Corticosteroids

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- Revise the synthesis of steroids, Mechanism of action

- Steroids agonists & antagonists and their therapeutic applications.

- Pharmacokinetics of cortisol, pharmacodynamic actions & therapeutic uses, Adverse reaction

- glucocorticoids (GCs) and mineralocorticoids (MCs) from different perspectives:

  Their synthesis, Their Mechanism of actions, Their Metabolic, catabolic, anti-inflammatory and immunosuppressive effects, Some examples of GCs and MCs, Some of their clinical uses, Toxicity, GCs and MCs antagonists

Biosynthesis of Adrenal Hormones

Mineralocorticoids | Glucocorticoids | Sex Hormones

Cholesterol

ACTH

- Pregnenolone → (11 αOH) → 11- OH Pregnenolone → (17.20 lyase) → Dehydroepiandrosterone
- Progesterone → (11 αOH) → 11- OH Progesterone → (17.20 lyase) → Androstenedione
- 11- Deoxycorticosterone
- 11- Deoxycortisol
- Testosterone
- Corticosterone
- Estradiol
- Aldosterone
- Cortisol
- Dihydrotestosterone

Corticosteroids

Steroid hormones produced by the adrenal cortex.

Glucocorticoids (Normal)

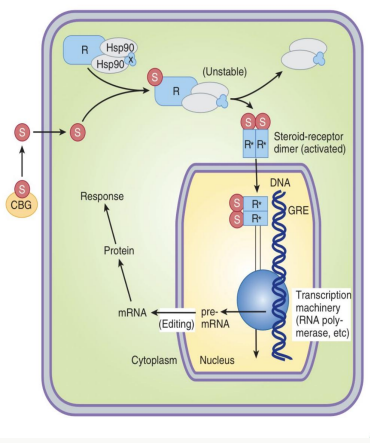
Major: Cortisol - Pharmaceutical Preparation: Hydrocortisone-
They have important effects on intermediary metabolism, catabolism, immune responses, growth, & inflammation.

Mineralocorticoids

Most important: Aldosterone
They have salt-retaining activity which regulate Na & K reabsorption in the collecting tubules of the kidney.

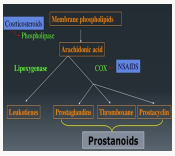
MOA

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).
3. When the complex binds a molecule of steroid, the Hsp90 and associated molecules are released
4. 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.
5. The resulting mRNA is edited and exported to the top cytoplasm for the production of protein that brings about the final hormone response.



Effects of Glucocorticoids

Anti-Inflammatory



- Inhibitory effects on distribution, function, & migration of leukocytes.
- Suppressive effect on the inflammatory cytokines & chemokines
- ↑ Neutrophils & ↓ lymphocytes, eosinophils, basophils and monocytes.
- MOA: Inhibit phospholipase A2 and subsequently inhibit Prostaglandins synthesis.

-Cytokines: they're proteins found in RBCs & immune cells.
-Chemokines: produced by inflammation.
-Neutrophils: anti-inflammation.

Immunosuppressive

- Inhibiting 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.

Metabolic

Occurs when the patient's treated with:
100 mg (high dose) of hydrocortisone or for longer than 2 weeks.
Stimulation of gluconeogenesis resulting in:

- ↑ Blood glucose
- ↑Insulin secretion → Lipolysis & lipogenesis are stimulated.
- Net increase of fat deposition in certain areas e.g. the face "moon face",shoulder & back "buffalo hump"

Catabolic

- Muscle protein catabolism: ↓ muscle mass
- Lymphoid and connective tissue fat and skin undergo wasting
- Catabolic effects on bone lead to osteoporosis
- Growth is inhibited in children

Others

- 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 resistance to ulcer formation (peptic ulcer)

Corticosteroids

- **Agonists**
  - **Glucocorticoids**
    - **Natural**: Cortisol, Hydrocortisone
    - **Synthetic**: Prednisone, Dexamethasone, Budesonide, Beclomethasone
  - **Mineralocorticoids**
    - **Natural**: Aldosterone
    - **Synthetic**: Fludrocortisone
- **Antagonists**
  - **Synthetic inhibitors**
    - Ketoconazole
  - **Receptor antagonists**
    - **Glucocorticoid receptors**: -Mifepristone
    - **Mineralocorticoid receptors**: -Spironolactone

Ia. Agonists : Glucocorticoids:

Natural Cortisol

Synthetic prep Hydrocortisone	• Cortisol is the major natural glucocorticoid • The physiologic secretion of cortisol is regulated by adrenocorticotropic (ACTH) & secretion rate varies during the day (follows circadian rhythm), peaks in the morning and declines at midnight.
Pharmacokinetics :	• Given orally, well absorbed from GIT • Cortisol in the plasma is 95% bound to CBG (corticosteroid binding globulin). • Metabolized by the liver & has short duration of action compared with the synthetic congeners (analogue). • Diffuses poorly across normal skin & mucous membranes. • 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).

Synthetic Cortisol

➔**Prednisone , Prednisolone (active metabolite) | Dexamethasone -long acting cortisol- | Beclomethasone | Budesonide** (It's the most used, mainly in neurological disorders).

➔Their properties in **compared to cortisol:**(Dr asked about it).

- **Longer** half life & duration of action
- **Reduce salt retaining effect**
- **Better penetration** of lipid barriers for topical activity.

Agent	Activity[1]			Equivalent Oral Dose (mg)	Forms Available
	Anti-Inflammatory	*Topical*	*Salt-Retaining*		
Short- to medium-acting glucocorticoids					
Hydrocortisone (cortisol)	1	1	1	20	Oral, injectable, topical
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, topical
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, topical
Dexamethasone	30	10	0	0.75	Oral, injectable, topical
Mineralocorticoids					
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone acetate[2]	0	0	20		Injectable, pellets

[1]Potency relative to hydrocortisone.
[2]Outside USA.
[3]Triamcinolone acetonide: Up to 100.

Ia. Agonists : *Glucocorticoids*

Uses

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).

Non-Adrenal Disorders

1. **Allergic reactions**:
   (e.g. bronchial asthma, angioneurotic edema, drug reactions, urticaria, allergic rhinitis):
   - **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.
   - 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.**
2. **Collagen vascular disorders** (e.g rheumatoid arthritis, SLE, giant cell arteritis, polymyositis, mixed connective tissue syndrome)
3. **Organ transplants:** prevention & treatment of **rejection** – immunosuppression
4. **GI disorders**: inflammatory bowel disease
5. **Hematologic disorders**: leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura
6. **Infections:** acute respiratory distress syndrome (associated with high immune response) & sepsis
7. **Neurologic disorders**: to minimize cerebral edema after brain surgery,multiple sclerosis
   *__Dexamethasone :__ long acting corticosteroid used to prevent cerebral edema in brain surgery due to its anti-inflammatory effect
8. **Pulmonary diseases**: aspiration pneumonia, bronchial asthma, sarcoidosis
9. **Thyroid diseases**:autoimmune diseases:malignant exophthalmos & subacute thyroiditis
10. **Renal disorders**: nephrotic syndrome
11. **Miscellaneous** : hypercalcemia -inhibiting Ca absorption in the intestine-
    mountain sickness travel to a high altitude quickly

Toxicity

★ ***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 & Hypertension
- Osteoporosis | aseptic necrosis of the hip -by decreasing blood perfusion-
  | impaired wound healing
- Peptic ulcer (↑GI acidity)
- Acute psychosis | depression brain plasticity impairment
- Subcapsular cataract
- Growth & Adrenal suppression

Methods for minimizing toxicity :

1. Local application (e.g; aerosol for asthma)
2. Alternate day therapy (to reduce pituitary suppression)
3. Tapering -decreasing- 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

Ib. Agonists: *Mineralocorticoids*

Drug	Aldosterone (natural)	Fludrocortisone (synthetic)
MOA	Same as that of glucocorticoids (slide 3) but binds to **mineralocorticoids response element**	
PK	• The major natural mineralocorticoid in human • Aldosterone has short half life & little glucocorticoid activity.	
PD	• 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.	
Uses	**Fludrocortisone** is favored for replacement therapy after **adrenalectomy** & in other conditions in which mineralocorticoid therapy is needed. - used in : postural hypotension-	

II. Corticoids Antagonists

1	Receptor Antagonists	
Drug	**Spironolactone**	**Mifepristone**
MOA	• **Mineralocorticoid antagonist & K-sparing diuretic** • **Antagonists of aldosterone at its receptor.**	• **Competitive inhibitor of glucocorticoid receptors**
Uses	Treatment of primary aldosteronism (Conn's syndrome).	Treatment of Cushing's syndrome due to ectopic ACTH production or adrenal carcinoma.

2	**Synthetic Inhibitors**
Drug	**Ketoconazole (Anti-Fungal)**
MOA	• *In low doses it acts as an* **antifungal** • *In high doses it* blocks the synthesis of **all steroids** • Inhibits cytochrome p450 enzymes necessary for synthesis of all steroids • "Non-specific corticosteroids synthesis inhibitor"
Uses	Number of conditions in which reduced steroid level are desirable such as: • **Adrenal cancer** (carcinoma), when surgical therapy is impractical or unsuccessful because of metastasis. • Hirsutism • Breast cancer (Anti- estrogen). • Prostate cancer (Anti- testosterone).

MCQ

1. Which one of the following is a mineralocorticoids antagonist and has potassium sparing effect?

A. Spironolactone	B. Ketoconazole	C. Mifepristone	D. Aldosterone

2. Which one of the following is used for the treatment of addison's disease

A. Aldosterone	B. Mifepristone	C. Ketoconazole	D. Hydrocortisone

3. A 43-year-old man presented to the hospital complaining of weight gain, mild but continuing facial acne, and decreased muscle strength. A computed tomography scan disclosed an adrenal adenoma in the left adrenal gland, and the patient was scheduled for surgery. Which of the following drugs would be appropriate as a replacement therapy after adrenalectomy

A. Spironolactone	B. Aldosterone	C. Fludrocortisone	D. Mifepristone

A 46-year-old male patient has Cushing's syndrome due to an adrenal tumor. Which of the following drugs would be expected to reduce the signs and symptoms of this man's disease?

A. Dexamethasone	B. Budesonide	C. Ketoconazole	D. Hydrocortisone

5. A 57-year-old man suffering from severe dermatomyositis had been receiving high-dose prednisone for 6 months. Which of the following laboratory results would be most likely to occur in this patient?

A. Hypocalcemia	B. Hyponatremia	C. Hypoglycaemia	D. Hyperkalemia

6.Which of the following synthetic steroids shows predominantly mineralocorticoid action?

A. Hydrocortisone	B. Fludrocortisone	C. Spironolactone	D. Dexamethasone

1:A ,2:D ,3:C ,4:C ,5:A ,6:B

SAQ

1 **Mention some of the adverse drug reaction associated with the use of Glucocorticoids?**

Answer: slide 7

2 **Mention the methods used to minimise the toxicity caused by glucocorticoid?**

Answer:slide 7

3 **List the uses of Fludrocortisone?**

Answer: slide 8

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