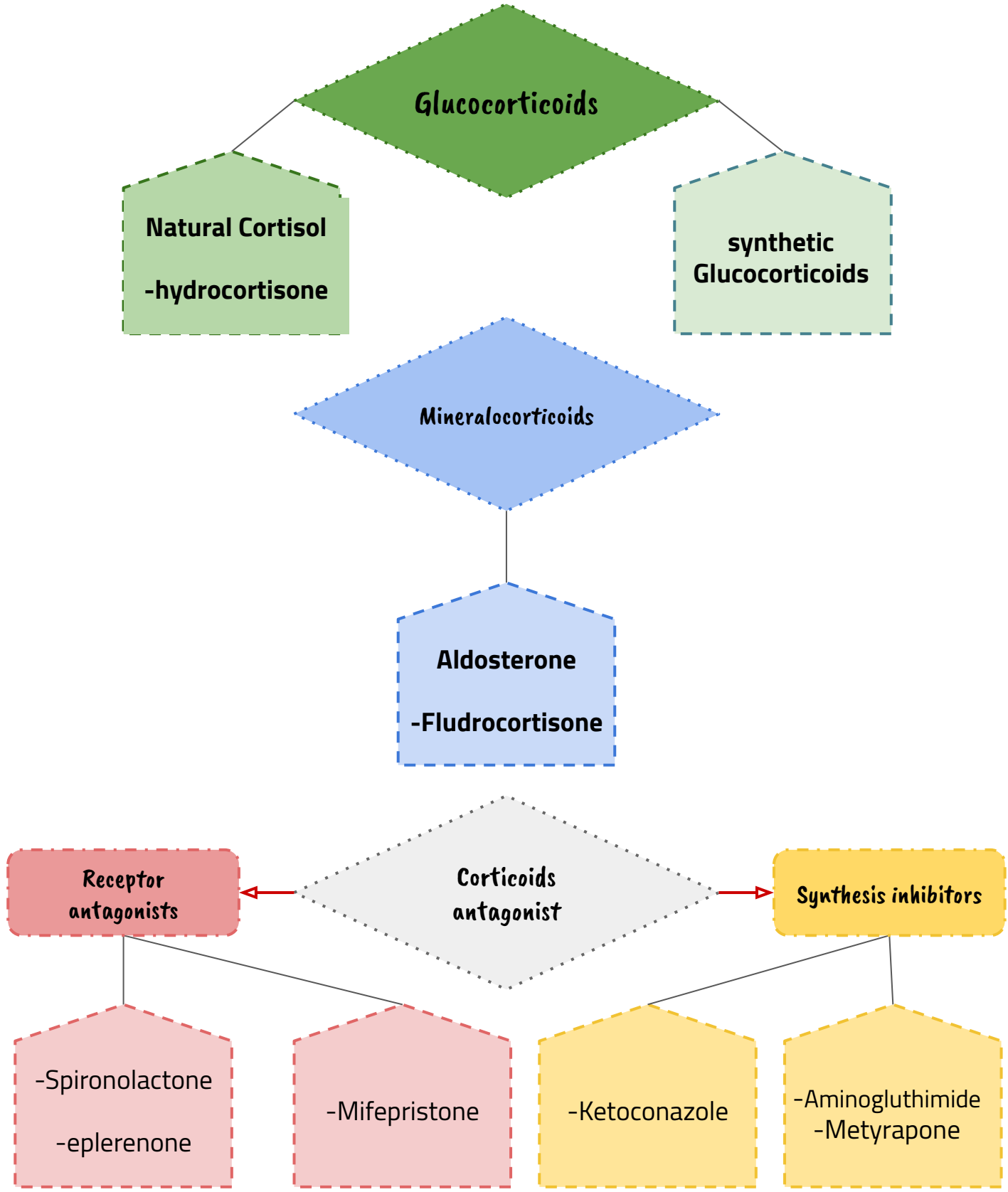
Editing File

Mind Map


Glucocorticoids
Natural Cortisol
-hydrocortisone
synthetic
Glucocorticoids
Mineralocorticoids
Aldosterone
-Fludrocortisone
Receptor
antagonists
Corticoids
antagonist
Synthesis inhibitors
-Spironolactone
-eplerenone
-Mifepristone
-Ketoconazole
-Aminogluthimide
-Metyrapone

Corticosteroids

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

1 Glucocorticoids

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

2 Mineralocorticoids

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

Just know the **starting** materials & **end** products

Biosynthesis of adrenal hormones

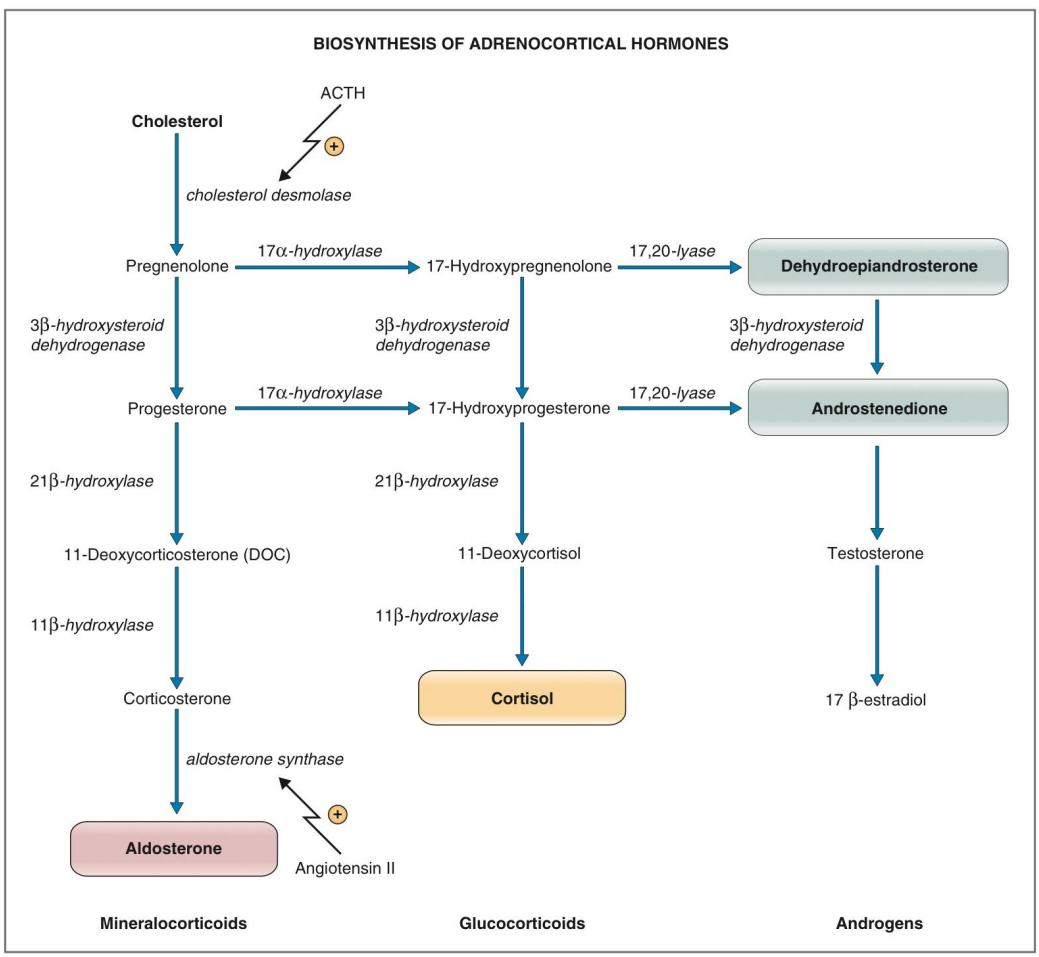


Figure 9–23 Biosynthetic pathways for glucocorticoids, mineralocorticoids, and androgens in the adrenal cortex. ACTH, Adrenocorticotropic hormone. The major secretory products of the adrenal cortex are shown in colored boxes.

Mechanism of Action

1 Corticosteroids

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

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

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

The resulting mRNA is **edited** and exported to the cytoplasm for the production of protein that brings about the final hormone response.

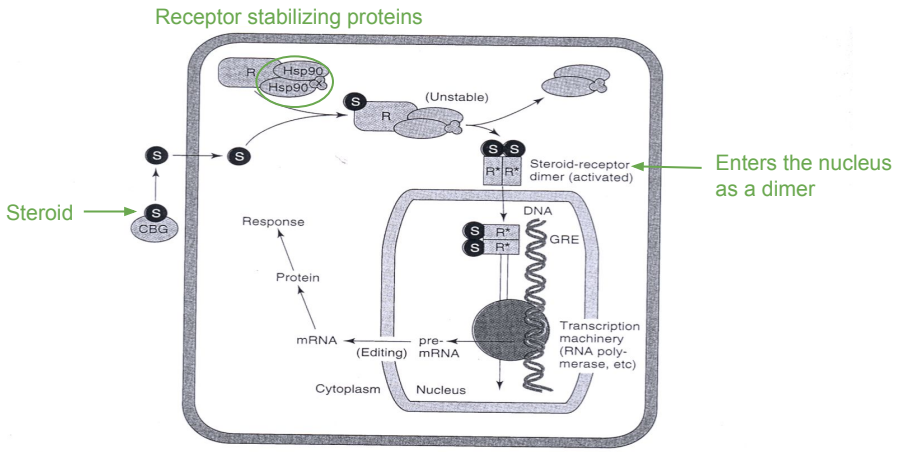


Figure 39–1. Mechanism of glucocorticoid action. This figure models the interaction of a steroid (S; eg, cortisol), with its receptor (R) and the subsequent events in a target cell. The steroid is present in the blood bound to the corticosteroid-binding globulin (CBG) but enters the cell as the free molecule. The intracellular receptor is bound to 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. 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 II and associated transcription factors. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 10th ed. McGraw-Hill, 2007.)

Effects of steroids

1- Metabolic effects:

- **Glucocorticoids stimulate gluconeogenesis, as a result:**
- Blood **glucose** rises
- **Insulin** secretion is stimulated
- Stimulate **lipolysis & lipogenesis** (due to increased insulin) with a net increase of fat deposition in certain areas e.g, the face (moon face) & shoulder & back (buffalo hump).

These effects occur when the patient is treated with 100 mg of hydrocortisone or > for longer than 2 weeks.

So after activating GRE and protein synthesis what are the expected responses?
GCs are similar to catecholamines are called stress hormones
Stimulate lipolysis (increase release of FA in the blood)
Insulin promotes lipogenesis

2-Catabolic effects:

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

Stimulate the conversion of protein aa to carbohydrates as glucose (gluconeogenesis) and promote the storage of carbohydrates as glycogen.

3-Anti–inflammatory effects:

- Glucocorticoids have important inhibitory effects on the distribution, function & migration of **leukocytes**
- Suppressive effect on the inflammatory **cytokines** & **chemokines**
- These drugs increase neutrophils & decrease lymphocytes, eosinophils, basophils & monocytes
- Inhibit phospholipase A2 & Prostaglandins synthesis.
- The migration of leukocytes is also inhibited

Effects of steroids

4-Immunosuppressive effects:

- Glucocorticoids inhibit **cell-mediated immunologic functions**, especially dependent on lymphocytes & decrease interleukins secretion.

- Glucocorticoids do not interfere with the development of normal acquired immunity but **delay rejection reactions** in patients with organ transplants.

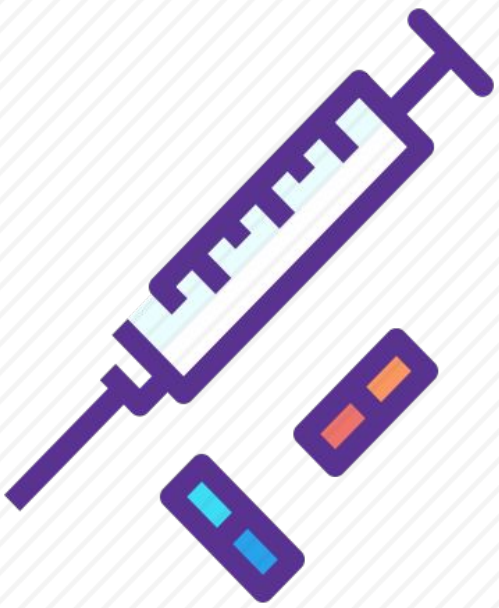
5-Other effects:

- 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 & decrease resistance to ulcer formation.

Physiologically GC help to control renal excretion of water



Corticosteroid Agonists and Antagonists

- **Agonists**
  - **Glucocorticoids (prednisone)**
  - **Mineralocorticoids (fludrocortisone)**
- **Antagonists**
  - **Receptor antagonists**
    - **Glucocorticoides (mifepristone)**
    - **Mineralocorticoids (spironolactone)** — K+ sparing diuretic
  - **Synthesis inhibitors (ketoconazole)** — Anti-fungal

All the following is the actual **pharmacology** part pf the lecture

Glucocorticoids

Know all drugs Q

TABLE 39–1 Some commonly used natural and synthetic corticosteroids for general use.

physiological

Agent	Activity[1] Anti-Inflammatory	Topical	Salt-Retaining	Equivalent Oral Dose (mg)	Forms Availabl
Short- to medium-acting glucocorticoids					
→ Hydrocortisone (cortisol)	1	1	1	20	Oral, injectable,
Cortisone	0.8	0	0.8	25	Oral
Prednisone	4	0	0.3	5	Oral
Prednisolone	5	4	0.3	5	Oral, injectable
Methylprednisolone	5	5	0.25	4	Oral, injectable
Meprednisone[2]	5		0	4	Oral, injectable
Intermediate-acting glucocorticoids					
Triamcinolone	5	5[3]	0	4	Oral, injectable,
Paramethasone[2]	10		0	2	Oral, injectable
Fluprednisolone[2]	15	7	0	1.5	Oral
Long-acting glucocorticoids					
Betamethasone	25–40	10	0	0.6	Oral, injectable,
Dexamethasone	30	10	0	0.75	Oral, injectable,
Mineralocorticoids					
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone acetate[2]	0	0	20		Injectable, pelle

All of them less than cortisol — higher — lower

[1] Potency relative to hydrocortisone
> 1, These drugs have Higher affinity and greater bioavailability, **poorly** metabolised
Cortisol has the most salt retaining properties

Important Glucocorticoids

Drug	Cortisol (Hydrocortisone)	Synthetic Glucocorticoids To avoid disadvantages
General Information	• The major **natural** glucocorticoid • The physiologic secretion of cortisol is regulated by adrenocorticotropic hormone (ACTH) & secretion rate varies during the day (circadian rhythm), peaks in the early morning & declines about midnight.	**Large number are available for use:** • Prednisone & its active metabolite prednisolone • Dexamethasone • Beclomethasone • Budesonide
P.K	• 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).	**Their properties (compared with cortisol) include:** • longer half life & duration of action • reduce salt retaining effect • better penetration of lipid barriers for topical activity
	Disadvantages of cortisol: 1. **short** duration of action 2. **diffuses poorly** across normal skin & mucous membranes 3. This is an important cause of **hypertension** in patients with cortisol secreting adrenal tumor or a pituitary ACTH secreting tumor (Cushing's syndrome)	• **Beclomethasone** & **budesonide** have been developed for use in **asthma** & other conditions in which good surface activity on **mucous membrane or skin** is needed & systemic effects are to be avoided. • These drugs **rapidly** penetrate the **airway mucosa** but have very short half lives after they enter the blood, so that systemic effects & toxicity are greatly **reduced**. Can be used locally on respiratory tract

Clinical Uses of Corticoids

➢ Adrenal disorders:

- **Addison's disease** (chronic adrenocortical insufficiency)
- **Acute adrenal insufficiency** associated with life threatening shock, infections or trauma
- **Congenital adrenal hyperplasia** (in which synthesis of abnormal forms of corticosteroids are stimulated by ACTH).فنحتاج نعوضها

➢ Non-adrenal disorders:

- Allergic reactions (e.g. bronchial asthma, angioneurotic edema, drug reactions, urticaria, allergic rhinitis) due to anti-inflammatory effects
- Collagen vascular disorder (e.g; rheumatoid arthritis,systemic lupus erythematosus, giant cell arteritis, polymyositis, mixed connective tissue syndrome) all autoimmune disorders
- Organ transplants (prevention & treatment of rejection immunosuppression).
- GI disorders such as inflammatory bowel disease, non tropical sprue
- Hematologic disorders (leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura)
- Infections (acute respiratory distress syndrome, sepsis)
- Neurologic disorders (to **minimize cerebral edema** after brain surgery, multiple sclerosis).*
- Pulmonary diseases (e.g.; aspiration pneumonia, bronchial asthma, sarcoidosis).
- Thyroid diseases (malignant exophthalmos, subacute thyroiditis)
- Renal disorders (nephrotic syndrome)
- Miscellaneous (hypercalcaemia, mountain sickness).

***We give dexamethasone in brain surgery due to its long duration. But short period during respiratory problems**

Toxicity (Adverse effects)

- Cushing's syndrome (iatrogenic, by higher doses > than 100 mg hydrocortisone daily for > than 2 weeks characterized by moon shape face & buffalo hump)
- Increased growth of fine hair on face, thighs & trunk. Myopathy, muscle wasting, thinning of skin, Diabetes Mellitus
- Osteoporosis & aseptic necrosis of the hip Inhibition of blood supply to a part of the hip increases the risk of infection
- Wound healing is impaired
- Peptic ulcer
- Acute psychosis, depression
- Subcapsular cataracts
- Growth suppression
- Hypertension
- Adrenal suppression.

➢ Methods For Minimizing These Toxicities Include.

- Local application (e.g, aerosol for asthma)
- Alternate day therapy (to reduce pituitary suppression) تقول وشوله اشتغل
- Tapering the dose soon after achieving a therapeutic response (decrease the dose gradually)
- To avoid adrenal insufficiency in patients who have had long term therapy, additional stress doses may need to be given during serious illness, or before major surgery. To avoid withdrawal symptoms

Mineralocorticoids

Drug	Aldosterone
M.O.A	Same as that of **glucocorticoids**.
General Information	• 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	**Fludrocortisone** (aldosterone agonist) is favored for replacement therapy after adrenalectomy & in other conditions in which mineralocorticoid therapy is needed. Eg. postural hypotension it is a mineralocorticoid that has a long duration of action and significant glucocorticoid activity

Angiotensin II also stimulates the secretion of the hormone aldosterone from the adrenal cortex

Corticosteroid Antagonists

Antagonists of corticosteroids can either block corticosteroids Receptors or inhibit steroid synthesis.

Drug	Receptor Antagonists		Synthesis inhibitors
	spironolactone eplerenone	Mifepristone	Aminoglutethimide, Metyrapone and **Ketoconazole** (anti fungal)
M.O.A	**antagonists** of aldosterone at its receptor. (mineralocorticoid antagonist & K-sparing diuretic) **How**? Via antagonist of aldosterone	A **competitive inhibitor** of glucocorticoid receptors. As well as a progesterone receptors.	**Ketoconazole:** It **inhibits** the **cytochrome p450** enzymes necessary for the synthesis of all steroids **Aminogluthemide:** -It **blocks** the conversion of **cholesterol to pregnelone** - it inhibits the synthesis of all **hormonally active steroids.**
Uses	treatment of primary aldosteronism Conn's syndrome, is excess production of the hormone aldosterone by the adrenal glands	useful in the treatment of Cushing's syndrome	**Ketoconazole:** is used in a no. of conditions in which reduced steroid level are desirable such as: 1. Adrenal carcinoma 2. Hirsutism 3. Breast cancer 4. Prostate cancer Adrenal cancer, when surgical therapy is impractical or unsuccessful because of metastasis. **Aminogluthemide:** Adrenocortical cancer (steroid producing tumor) in conjunction with other drugs.

MCQs

1- all of the following are properties of synthetic glucocorticoids except :

a) Longer half life and duration of action than natural glucocorticoids.
b) Better penetration of lipid barriers.
c) Can be used topically.
d) Increased salt retaining effect.

2- which of the following is best used for asthma :

a) Prednisone
b) Dexamethasone
c) Budesonide
d) Cortisol

3- a 40 year 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. Which of the following drugs will reduce the symptoms?

a) Beclomethasone
b) fludrocortisone
c) Spironolactone
d) Mifepristone

4- a patient with Crohn's disease was treated with glucocorticoids. Which of the following side effects may develop?

a) Osteoporosis
b) Weight loss
c) Lupus like syndrome
d) Hepatotoxicity

5- a patient with an adrenal tumor underwent adrenalectomy, which of the following drugs is favored for replacement therapy ?

a) Fludrocortisone.
b) Budesonide
c) Beclomethasone
d) Mifepristone.

6- a patient with a large adrenal tumor had unsuccessful surgical therapy due to metastasis. What is the next step in the management of this patient.

a) spironolactone.
b) Ketoconazole
c) Mifepristone
d) Fludrocortisone.

Answers:

1) D
2) C
3) D
4) A
5) A
6) B

SAQ

A 45 year old female patient presented with hypotension ,hypoglycemia , weight loss and hyperpigmentation of the skin and other mucosal surfaces. After investigations , she was diagnosed with Addison's disease.

1)Name a drug that can be used in her case
Dexamethasone

2) name three other uses of the drug you mentioned.
Rheumatoid arthritis
Prevention of rejection in organ transplantation
Inflammatory bowel diseases

3) List three side effect of the drug
Cushing syndrome
Osteoporosis
Subcapsular cataracts.

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References:

✓ Doctors' slides and notes

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