ENDOCRINE SYSTEM

Pharmacology

Lec. Enter no.

WRITER: Farah Alayan & Mais Salman

CORRECTOR: Farah Thaher

DOCTOR: Suheil Zmeili

ما ينطق به الدكتور من شرح سيكون باللون الاحمر
وما يكون مهم في شرح الدكتور يكون باللون البنفسجي
ما يكون مهم في السلايدات يكون بخطين أو بخط

Adrenal Steroids
Mineralocorticoids & Glucocorticoids

- Release and transport of glucocorticoids
- Glucocorticoids receptors
- Pharmacological effects/side effects:

1. On proteins

↑ Catabolism ↓ anabolism

Cortisol increases the break down of proteins , and inhibits the build up of proteins

→ Osteoporosis (it affects the bones); steroid myopathy

(it affects the muscles) ; delayed wound healing; delayed peptic ulcer healing...

Myopathy = weakness of muscles , in this case it's due to protein degradation

2. On CHO (Carbohydrates)

↑ blood sugar level (↑ gluconeogenesis; ↓ peripheral utilization of glucose) , (Diabetogenic effect)

3. On lipids

Increases lipolysis, which leads to : Fat redistribution , rustling in easily diagnosed symptoms such as : moon face , buffalo hump , truncal obesity with striae

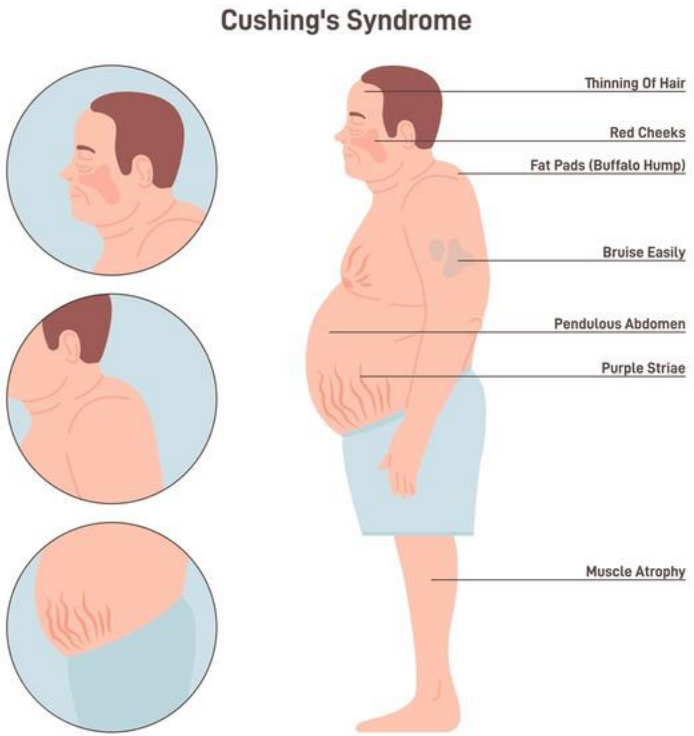
(accumulation of fat in the abdomen)

*striae = جلده متشقق من كثر الانتفاخات

4. On electrolytes

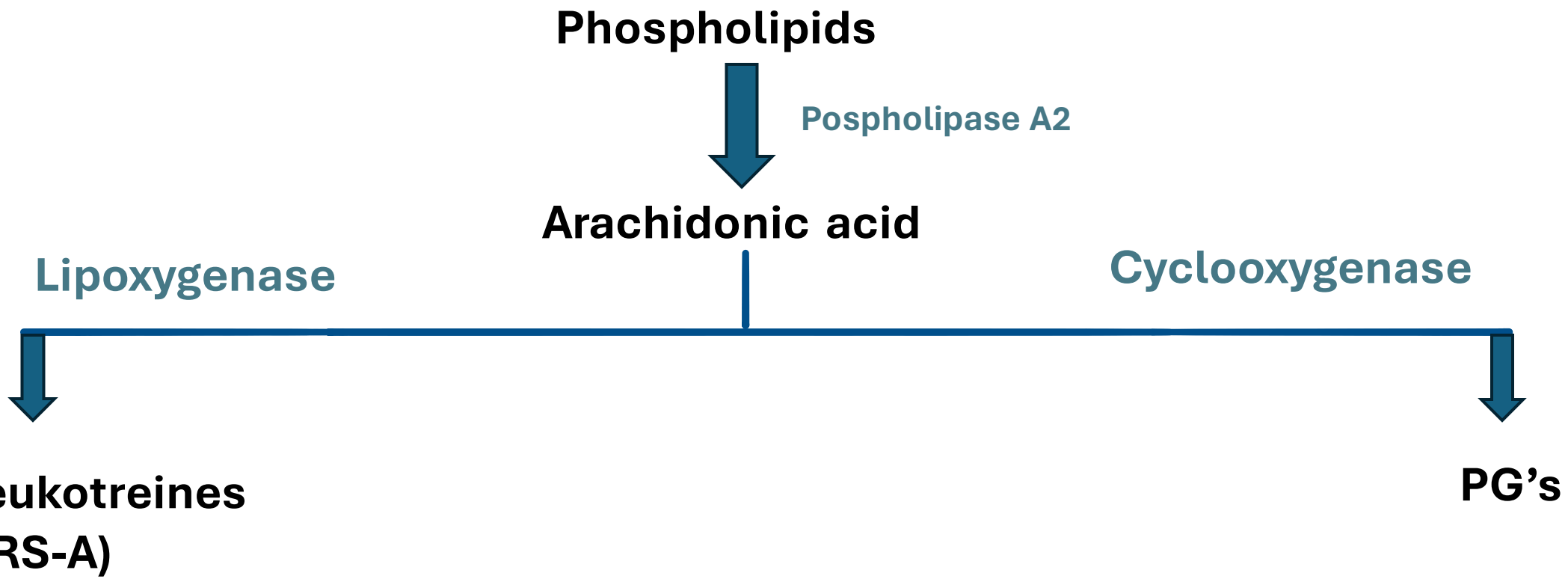
Aldosterone-like effect

- ↑ Na reabsorption
- ↓ Ca^{++} absorption from intestine
- ↑ Ca^{++} excretion by kidney (so it's used in the management of hypercalcemia in respective to Phosphorus)
- ↑ uric acid excretion (used in the management of hyperuricemia and in patients with gout)



- Antiinflammatory effect (stronger than NSAIDs)

major mechanism:



(It's responsible for the severe bronchoconstriction in patients with asthma)

SRS-A : Slow-reacting substance of anaphylaxis

As we know, prostaglandins and Leukotreines >> Are inflammatory mediators . These 2 mediators are synthesized by the enzyme (Phospholipase A2) which converts the membrane phospholipids to Arachidonic acids . Steroids produce their anti-inflammatory effect by inhibiting phospholipase A2 , so steroids inhibit BOTH pathways (steroids and Leukotreines) , whereas NSAIDs inhibit ONLY the cyclooxygenase pathway (PGs synthesis) . So Steroids are more potent anti-inflammatory agents than NSAIDs.

IT'S A MAGIC !!!!!!

- **Because NSAIDs inhibit the cyclooxygenase pathway , they shift the Arachidonic acids towards the Lipooxygenase pathway , thus producing more leukotreines , which are the main cause of bronchoconstriction in asthma patients. That's why NSAIDs ARE CONTRAINDICATED IN PATIENTS WITH ASTHMA. However, Steroids aren't contraindicated in those patients and even used as treatment (steroid dependent asthma) , because they inhibit the leukotreines formation.**
- Steroid dependent asthma: a type of asthma whereby there is a need for daily administration of oral corticosteroids to manage asthmatic attacks and flareups.

- **Prostaglandins are powerful inhibitors for gastric acid secretion, they protect the stomach from hyperacidity so they're protective against peptic ulcers.**

- **Both steroidal and non steroidal drugs are contraindicated in patients with peptic ulcer disease even in healed peptic ulcer patients.**

Other possible mechanisms explaining the anti-inflammatory effect of steroids :

1. **Also inhibit neutrophil and macrophage function**
2. **Inhibition of platelet activation factor (PAF)**
3. **Inhibition of tumor necrosis factor or receptor (TNF; TNR)**
4. **Inhibition of nitric oxide reductase…**

- Immunosuppressant effect

Major mechanisms

↓ initial processing of Ag (antigen)

↓ Ab(antibody) formation

↓ effectiveness of T-lymphocytes

↓ lymphocyte induction & proliferation

↓ lymphoid tissue including leukemic lymphocytes (antileukemic effect)

Steroids have ANTI-INFLAMMATORY, ANTI-TUMOR , ANTI- ALLERGIC AND ANTI-LEUKEMIC effects .

- Antiallergic effect

Suppress allergic response by :

↓ histamine release

↓ eosinophils

- CNS manifestations

Euphoria : feeling of well- being

Psychosis

No addiction

It’s considered the last resort in treatment

- **Glucocorticoids dosage forms**

Available in all dosage forms

Available in many preparations

Steroids are Widely used by dermatologists for skin preparations, like ointments and powders , as well as eye and ear droplets , or inhaled by bronchial asthma patients . Another one important use is intra-articulate injections (injected inside joints) and they are long acting drugs .

- **Structure activity relationship**

Major objective: Good antiinflammatory effect, less or no aldosterone-like activity

- **The main goal is to have a drug with Better pharmacokinetics and less side effects**

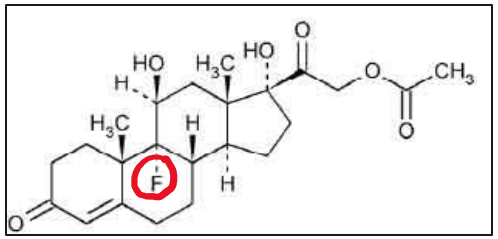
- **Metabolism:**

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

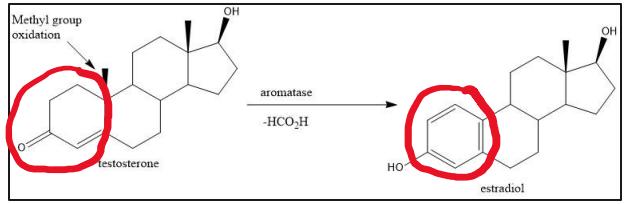
Additional pictures

Some notes related to the chemical structure of some steroids:

- Fludrocortisone ,for simplicity , we can say that it is a flourine added to steroid , this will result in high aldosterone like activity
- If we change a ring in androgens to a benzene ring it will become estrogen



Fludrocortisone



Why do we have different synthetic analogs? To have drugs with better pharmacokinetics , less side effects , act longer and more convenient to patients … Etc

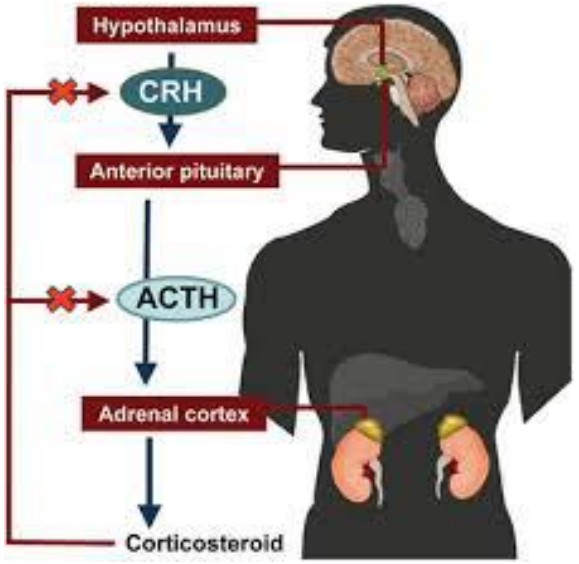
IMPORTANT !!

The Major limitation in manafacturing glucocorticoids is to have glucocorticoids that :

1- have good antiinflammatory effect

2- without aldosterone like effect

The Major side effect of glucocorticoids: suppression of hypothalamic-pituitary-adrenal axis



This note was mentioned by the doctor to show the effect of glucocorticoids:
If someone come with allergy (itching and rashes) to emergency we give him antihistamines (IM) and hydrocortisone (other name for cortisol) (IV) , within 15 min there will be complete recovery .

You do not have to memorize the numbers , you have to compare between them only

- Glucocorticoid preparations

Anti inflammatory like activity

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

Aldosterone like activity

The most widely used among all steroids

Although it has more anti inflammatory effect than cortisol, it has a very high aldosterone like activity, because of this ➡ we do NOT use them as anti inflammatory drug instead , we use it in case of hypoaldosteronism

Remember:
The Major limitation in manafacturing glucocorticoids is to have glucocorticoids that :
1- good antiinflammatory effect
2- without aldosterone like effect

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

All these drugs have higher anti inflammatory effect and zero aldosterone like activity

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

The doctor mentioned here that low levels of steroids in blood does not indicate low activity , some steroids have long Nuclear half lives so it may be low in plasma but acting in nucleus .

!!As we said the major limitation is aldosterone like activity so we are looking for drugs that have good anti inflammatory effect without aldosterone like activity

- **Clinical uses to glucocorticoids:**

- Adrenal insufficiency (acute; chronic, Addisonian crisis, Addison's disease…) Replacement therapy: the axis is deficient so no worries if it will inhibit it ☺

Will be explained in the next slide

- Inflammatory conditions (rheumatoid arthritis, SLE, arteritis, dermatomycosis, cerebral edema , ulcerative colitis, rheumatic carditis, active chronic hepatitis, proctitis, acute gout…) Used in almost all inflammations ..The Magical drug!!

- Allergic reactions (hay fever, eczema, dermatitis), bronchial asthma, status asthmaticus , attacks of bronchoconstriction

Cerebral edema : pay attention that the case of edema here is inflammatory and NOT related to salt and water retention, so we need drugs that minimize this inflammatory edema (drugs with anti inflammatory effect)

Additional : Do not use drugs that have aldosterone like activity, they will cause salt and water retention and thus increase edema !

- Immunosuppressant effect (organ transplantation, hemolytic anemia, leukemias, many tumors…)
- Hypercalcemia associated with Vit. D intoxication or sarcoidosis or hyperparathyroidism or cancer…)
- Many eye, ear, and skin diseases (allergic or inflammatory)

• Side effects to glucocorticoids:

- Suppression of hypothalamic-pituitary-adrenal axis

(major and most dangerous side effect) (معلومة مهمة جداً جداً)

organ transplantation to suppress immunity, associated with many side effects .

Hypercalcemia : by inhibiting reabsorption of calcium from intestine and increasing calcium execretion by the kidneys

Tumors : Cancers are never treated with a single drug. It is usually a combination of different drugs, because some cancers have some resistance (defense mechanisms to drugs especially in leukemia and lymphoma. Usually we use anti cancerous agents with glucocorticoids. Anti cancerous agents could suppress bone marrow unlike glucocorticoids.

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

Here we start first with simple drugs

For example if the eye appears red due to allergy start first with anti histamine drugs, the improvement will not be right away like steroids.

Do not use steroids as first drug ,because Cushing syndrome has been reported with the use of steroids locally

- Cushing's syndrome (The major cause of cushing's syndrome is drug induced)

- Salt & water retention, edema, ↑ BP, obesity (due to aldosterone like activity)

- Peptic ulcer disease and GIT ulcerations (because it inhibits prostaglandins)

- Osteoporosis (catabolism of proteins)

- Diabetes mellitus (because it causes hyperglycemia)

- ↑ incidence of viral and fungal infections (because of immune suppression)(No antibacterial effect)

- ↓ wound healing and skin atrophy and myopathy

- Suppression of growth of children (due to its effect on proteins)

- Cataract...

- **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

- 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

- Don’t stop glucocorticoid therapy abruptly

Past Paper

• The following is a side effect shared by all steroids:

A. Peptic ulcers.
B. Virilization.
C. Feminization.
D. Salt water retention and hypertension.
E. Osteoporosis.

Answer: D

The following is considered the major and most dangerous side effect to glucocorticoids (e.g. cortisol):

A. Ulcers in the stomach.
B. Salt and water retention due to aldosterone-like activity.
C. Suppression to hypothalamus-pituitary-adrenal axis.
D. Osteoporosis.
E. Psychosis.

Answer: C

Which of the following is unlike the others in its mechanism of action:

A. Triamcinolone.
B. Prednisolone.
C. Cortisol.
D. Dexamethasone.
E. Metyrapone.

Answer: E

☐Glucocorticoids have all of the following pharmacological effects EXCEPT:

☐A. Antibacterial effect.
☐B. Antiinflammatory effect.
☐C. Antiallergic effect.
☐D. Immunosuppresant effect.
☐E. All answers are correct.

☐Answer: A

Regarding the pharmacological actions of steroids, which is false:

A. Glucocorticoids used to suppress inflammation.
B. Glucocorticoids used to suppress allergy.
C. Beclomethasone is better used orally than topically.
D. Glucocorticoids used in cases of tissue transplantation and lymphopoiesis.
E. Glucocorticoids used in cases of eye and skin inflammations.

Answer: C

Which of the following glucocorticoids has the best anti inflammatory effect without suppressing hypothalamic-pituitary-adrenal axis:

A. Dexamethasone.
B. Triamcinolone.
C. Cortisol.
D. Prednisone.
E. None of the above.

Answer: E