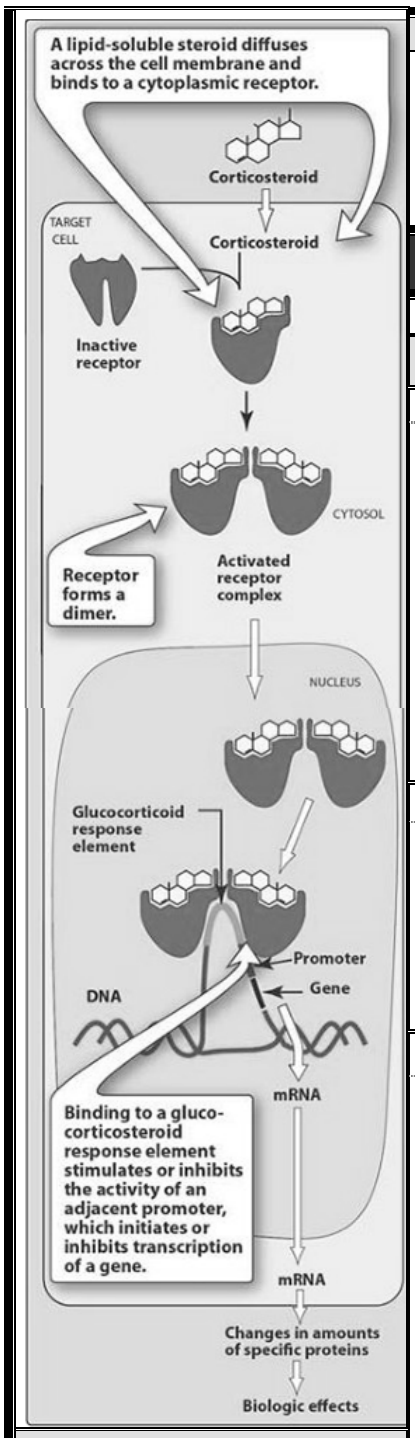
Adreno-Corticosteroids



Mechanism of action

- They are steroid hormone (lipid soluble) , enters the cell easily by passive diffusion and binds to specific **intracellular cytoplasmic receptors** in the target tissues → resulting in their activation.
- After dimerizing, the activated receptor-hormone complex translocates into the nucleus, where it attaches to **gene promoter elements** (gluco-corticosteroid response element), acting as a transcription factor to turn genes on or off.
- Binding to a gluco-corticosteroid response element stimulates or inhibits the activity of an adjacent promoter which initiates or inhibits transcription of a gene into mRNAs to synthesis protein and exerts biological effects.

1- Glucocorticoids

N.B. *Read the actions of glucocorticoids on various tissue in Bio and Physio books.*

Pharmacological actions

1- Promote normal intermediary metabolism

- Glucocorticoids favor gluconeogenesis through:
  1- increasing amino acid uptake by the liver and kidney
  2- elevating activities of gluconeogenic enzymes.

They stimulate protein catabolism (except in the liver) and lipolysis, thereby ➔ providing the building blocks and energy that are needed for glucose synthesis.

N.B.:

1- Glucocorticoid insufficiency may result in hypoglycemia (e.g. during stressful periods or fasting).

2- Lipolysis results as a consequence of the glucocorticoid augmenting the action of growth hormone on adipocytes, causing an increase in the activity of hormone sensitive lipase.a

Read the metabolical actions of gulcocorticoids in details in Bio & physio books.

2- Increase resistance to stress (Anti-Stress)

- **By raising plasma glucose levels,** glucocorticoids provide the body with the energy it requires to combat stress caused, for example, by trauma, fright, infection, bleeding, or debilitating disease.
- **By enhancing the vasoconstrictor action of adrenergic stimuli on small vessels,** it can cause a modest rise in blood pressure vessels.

N.B. *Individuals with adrenal insufficiency may respond to severe stress by becoming hypotensive*.

Used in shock & stress conditions

3- Anti-Inflammatory & Anti-Allergic actions :

- **They can reduce the inflammatory response and to suppress immunity by:**
  1- Redistribution of leukocytes to other body compartments, thereby lowering their blood concentration (their function is also compromised).
  2- Increase ↑ in the concentration of neutrophils; a decrease ↓ in the concentration of lymphocytes (T and B cells), basophils, eosinophils, and monocytes.
  3- Inhibition of the ability of leukocytes and macrophages to respond to mitogens and antigens.
  4- Synthesis of lipocortin → resulting in indirect inhibition of phospholipase A_2 → resulting in decrease the arachidonic acid *(precursor of the prostaglandins & leukotrienes)* from membrane-bound phospholipid → resulting in decrease of Prostaglandins & leukotrienes. (anti-inflammatory action)
  5- Cyclooxygenase-2 synthesis in inflammatory cells is further reduced, lowering the availability of prostaglandins.
  6- Interference in mast cell degranulation (causes stabilization of mast cells) → results in decreased histamine and capillary permeability → resulting in decrease inflammatory edema.

5- Anti-Vitamin D effect :

It decreases Ca absorption from GIT → resulting in hypocalcemia

4- Immunosuppressant :

- Decreases anti-body formation.
- Decrease antigen / antibody formation .

4- Alter blood cell levels in plasma

- **They cause a decrease in :**
  eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue.
- **They cause increase the blood levels of:**
  hemoglobin, erythrocytes, platelets, & polymorphonuclear leukocytes.

5- Affect other components of the endocrine system:

Feedback inhibition of corticotropin production by elevated glucocorticoids causes:

10- Inhibition of further glucocorticoid synthesis

11- as well as further production of thyroid-stimulating hormone.

12- In contrast, growth hormone production is increased.

Therapeutic Uses

1-Replacement therapy for 1ry Addison's disease)

In 1ry addison's → replace both gluco & mineralo corticoid activities

Hydrocortisone (which is identical to natural cortisol) is given to correct the deficiency.

The dosage of hydrocortisone is divided:
- Two-thirds of the normal daily dose is given in the morning
- One-third is given in the afternoon.

Fludrocortisone,
- Synthetic mineralocorticoid with some glucocorticoid activity,
- Necessary to raise the mineralocorticoid activity to normal levels

2- Replacement therapy for 2ry & 3ry Addison's disease .

In 2ry & 3ry addison's → glucocorticoid activities
Replace only glucocorticoid activity.

Under these conditions, the synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids

The adrenal cortex responds to corticotropin (ACTH) administration by synthesizing and releasing the adrenal corticosteroids.

→ **Hydrocortisone** is also used for these deficiencies.

Relief of inflammatory symptoms

- Glucocorticoids reduce the manifestations of inflammations :
  (e.g. → rheumatoid and osteoarthritic inflammations, inflammatory conditions of the skin), including the redness, swelling, heat, and tenderness that are commonly present at the inflammatory site.

Treatment of Allergies

- Glucocorticoids used in treatment of the symptoms of :
  bronchial asthma, allergic rhinitis, and drug, serum, & transfusion allergic reactions.

Beclomethasone - **dipropionate** - **triamcinolone**
These drugs are applied topically to the respiratory tract through inhalation → This minimizes systemic effects and allows the patient to significantly reduce or eliminate the use of oral steroids.

- Used in :

1- Hypervitaminosis D .
2- Hypercalcemia

Immunosuppressive

1- Auto-immune diseases :
- Collagen disease: Polyarthritis , …
- Blood disease: hemolytic & aplastic anemia , …

2- Supress tissue & organ rejection.

Treatment of leukemia & lymphoma

-The decrease in circulating lymphocytes and macrophages compromises the body's ability to fight infections.

-This property is important in the **treatment of leukemia.**

1- Replacement therapy for congenital adrenal hyperplasia

Treatment of this condition requires administration of sufficient corticosteroids to normalize the patient's hormone levels by suppressing release of CRH and ACTH. This decreases production of adrenal androgens.

2- Diagnosis of Cushing's syndrome

The dexamethasone suppression test is used to diagnose the cause of an individual's case of Cushing's syndrome.

This synthetic glucocorticoid suppresses cortisol release in individuals with pituitary-dependent Cushing's syndrome, but it does not suppress glucocorticoid release from adrenal tumors.

Side effects of Glucocorticoids

1- Abrupt withdrawal after long use → Acute Addisonian Crisis.
2- Hyperglycemia → worsens diabetes mwllitus due to anti-insulin effect.
3- Moon face & Buffalo hump.
4- Osteoporosis → collapse of vertebrae
5- Myopahy & muscle weakness.
6- Retardation of growth in children.
7- Teratogenicity.
8- Cataract & ↑ I.O.P → Glaucoma.
9- Edema & Weight gain.
10- Hypertension → may lead to H.F.
11- Hypokalemia.
12 Mask manifestations of bacteria & viral infections.
13- Increase susceptibility to infection.
14- Delays healing of wounds.
15- Peptic ulceration.
16- Thromboembolic manifestations.
17- Psychological disturbances.
18- Anti-vitamin D → hypocalcemia → aggravate Osteomalacia & Osteoporosis

Preparations of commonly used glucocorticoids

Short Acting (8 – 12 H)				Intermediate Acting (12 – 36 H)							Beta & Dexa are Long acting (36 – 72 H)
Cortisone	Hydrocortisone (Cortisol)	Cortisone acetate suspension	Cortisole acetate suspension	Prednisone	Prednisolone	Methyl-Prednisolone	Cortisol Na succinate	Cortisol Na phosphate	Prednisolone 21- phosphate	Beclomethasone	Fluorinated Corticosteroids
It's inactivated Activated in liver into : **hydrocortisone** Effective after systemic administration BUT not locally .	Active & effective Effective : after systemic & local administra.	Longer Duration Effective : Oral & I.M.	Longer Duration Effective : Oral , I.M. & locally e.g. intra-articular	Stronger, longer than cortisone Activated in liver into **prednisolone** Effective : after systemic & not local use.	Stronger, longer than cortisol . Effective: Oral , I.M. & locally e.g. intra-articular	Stronger than Prednisolone.	- Soluble → I.M. & I.V. - In emergency acute addisonian crisis , status asthmatics & acute leukemia.			Inhalation in bronchial asthma	**Betamethasone** Similar to Beclomethasone **Triamcinolone** (Short Acting) **Dexamethasone** Both are potent Gluco without Mineralo – corticoids.

2- Mineralcorticoids

Aldesterone	
Des-oxy-corticosterone (DOCA)	S.L , I.M. & S.C. pellet implantation
Des-oxy-corticosterone Trimethyl Acetate	I.M.
Fludrocortisone Acetate	Orally, most convenient

Useful in replacement therapy NOT Anti-inflammatory or immunosuppressant

- Target cells for aldosterone action contain mineralocorticoid receptors that interact with the hormones in a manner analogous to that of the glucocorticoid receptor (see above).
- Mineralocorticoids help to control the body's water volume and concentration of electrolytes, especially sodium and potassium :
  →Aldosterone acts on kidney tubules and collecting ducts, causing a reabsorption of sodium, bicarbonate, & water.
  →Conversely, aldosterone decreases reabsorption of potassium, which, with H^+, is then lost in the urine
- Elevated aldosterone levels may cause alkalosis and hypokalemia, whereas retention of sodium and water leads to an increase in blood volume and blood pressure.
- Hyperaldosteronism is treated with **spironolactone**.