ENDOCRINE
PHARMACOLOGY

 # 8

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*The term steroids is usually used to represent glucocorticoids and cortisol only, while structurally speaking, androgens and aldosterone are also considered steroids because they have the common steroid nucleus.

■ **Release and transport of glucocorticoids**

Glucocorticoids receptors

PHARMACOLOGICAL EFFECTS/SIDE EFFECTS:

1. On proteins:↑ Catabolism ↓ anabolism, which leads to Osteoporosis because of the loss of proteins of bone (especially in chronic cases where glucocorticoid therapy is indicated, they produce great effects but are kept as the last option) **; steroid myopathy** (protein depletion in muscles)**; delayed wound healing; delayed peptic ulcer healing…**

2. On CHO (carbohydrates): **↑ blood sugar level (↑ gluconeogenesis; ↓ peripheral utilization of glucose)** ⟶ diabetogenic effect.

3. On lipids: *↑ lipolysis

***Fat redistribution:** it concentrates fat in the abdominal area, causing trunkal obesity, buffalo hump, and moon face.

4. On electrolytes:

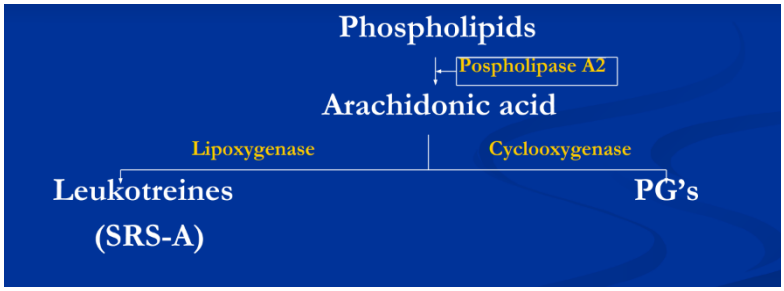
Aldosterone-like effect (water and sodium retention) which is the common side effect shared by all steroids leading to hypertension, it's the side effect we try to avoid the most while synthesizing steroid drugs.

↓ Ca++ absorption from intestine and ↑ Ca++ excretion by kidney which makes it useful for treating certain cases of hyperparathyroidism.

↑ uric acid excretion (used to treat gout)

5. Anti-inflammatory effect which is the useful effect

major mechanism:



normal inflammatory response includes converting phospholipids of membranes to arachidonic acid by the enzyme phospholipase A2, which gets converted to leukotrienes and prostaglandins, the major and most important inflammatory mediators. Glucocorticoids inhibit the enzyme

phospholipase A2, inhibiting the release of PGs and leukotrienes, hence their anti-inflammatory effect.

Other possible mechanisms by which glucocorticoids might produce their anti-inflammatory effects**:**

- Also inhibit neutrophil and macrophage function

- Inhibition of platelet activation factor (PAF)

- Inhibition of tumor necrosis factor or receptor (TNF; TNR)

- Inhibition of nitric oxide reductase…

(basically inhibiting other mediators involved in the inflammatory process, but prostaglandins and leukotrienes remain the major ones.)

6. Immunosuppressant effect

Major mechanisms :

↓ initial processing of Ag

↓Ab formation

↓ effectiveness of T-lymphocytes

↓ lymphocyte induction & proliferation

↓ lymphoid tissue including leukemic lymphocytes (antileukemic effect) used along with other anti-cancerous agents, better in that they don't cause bone marrow depletion unlike anti cancerous drugs.

7. Antiallergic effect

Suppress allergic response: ↓ histamine release, ↓ eosinophils

8. CNS manifestations: Euphoria, Psychosis

■ Glucocorticoids dosage forms

Available in all dosage forms

Available in many preparations (in any form you can think of: IM, SC, eyedrops, topical,…) however, even the topical forms can produce major side effects.

■ Structure activity relationship:

Major objective when synthesizing new steroid drugs: we try to make a structure that will **produce good anti-inflammatory effect, less or no aldosterone-like activity** as much as possible.

■ **Metabolism: In the liver by reduction and conjugation (90-95%); little hydroxylation reactions (5%)**

■ **Glucocorticoid preparations** are classified according to their duration of action:

Short-acting	Half-life	AIA	Ald.-like
Corisol	10	1	1
Cortisone	10	0.8	1
Corticosterone	10	0.3	30
Fludrocortisone	10	10	150
Intermediate-acting:			
Prednisone	20	4	0.8
Prednisolone	20	5	0.8

	Half-life	AIA	Ald.-like
Methylprednisolone	20	6	-
Triamcinolone	20	6	-
Beclomethasone	20	6	-
Long-acting:			
Betamethasone	50	25	-
Dexamethasone	50	30	-

*AIA: anti-inflammatory actions

*Do not worry about the numbers, were only put for clarification.

*Intermediate-acting are the most widely used preparations.

As mentioned previously, the most important goal we want to achieve in glucocorticoid drugs is for them to be able to produce the most anti inflammatory effect with the least aldosterone-like behavior possible. In the table above, lets take cortisol and assign to it the numbers above, for the sake of comparing it with the action of other drugs. Notice that Fludrocortisone has 150 times the aldosterone like activity for cortisol,

which is a major disadvantage, so we don't use it as a glucocorticoid rather it's used in cases of hypoaldosteronism.

Notice that the drugs in the second table have more anti inflammatory effects therefore are more potent, and are almost devoid of aldosterone like activity which meets our goal.

**** Plasma half-life; Nuclear half-life:**

the previous drugs bind to globulin in the plasma, the higher their duration of action is, the less affinity they have for globulin and the more affinity they have for nuclear receptors (the more the potency). That explains the failure of detection of drug in the blood while it's actually producing an effect inside the cells.

CLINICAL USES TO GLUCOCORTICOIDS:

You have to keep in mind that glucocorticoids are considered as a last resort and not first line therapy due to their major side effects.

1. Adrenal insufficiency (acute; chronic, Addisonian crisis, Addison's disease...) ⟶ hormone replacement therapy (HRT)

2. Inflammatory conditions (rheumatoid arthritis, SLE, arteritis, dermatomycosis, cerebral edema, ulcerative colitis, rheumatic carditis, active chronic hepatitis, proctitis, acute gout...)

3. Allergic reactions: first approach to treat allergies is giving anti-histamines **(hay fever, eczema, dermatitis), bronchial asthma** is usually treated by bronchodilators unless it's steroid-dependent type of asthma**, status asthmaticus.**

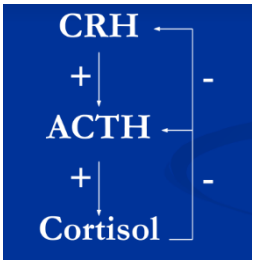
4. Immunosuppressant effect: glucocorticoids actually have less dangerous side effects compared to immunosuppressants **(organ transplantation, hemolytic anemia, leukemias, many tumors...)**

5. Hypercalcemia associated with Vit. D intoxication or sarcoidosis or hyperparathyroidism or cancer...) because they decrease the absorption of calcium and increase its excretion as mentioned before.

6.Many eye, ear, and skin diseases (allergic or inflammatory)

SIDE EFFECTS TO GLUCOCORTICOIDS:

1. Suppression of hypothalamic-pituitary-adrenal axis (major and most dangerous side effect) (the axis on the right): when the patient takes exogenous cortisol, it suppresses further release of CRH and ACTH, disrupting this axis, so the body won't synthesize endogenous cortisol anymore. That's why the medication must be stopped gradually, even if the metyrapone test indicated that the body is synthesizing its own cortisol we don't stop it at once or else it can lead to death.



2. Cushing's syndrome: the most common cause of Cushing syndrome is exogenous intake of steroids, so most of the time the disease is actually managed by stopping these medications.

3. Salt & water retention, edema, ↑ BP, obesity

4. Peptic ulcer disease and GIT ulcerations. This effect is shared by all steroids due to the inhibition of prostaglandin synthesis.

5. Osteoporosis because they increase protein catabolism.

6. Diabetes mellitus because they elevate blood glucose levels.

7. Increase incidence of viral and fungal infections due to their immunosuppressant effect.

8.↓ wound healing and skin atrophy and myopathy

9. Suppression of growth of children because of the depletion of proteins.

10. Cataract

…and many other side effects

STRATEGY IN THE USE OF GLUCOCORTICOIDS:

- Use a short-acting steroid

- Use a minimal possible dose

- Give 2/3 of the dose in morning and 1/3 in evening to try to mimic physiology as much as possible and therefore avoid side effects as much as we can, of course these doses must be reversed in people who work at night and sleep throughout the day.

- Use alternate day therapy which is associated with lee suppression to growth of children and to the hypothalamic-pituitary-adrenal axis and fewer side effects.

GOOD LUCK