Pharmacology of corticosteroids
II
BY

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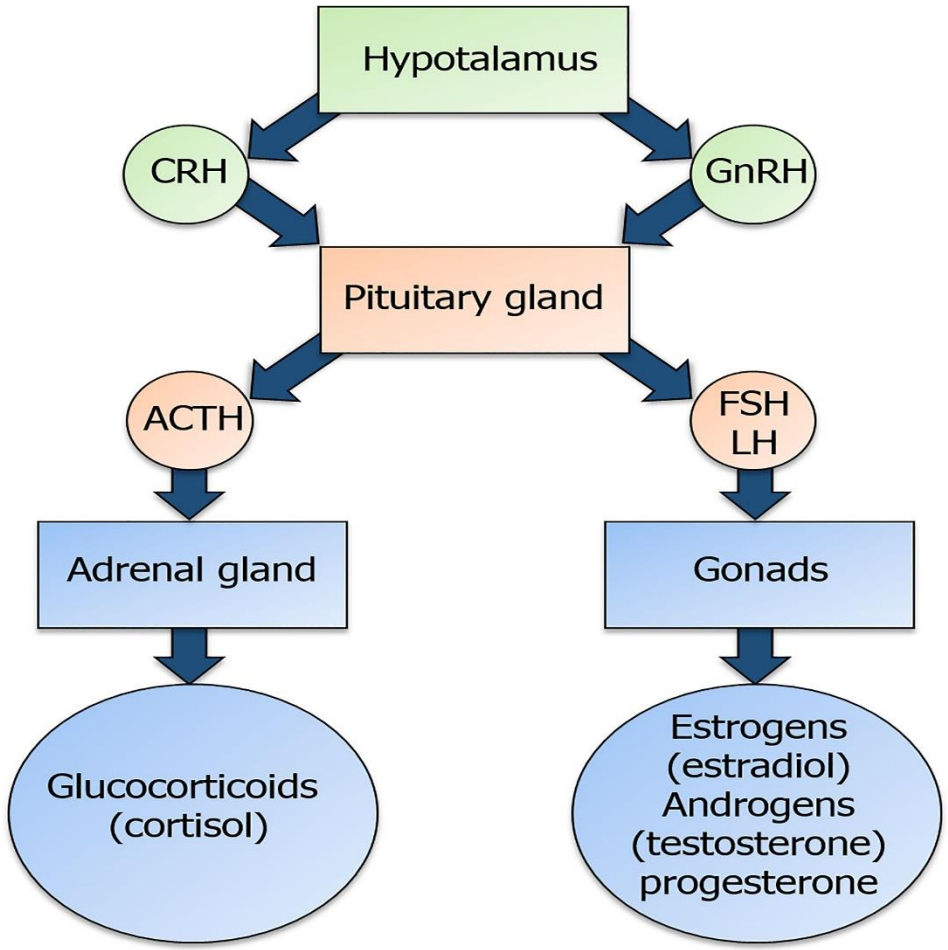
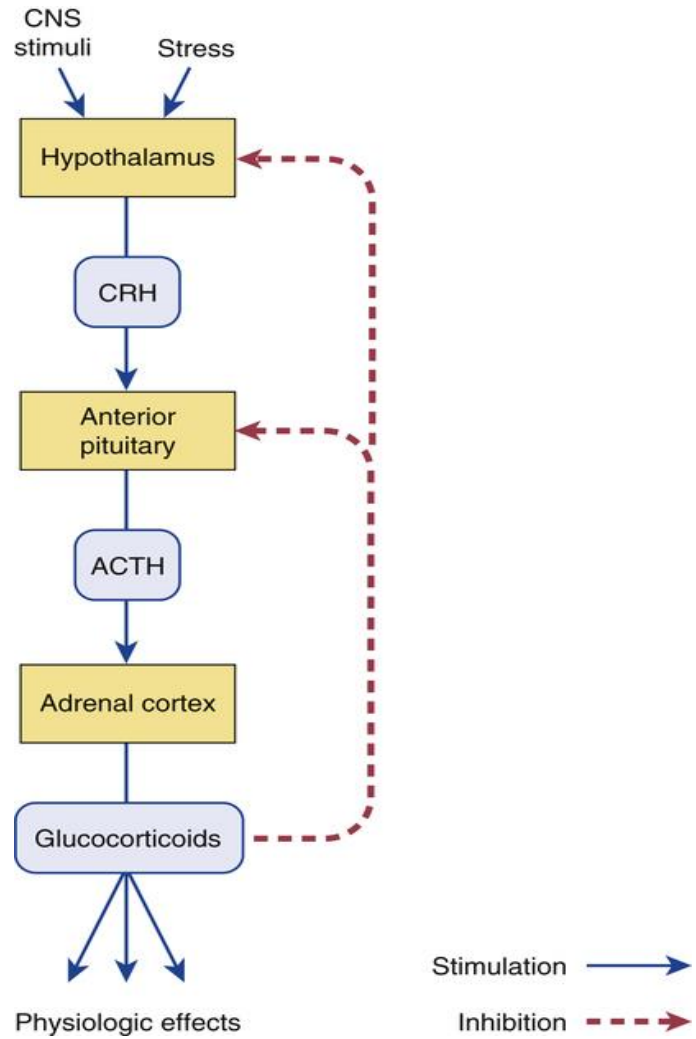
Objectives

- 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


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:

•**Absorption:**

•Oral absorption is good

•Some preparations are administered: 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 (85%) or albumin (transcortin)

•bound to other plasma proteins (5%).

•(10%) free drug

•**Metabolism:** by the liver microsomal-oxidizing enzymes.

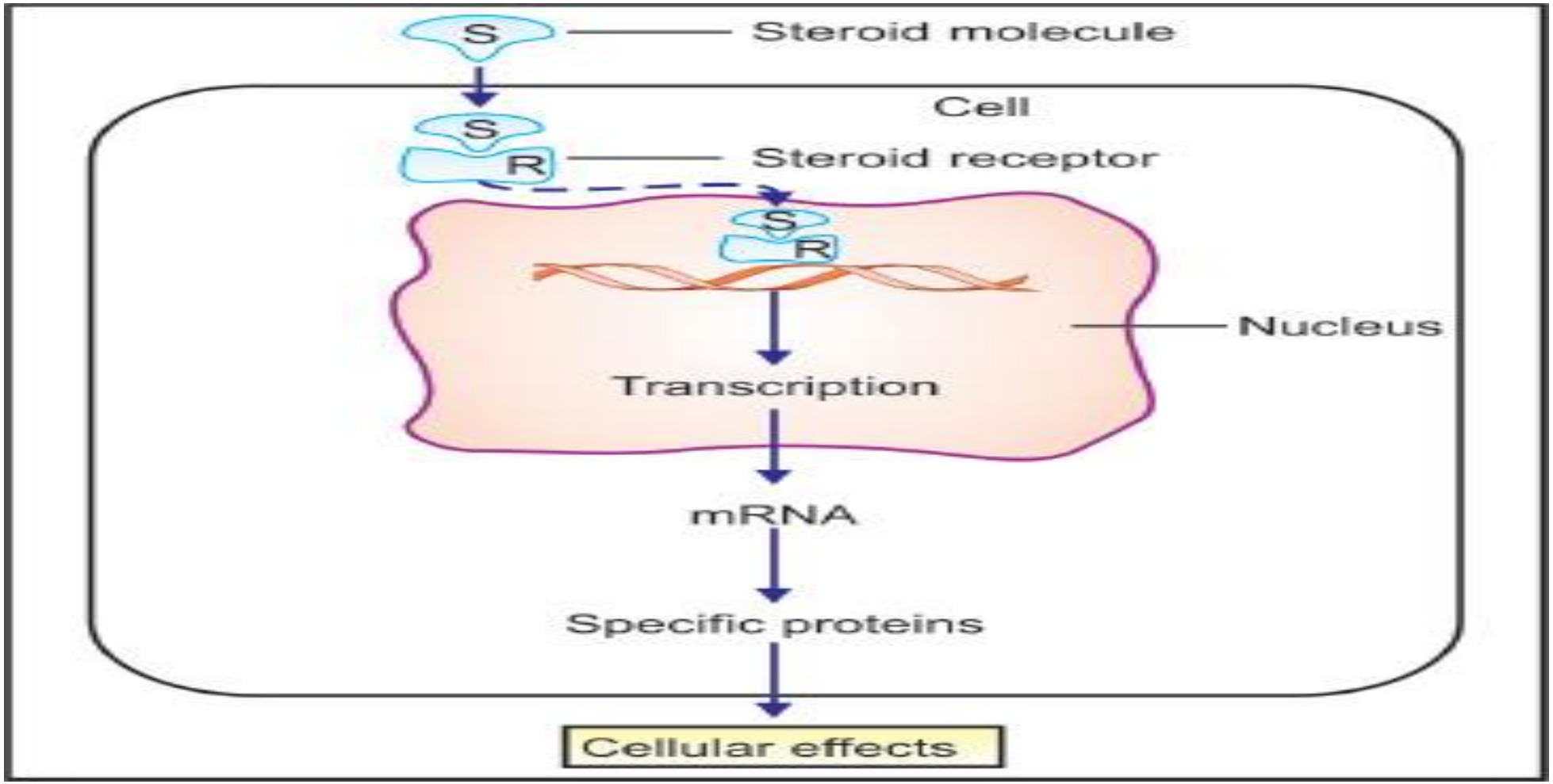
•The metabolites are conjugated to glucouronic acid or sulfate

•**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

- **N.B:**

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

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.**

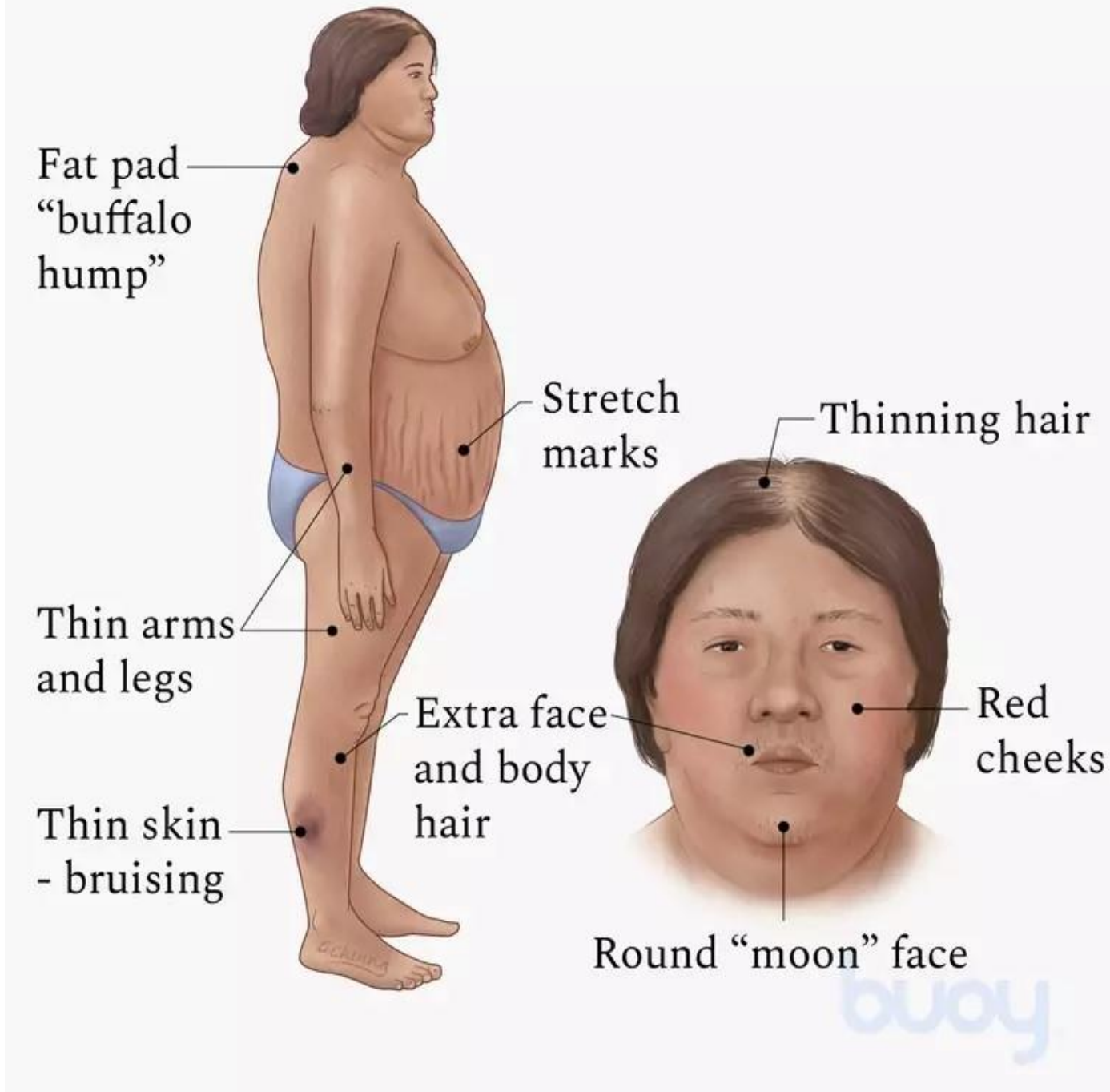
•Protein: (catabolic)

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 (non-genomic)**.

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).**


Fat pad
"buffalo
hump"
Stretch
marks
Thin arms
and legs
Extra face
and body
hair
Thin skin
- bruising
Thinning hair
Red
cheeks
Round "moon" face

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.

•**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

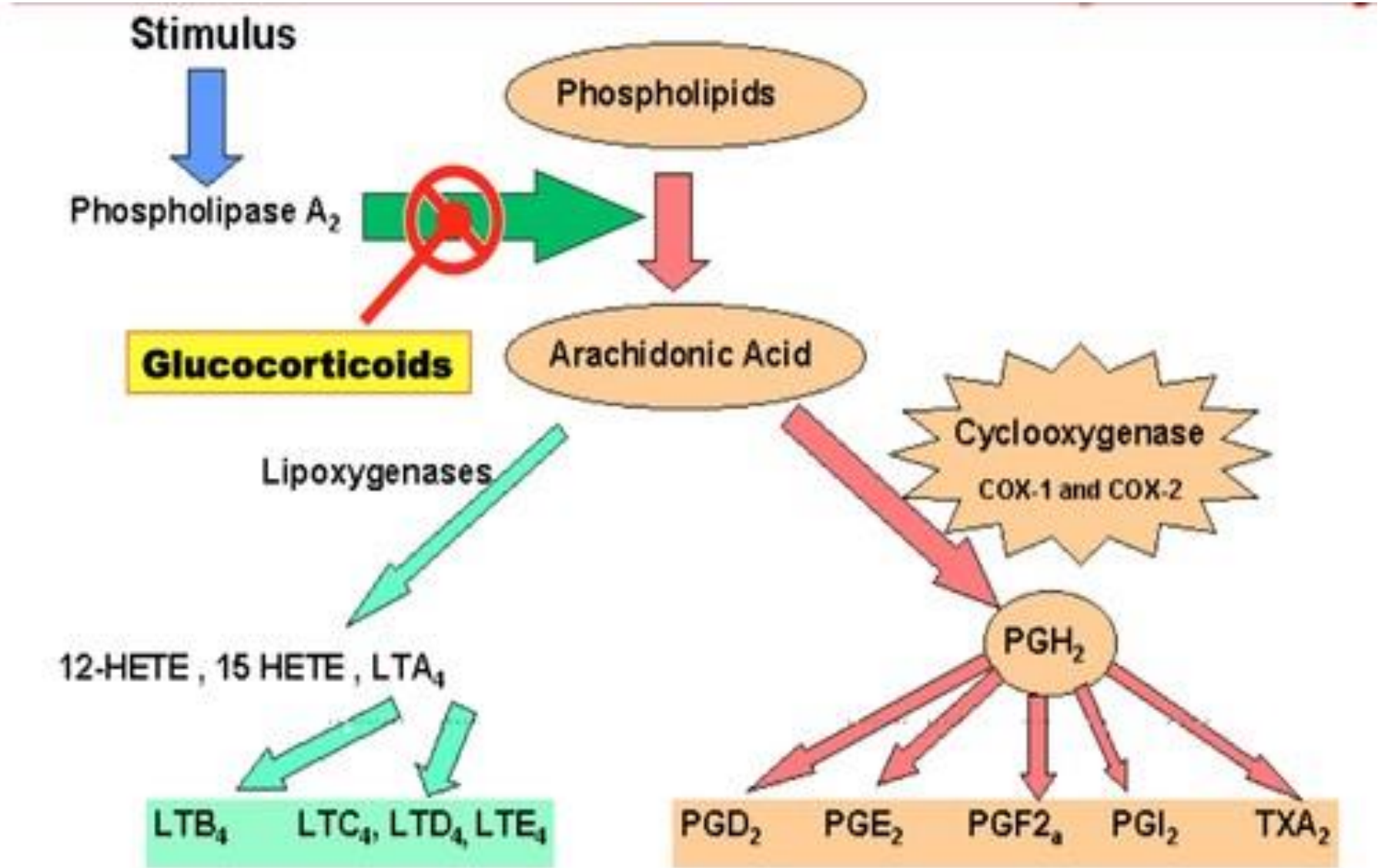
3- Blood

- **Decrease in** eosinophils 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 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: 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.


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
- **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.

•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.

Time of administration

- 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-Depression

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.

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Thank you