Pharmacology of glucocorticoids by

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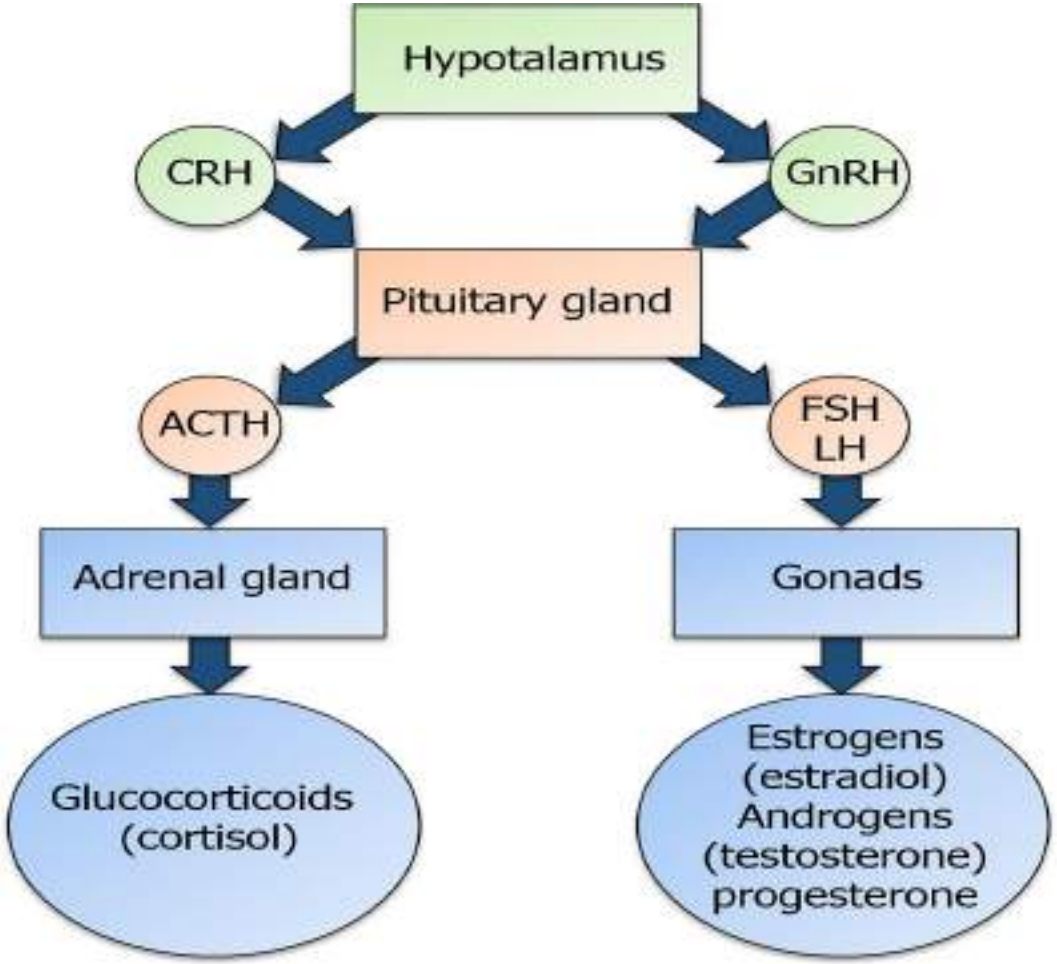
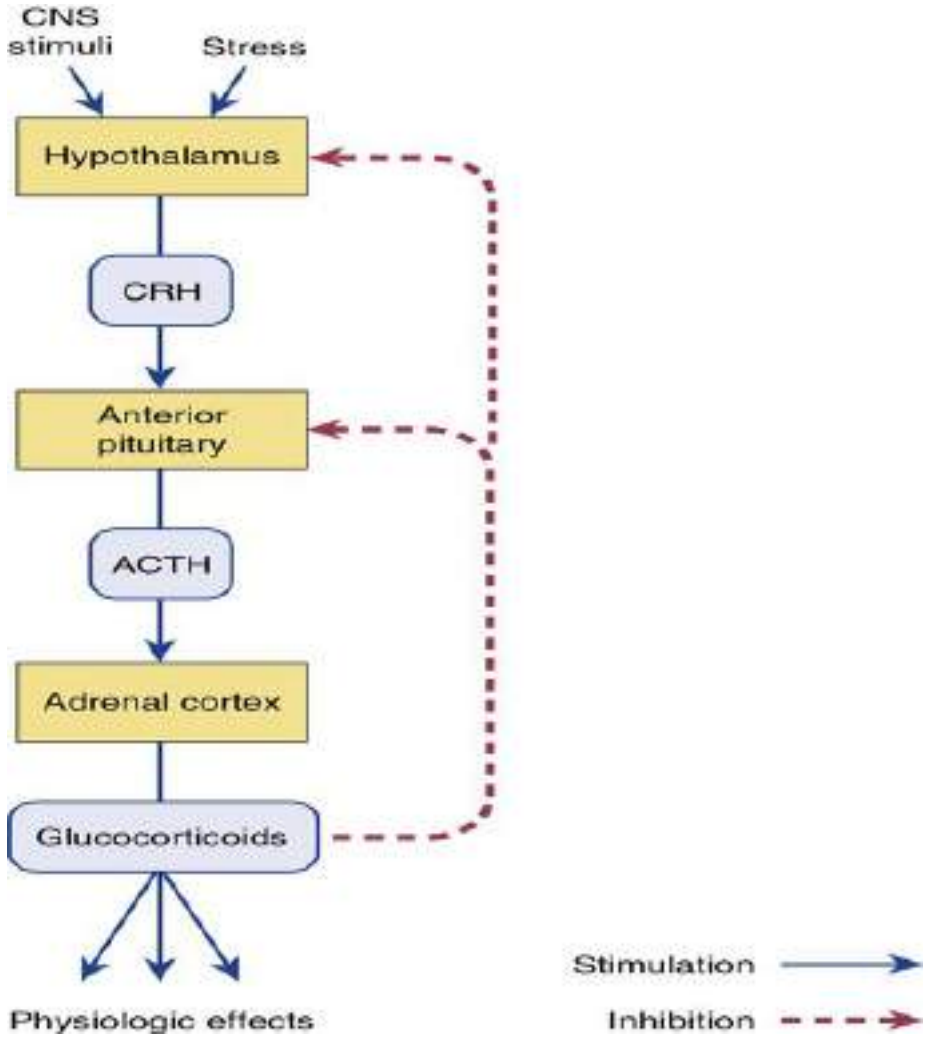
Objectives

- 1- Glucocorticoids pharmacokinetics
- 2- Mechanism of action of glucocorticoids
- 3- Glucocorticoid preparations
- 4- Pharmacological actions of glucocorticoids
- 5- Therapeutic indications
- 6- Can time of administration affect glucocorticoid action?
- 7- Adverse effects
- 8- Contraindications

Regulation of glucocorticoid synthesis and secretion

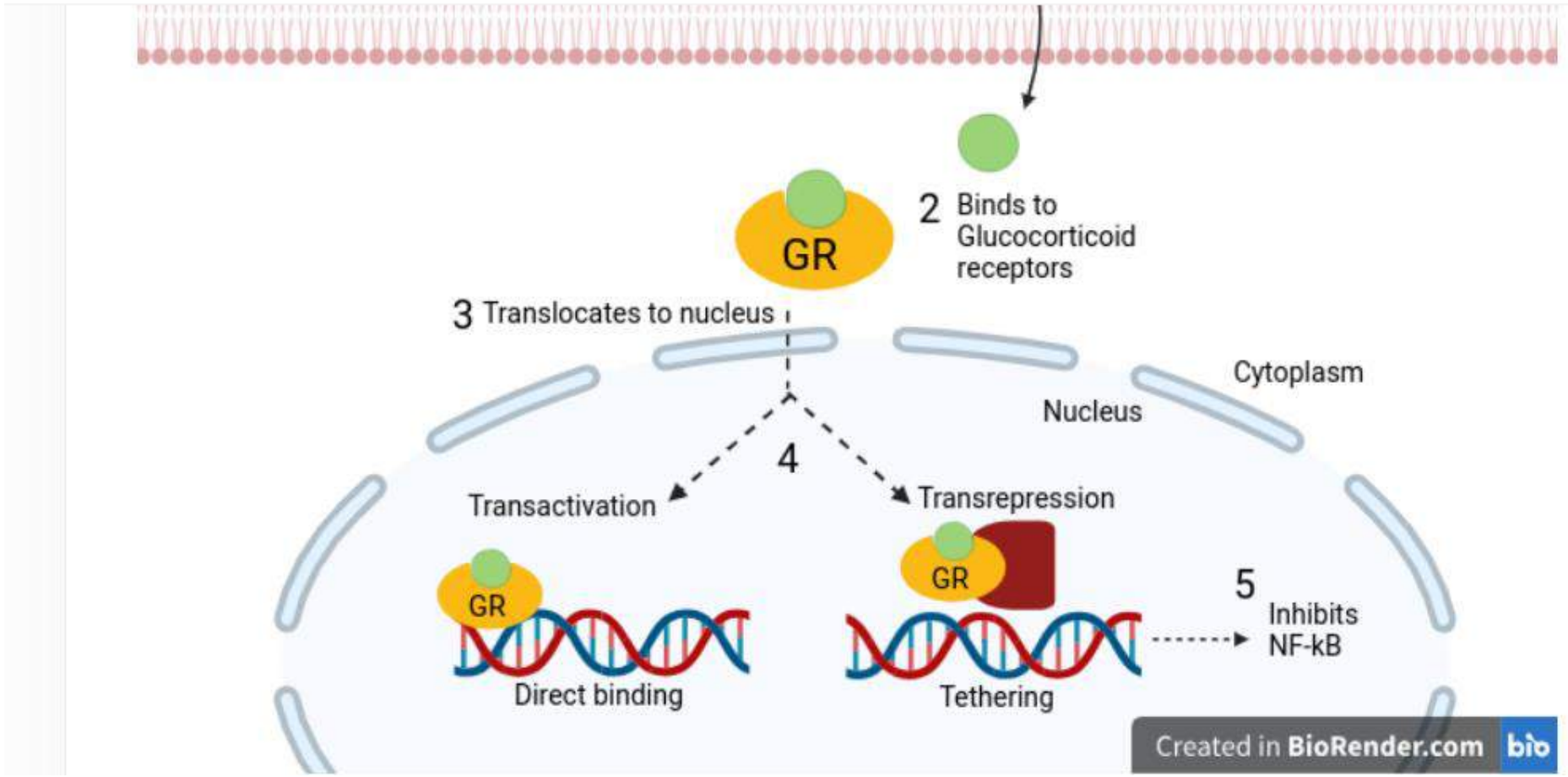




Pharmacokinetics

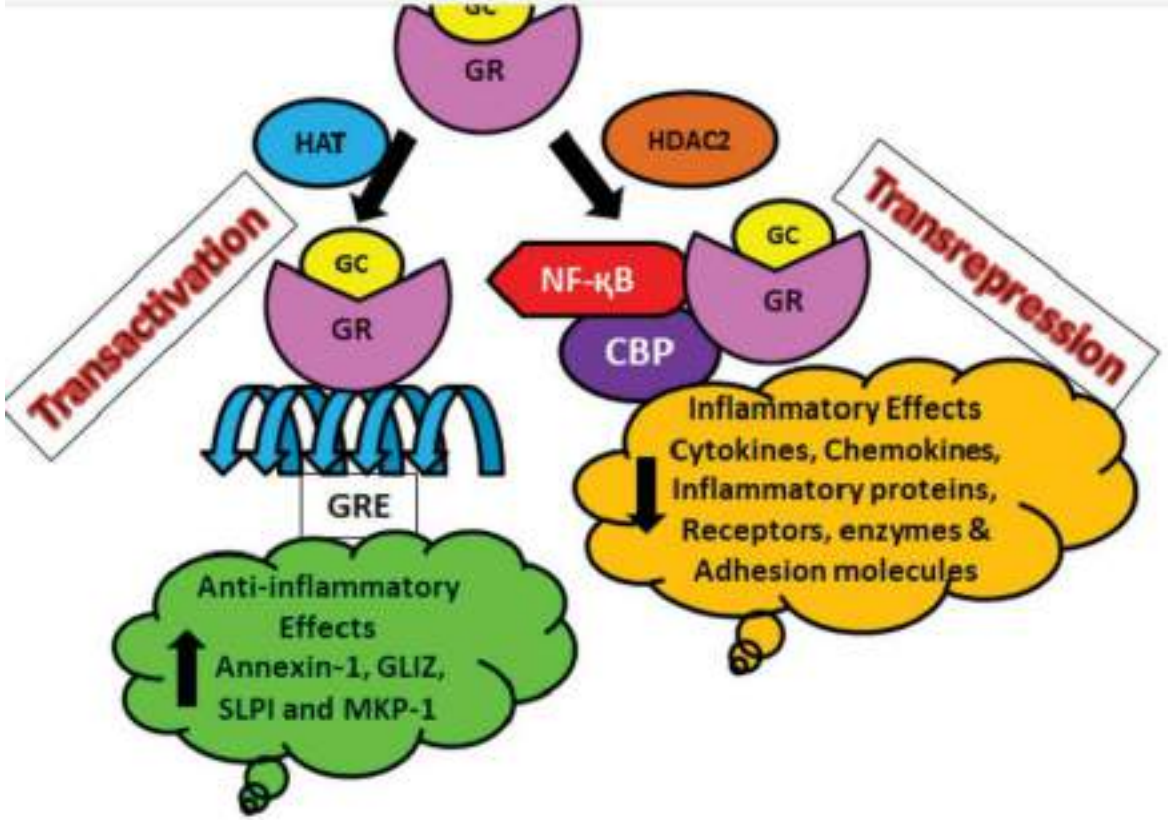
- **Absorption:**
- **Oral** absorption is **good**
- **Routes of administration:**
- intravenously, intramuscularly, intra-articular OR periartecular, topically, or aerosol.
- **Distribution:**
- **More than 90% of the absorbed glucocorticoids are bound to plasma proteins**:
- **Most** to either **corticosteroid-binding globulin** or **albumin (transcortin): (85%)**
- Bound to other plasma proteins **(5%).**
- **(10%) free drug**
- **Metabolism:**
- By the **liver** microsomal-oxidizing enzymes.
- The metabolites are **conjugated to glucouronic acid or sulfate**
- **Excretion:** excreted by the **kidney.**
- **N.B.**
- **Prednisone** is **preferred in pregnancy because it has minimal effects on the fetus.**

Mechanism of action



Mechanism of action

- **Glucocorticoids modulates the transcription rates of glucocorticoid-responsive genes positively or negatively.**



Preparations

	Glucocorticoid	Mineralocorticoid
Cortisol (hydrocortisone)	1	1
Prednisolone	4	0.8
Dexamethasone	30	Negligible
Betamethasone	30	Negligible
Aldosterone	0	80
Fludrocortisone	10	125

Glucocorticoid Preparations

Duration of action	Anti-Inflam potency
Short acting (< 12 hr)	
Hydrocortisone (identical to cortisol)	1
Topical use	
Intermediate acting (12 – 36 hr)	
Prednisolone and Prednisone	4
Methylprednisolone (has lipid antioxidant activity)	5
Triamcinolone	5
Alternate day administration	
Long acting (48 hr)	
Dexamethasone	30
Betamethasone	30
Highly potent glucocorticoids	

Pharmacological actions

1- Pharmacological actions of glucocorticoids:

1- Metabolic and systemic effects
2- Increasing 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**.

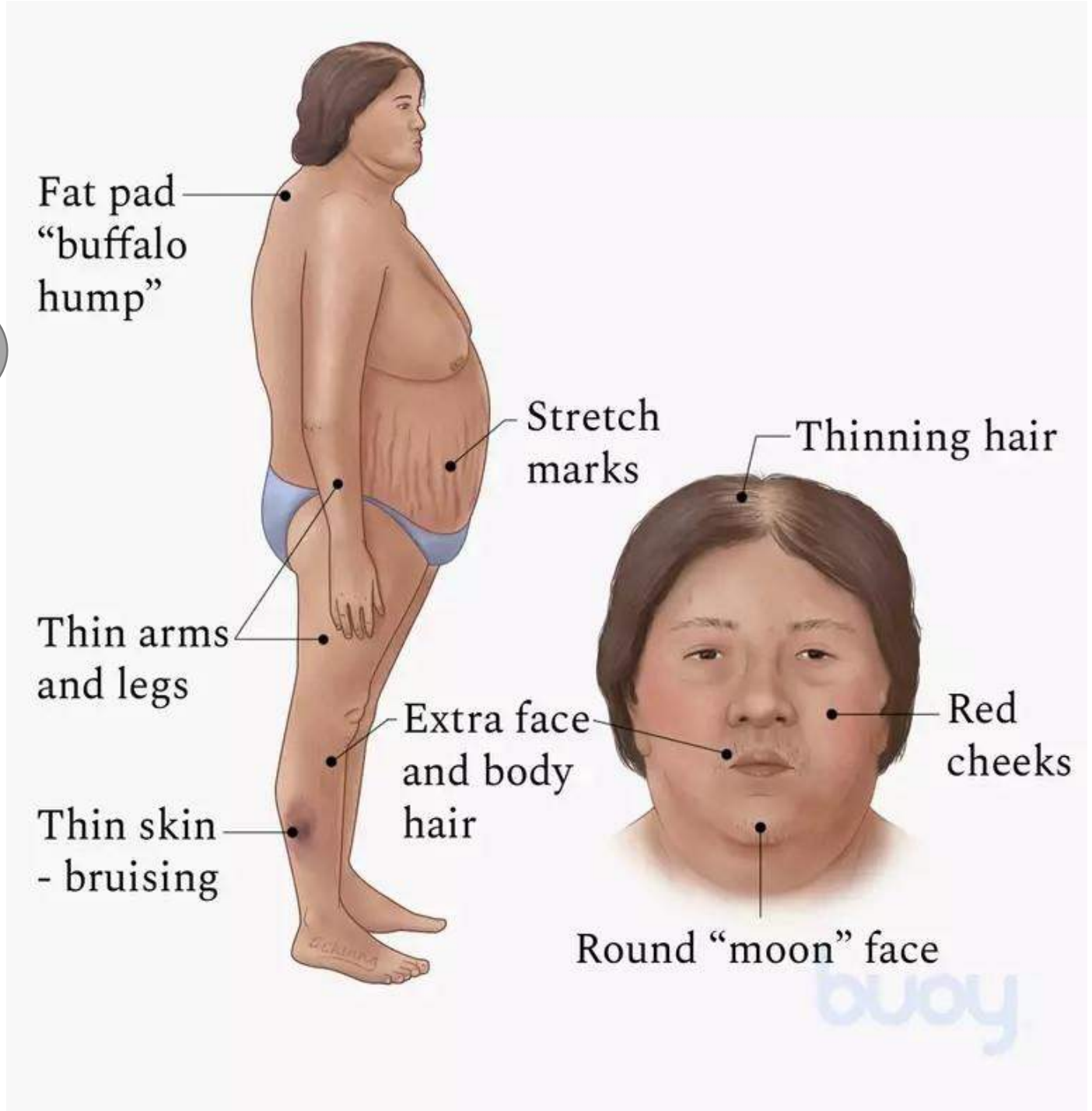
•**Protein: (catabolic)**

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

•**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).**

واحده أخذت cortisone بدها تنصح شوى و صار فيها هيك



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- Increasing 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 (obesity), very warm or cold temperatures**.

•**Rise in blood pressure**

•1- Enhancing the vasoconstrictor action of catecholamines on small vessels.

•2- Salt and water retention (mineralocorticoid action)

•**Anti-shock activity**: raising blood pressure, anti-inflammatory and anti-histaminic effects

3- Blood

- **Decrease in** eosinophils and lymphocytes.
- **Increase** erythrocytes and polymorphs (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 phospholipase A2**, thus blocks the release of **arachidonic acid,** the **precursor of the inflammatory mediators** prostaglandins and leukotrienes from membrane-bound phospholipids.

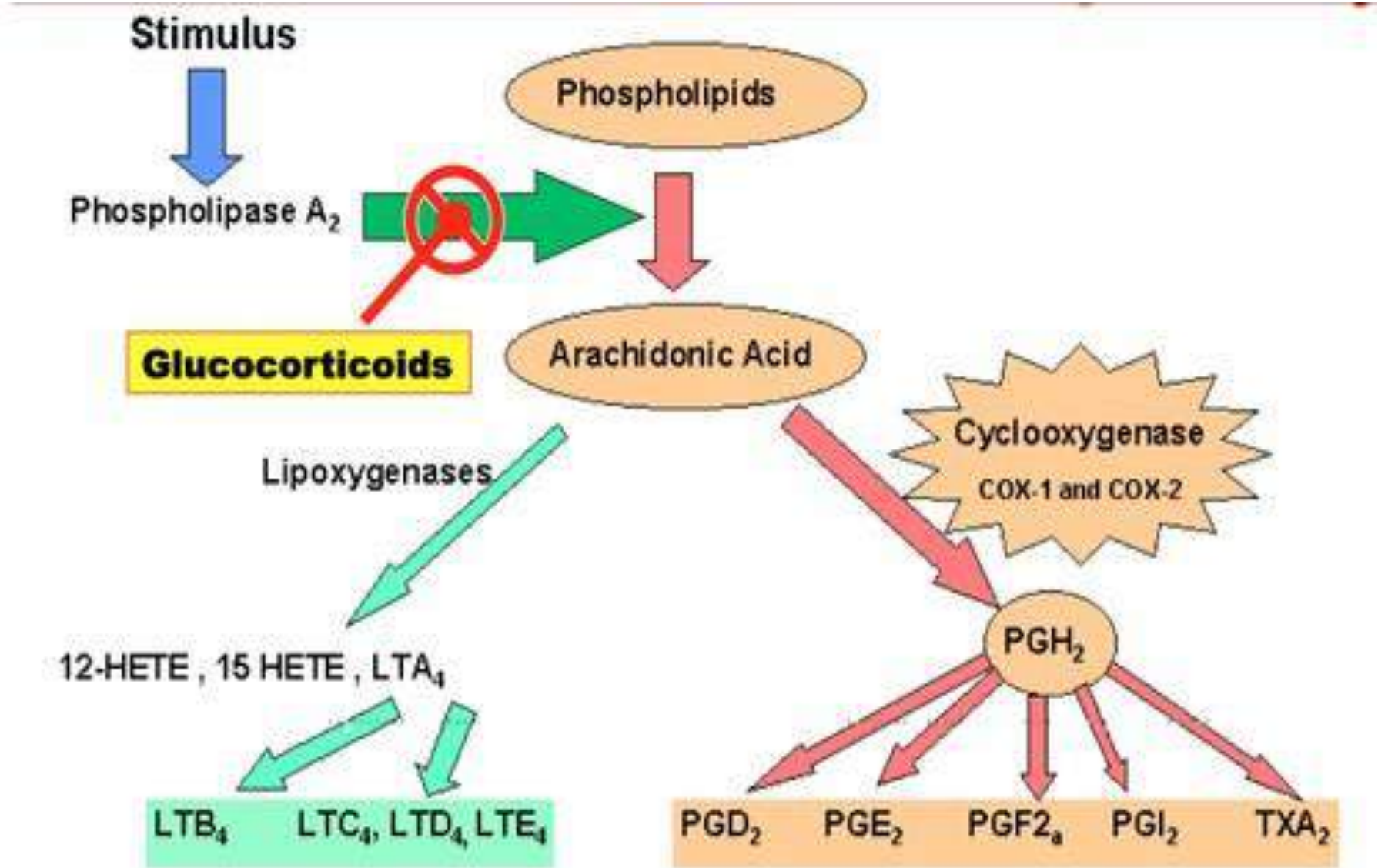
- **COX synthesis** in inflammatory cells is reduced, **lowering the availability of prostaglandins.**

B. Lowering and inhibition of peripheral lymphocytes and macrophages: decreasing 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.

Anti-inflammatory effects of glucocortecoids

- ↓ **leukocyte migration**
- ↓ **capillary permeability**
- ↓ **phagocytosis**
- ↓ **platelet-activating factor**
- ↓ **interleukins (e.g. IL-2)**
- May **trigger apoptosis** in **dividing and non-dividing cells**
- Used in **cancer chemotherapy**
- **Clinical use:**
- Anti-inflammatory
- Immunosuppression
- Cancer chemotherapy (**prednisone** most common)


Stimulus
Phospholipids
Phospholipase A_2
Glucocorticoids
Arachidonic Acid
Lipoxygenases
Cyclooxygenase
COX-1 and COX-2
12-HETE , 15 HETE , LTA_4
PGH_2
LTB_4
LTC_4, LTD_4, LTE_4
PGD_2
PGE_2
$PGF2_a$
PGI_2
TXA_2

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: Osteoprosis
- **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 GVH (graft-versus- host) disease

5) Acceleration of lung maturation

6) Shock and hypotension

7) Cancer chemotherapy

Relief of inflammatory symptoms

•Glucocorticoids **dramatically decrease of manifestations of inflammation** including redness, swelling, hotness and tenderness that are commonly present at the inflammatory site.

•**Examples**: **rheumatoid** and **osteoarthritis** and **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 (or in the umbilical cord) 48& 24 hours before delivery.

•**N.B.** **betamethasone is preferred to dexamethasone** because it is less plasma protein bound.

Time of administration of glucocortecoids

- **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 (dose tapering)** is indicated if glucocorticoids administered **more than 3 weeks**.

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

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: 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-Depression

19-Delays healing of wounds

Contraindications of Glucocorticoids (abcd & ghout)

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

References

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Thank you