Pharmacology of corticosteroids

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BY

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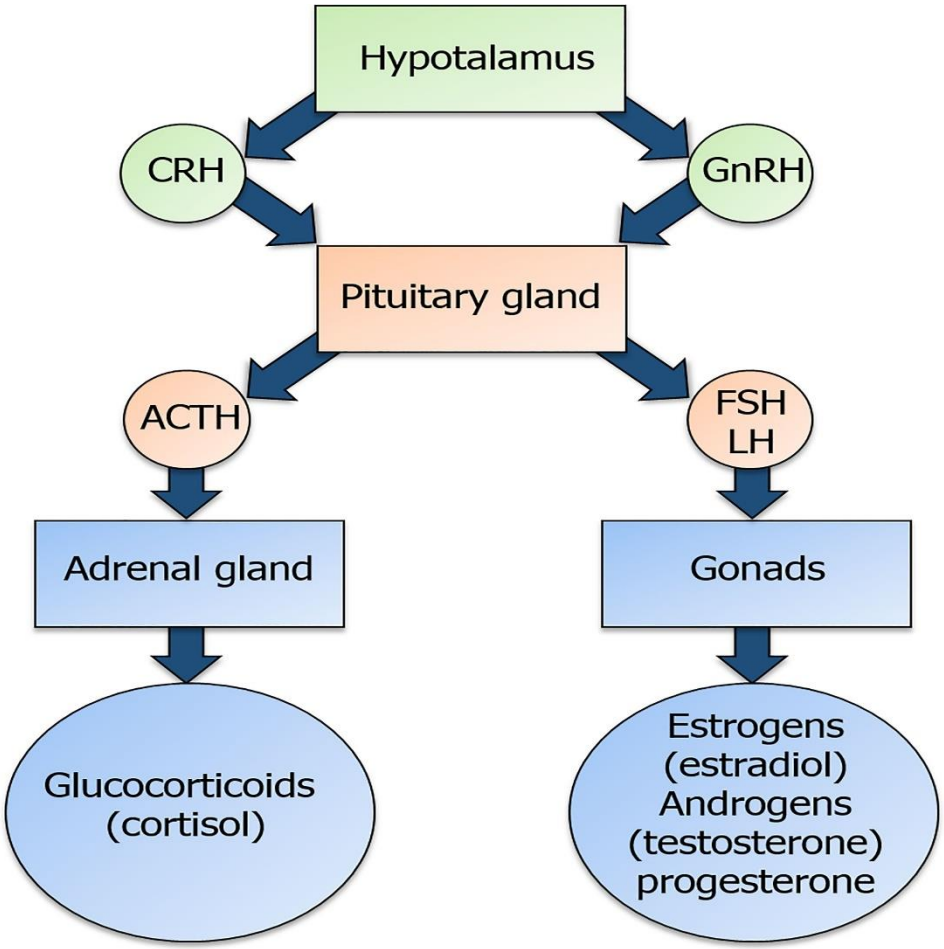
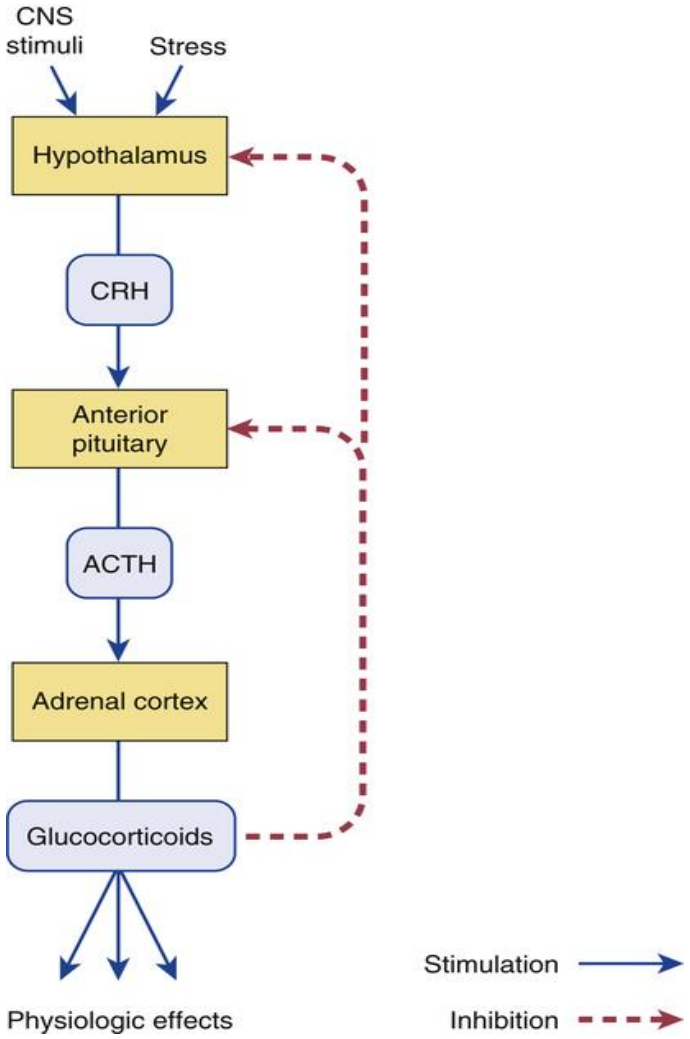

Hypotalamus
CRH
GnRH
Pituitary gland
ACTH
FSH
LH
Adrenal gland
Gonads
Glucocorticoids
(cortisol)
Estrogens
(estradiol)
Androgens
(testosterone)
progesterone


CNS
stimuli
Stress
Hypothalamus
CRH
Anterior
pituitary
ACTH
Adrenal cortex
Glucocorticoids
Physiologic effects
Stimulation
Inhibition

- **Pharmacokinetics:**
- They are readily absorbed form the gastrointestinal tract (oral).
- Selected compounds can also be administered intravenously, intramuscularly, intra-articularly, topically, or aerosol.
- Greater than 90% of the absorbed glucocorticoids are bound to plasma proteins, most to either corticosteroid-binding globulin (85%) or albumin (10%) free drug or bound to other plasma proteins (5%).
- Corticosteroids are **metabolized** by the liver microsomal-oxidizing enzymes.
- The metabolites are conjugated to glucouronic acid or sulfate and then excreted by the kidney.
- **Prednisone** is preferred in pregnancy because it has minimal effects on the fetus.

Mechanism of action:

- **N.B:**

This mechanism requires time to produce **delayed effect**, while **glucocorticoids have immediate effects (non-genomic effects)**, such as relaxation of bronchial smooth muscle or lipolysis.

Preparations:

Corticosteroid	Gluco-	Mineralo-	Daily requirements
A) Short Acting (8-12Hours):			
1- Cortisol	1	1	20 mg
2- Cortisone (pro-drug)	0.8	0.8	25 mg
B) Intermediate Acting (12 - 36 Hours):			
1- Prednisone (pro-drug)	4	0.8	5mg
2- Prednisolone	4	0.8	5mg
3- Methyl-Prednisolone	5	0.5	4mg
4- Triamcinolone	5	N0	4mg
C) Long Acting (36 - 72 hours):			
1- Betamethasone	25	N0	0.75 mg
2- Dexamethasone	25	N0	0.75 mg
D) Mineralocorticoids:			
1- Aldosterone	±	500	Not used
2- D.O.C.A. (desoxycorticosteron)	N0	50	S.L. 2 - 6 mg
3- Fludrocortisone (12-36 hours)	10	125	Oral0.1-0.3mg

Pharmacological actions :

1- Pharmacological actions of glucocorticoids:

1- Metabolic and systemic effects

2- Increases resistance to stress

3- Blood

4- Anti-inflammatory and immunosuppressive effects.

5- others

2- Pharmacological actions of mineralocorticoids

1- Metabolic and systemic effects:

- **Carbohydrates:**

1- Decrease the uptake and utilization of glucose(decreases peripheral glucose utilization)

2- Increase gluconeogenesis→**hyperglycemia.**

- **Protein: (catabolic)**

Decrease protein synthesis and increased protein breakdown, particularly in muscle, and this can lead to **wasting (thin limbs).**

Metabolic and systemic effects

- **Lipids:**

Lipolysis: lipase activation through a **cAMP-dependent kinase**.

Large doses of glucocorticoids given over a long period result in the redistribution of body fat characteristic of **Cushing's syndrome (moon face, buffalo hump).**

Metabolic and systemic effects

- **Minerals:**

A **negative calcium balance** by decreasing Ca2+ absorption in the gastrointestinal tract and increasing its excretion by the kidney. This may result in **osteoporosis.**

- **In non-physiological concentrations**, the glucocorticoids have some **mineralocorticoid** actions, causing **Na+ & water retention and K+ loss.**

2- Increases resistance to stress through:

- By **raising plasma glucose levels**, glucocorticoids provide the body with the energy required to combat stress caused, by trauma, fear, infection, bleeding or debilitating disease.
- **Rise in blood pressure**
- 1- Enhancing the vasoconstrictor action of catecholamines on small vessels.
- 2- Salt and water retention
- **Anti-shock activity**: raising blood pressure, anti-inflammatory and anti-histaminic effects

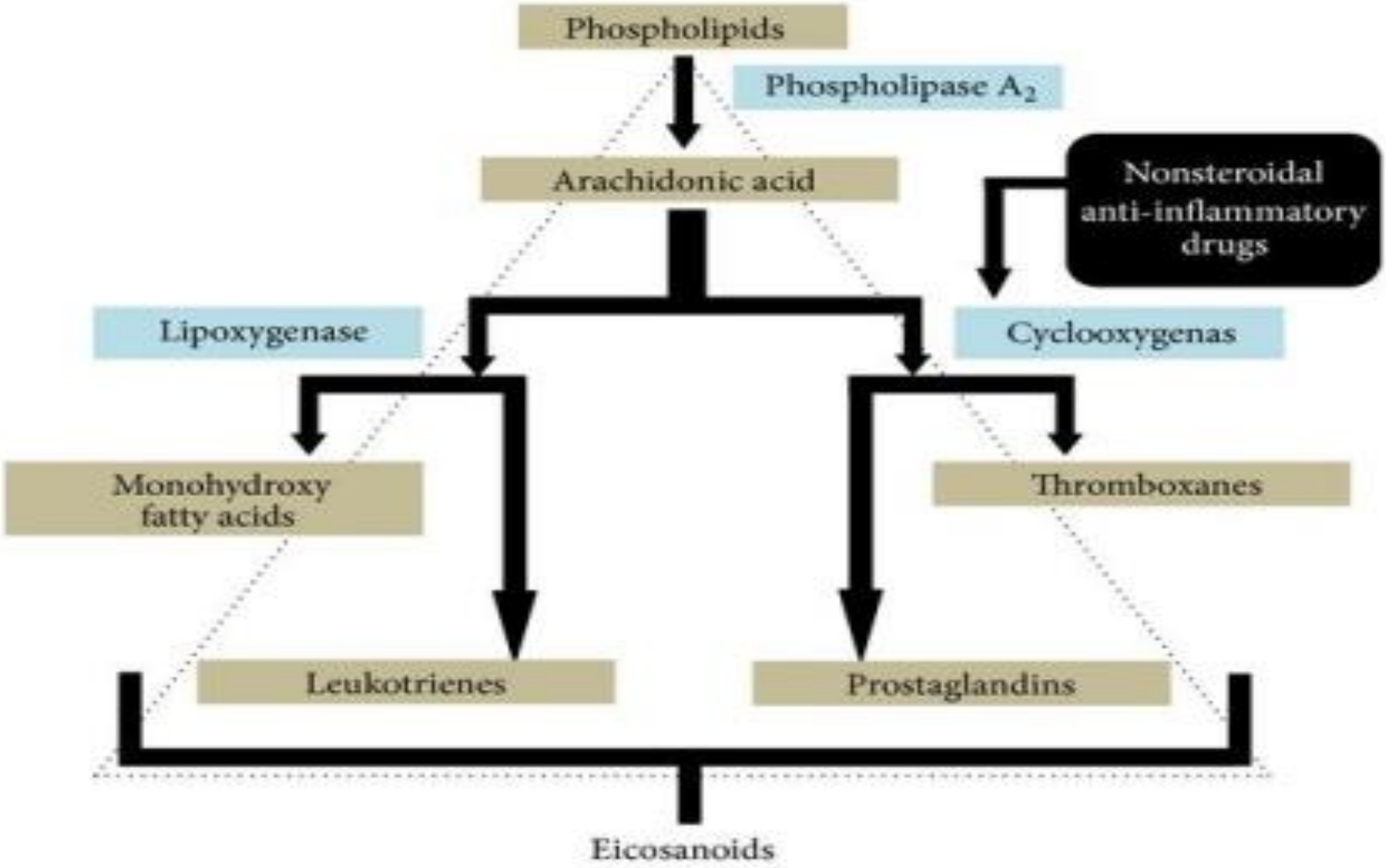
3- Blood:

- **Decrease in** eosinophils, basophils, monocytes and lymphocytes.
- **Increase** erythrocytes and polymorphonuclear(neutrophils)
- **Increase** platelets and coagulation factors
- **Increase** plasma lipids

4- Anti-inflammatory and immunosuppressive effects:

They can dramatically **reduce the inflammatory response** and to suppress immunity, through:

- **a. Inhibition of phospholipaseA2**, thus blocks the release of arachidonic acid, the precursor of the inflammatory mediators prostaglandins and leukotrienes from membrane-bound phospholipids.COX-2 synthesis in inflammatory cells is reduced, **lowering the availability of prostaglandins.**
- **b. Lowering and inhibition of peripheral lymphocytes** and macrophages that compromises the body ability to fight infection(decrease antibody formation ,antigen antibody reaction, release of cytokine from T-cells, stabilization of lysosomal membranes).
- **c.** Glucocorticoids **interfere with mast cell degranulation** results in decreased histamine release and capillary permeability.



Corticosteroid inhibits phospholipaseA2

5- Others:

- **Adequate** glucocorticoid levels are essential for **normal glomerular filtration.**
- **High doses** stimulate gastric acid and pepsin production leading to **peptic ulcer.**
- Glucocorticoids can influence **mental and psychic status (euphoria in early doses followed by depression).**
- **Eye:** increase IOP
- **Bone:** catabolic and decreasing bone calcium
- **Growth:** growth retardation in children due to catabolic effect and inhibition of GH release

Therapeutic uses of corticosteroids:

1)Replacement therapy for

- Primary adrenocortical insufficiency (Addison's disease)
- Secondary adrenocortical insufficiency
- Congenital adrenal hyperplasia

2) Relief of inflammatory symptoms:

3) Anti-allergic: bronchial asthma, allergic rhinitis

4) immunosuppressive: autoimmune disease and graft rejection

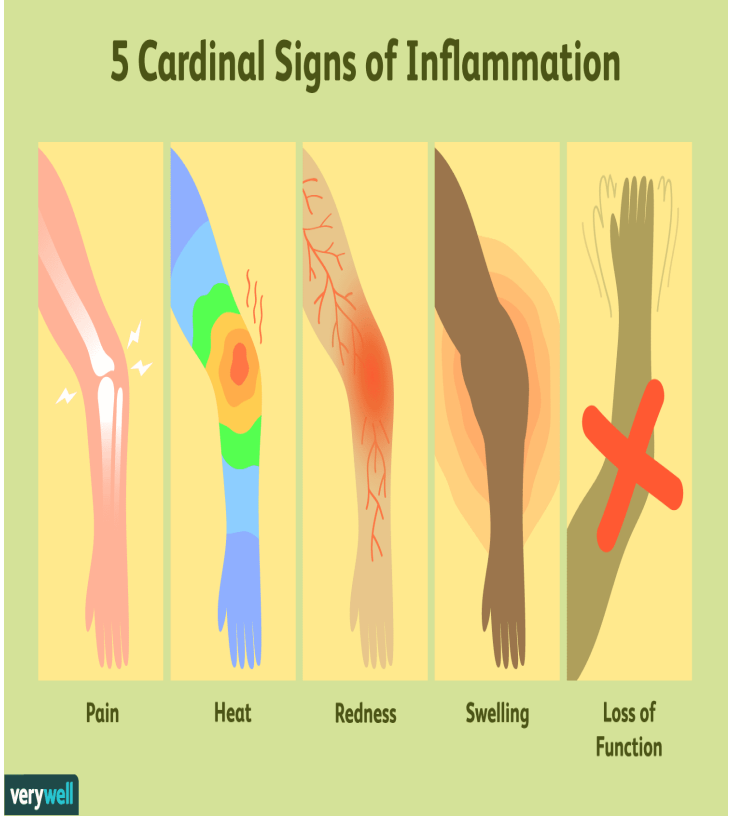
5) Acceleration of lung maturation:

6) Shock and hypotension

7) Malignant tumors

Relief of inflammatory symptoms:

- Glucocorticoids dramatically ↓↓ **manifestations of inflammation** including redness, swelling, hotness and tenderness that are commonly present at the inflammatory site.
- AS in cases of rheumatoid and osteoarthritis as well as inflammatory conditions of the skin



Acceleration of lung maturation:

- Fetal cortisol is a regulator of lung maturation.
- Two doses of **betamethasone** are administered intramuscularly or IV to the mother 48& 24 hours before delivery.

N.B

- Time of administration: 6-8 AM: mimic circadian rhythm
- When **large doses** of glucocorticoids are required for more than 2 weeks suppression of the HPA axis and adrenal atrophy occurs, avoided by: **alternate-day therapy**
- This schedule allows the HPA axis to recover/function on the days the hormone is not taken.
- **gradual withdrawal** is indicated if glucocorticoids administered more than 3 weeks.

Adverse Effects of Glucocorticoids: (CORTICOSTEROIDS+2 hyper+2hypo+2m)

1. **C-** Iatrogenic **C**ushing's syndrome (moon face, buffalo hump).
2. **O-** **O**steoporosis; Collapse of vertebrae & fracture neck of femur.
3. **R-** **R**etardation of growth in children.
4. **T-** **T**eratogenicity (less with prednisone): cleft balat
5. **T-** **T**hromboembolic manifestations.
6. **I-** **I**mmunosuppressant;↑ Susceptibility to infection, flare up present infection & reactivation of latent T.B. lesion.

7- C- Cataract &↑ Intra-ocular pressure; Glaucoma.

8- O- Oedema & weight gain.

9-S- suppresion of hypothalamic- pituitary- adrenal axis, so Abrupt withdrawal after long use lead to acute Addisonian crisis.

10- T- Thinning and ulceration of gastric mucosa (Peptic ulceration).

11-Hyperglycemia → Worsens Diabetes mellitus due to their Anti-Insulin effect.

12-Hypertension → May lead to Heart failure.

13-Hypokalemia → Worsens Digitalis toxicity

14-Hypo*calcemia*→ *Osteomalacia & Osteoporosis*

15-Moon face & Buffalo hump..

16-Myopathy & muscle weakness.

18-Depresion

19-Delays healing of wounds.

Contraindications of Glucocorticoids:

- **1- Abrupt withdrawal.**
- **2- Cushing's disease.**
- **3- Diabetes mellitus.**
- **4- Osteoporosis.**
- **5-Hypertension & Heart failure**
- **6- Uncontrolled infection: esp. viral and TB (ABSOLUTE)**
- **7- Peptic ulcer.**
- **8- Thromboembolic diseases.**
- **9- Psychological disturbance**
- **10- During pregnancy (EARLY).**
- **11- Glaucoma.**

References

Lippincott's Illustrated Review

Pharmacology, 5th edition

Lippincott Williams & Wilkins

Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters .*

last edition McGraw Hill,

Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M. Ritter ; Rod Flower Churchill Livingstone; 6 edition*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