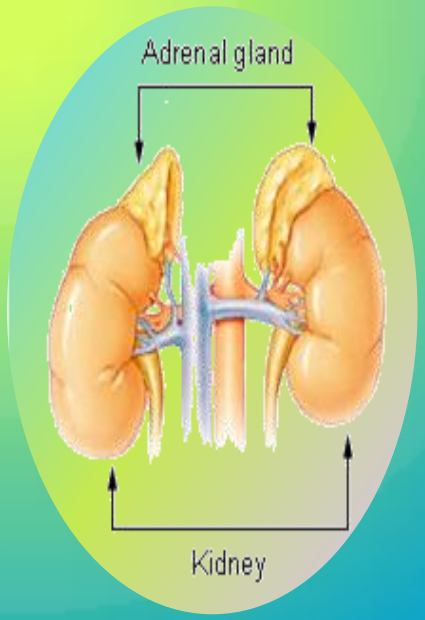
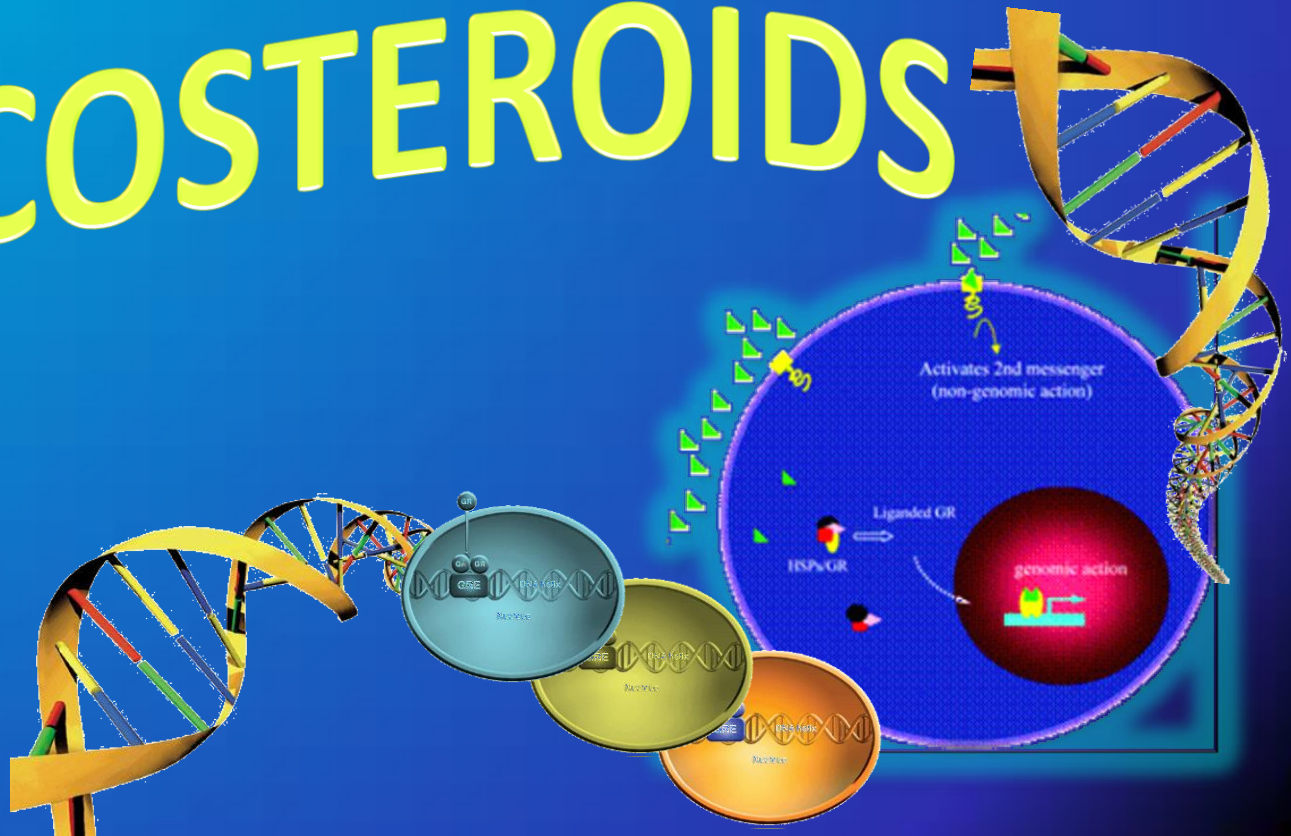


CORTICOSTEROIDS

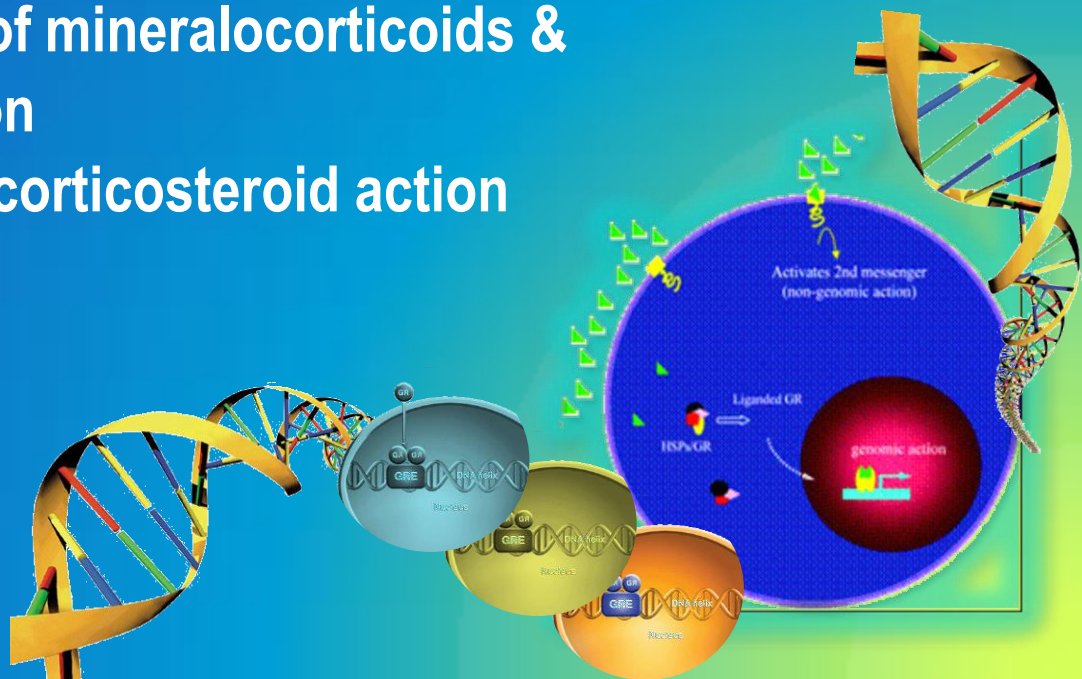


CORTICOSTEROIDS

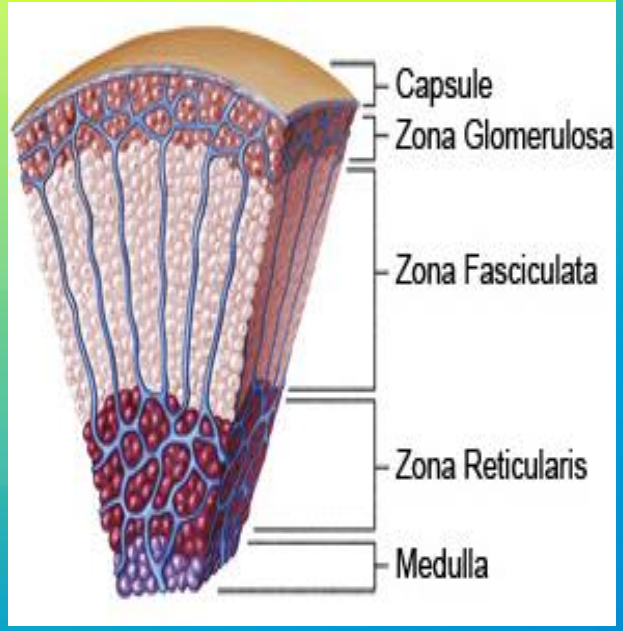
ILOs

By the end of this lecture you will be able to:

- Revise synthesis, regulations & dysregulations of corticosteroids
- Classify available natural vs synthetic glucocorticoides; whether systemic or topical; expanding on their properties & indications
- Contrast their different ADRs & methods of prevention or treatment
- Focus on therapeutic roles of mineralocorticoids & relevant mechanism of action
- Hint on drugs antagonizing corticosteroid action



CORTICOSTEROIDS



Are a class of steroid hormones that are produced in the adrenal cortex

Glucocorticoids [GC] ➜

Released from Zona Fasciculata ➜

as Cortisol , Cortisone & Corticosterone ➜

Regulated by ACTH + cytokines (IL-1, IL-6, TNF), neuropeptides & catecholamines (stressors)

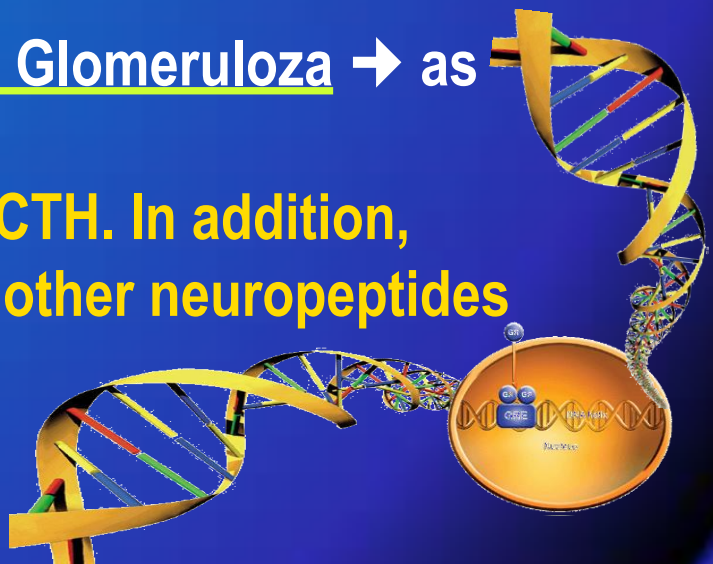
Control carbohydrate, fat & protein metabolism.

They are also anti-inflammatory & immunosuppressants

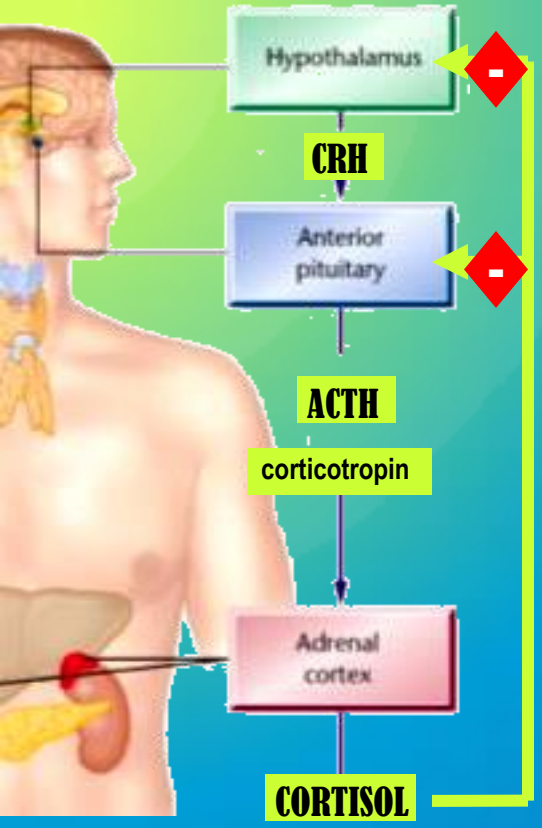
Mineralocorticoids [MC] ➜ Released from Zona Glomeruloza ➜ as Aldosterone ➜

Regulated by angiotensin II, potassium, and ACTH. In addition, dopamine, atrial natriuretic peptide (ANP) and other neuropeptides

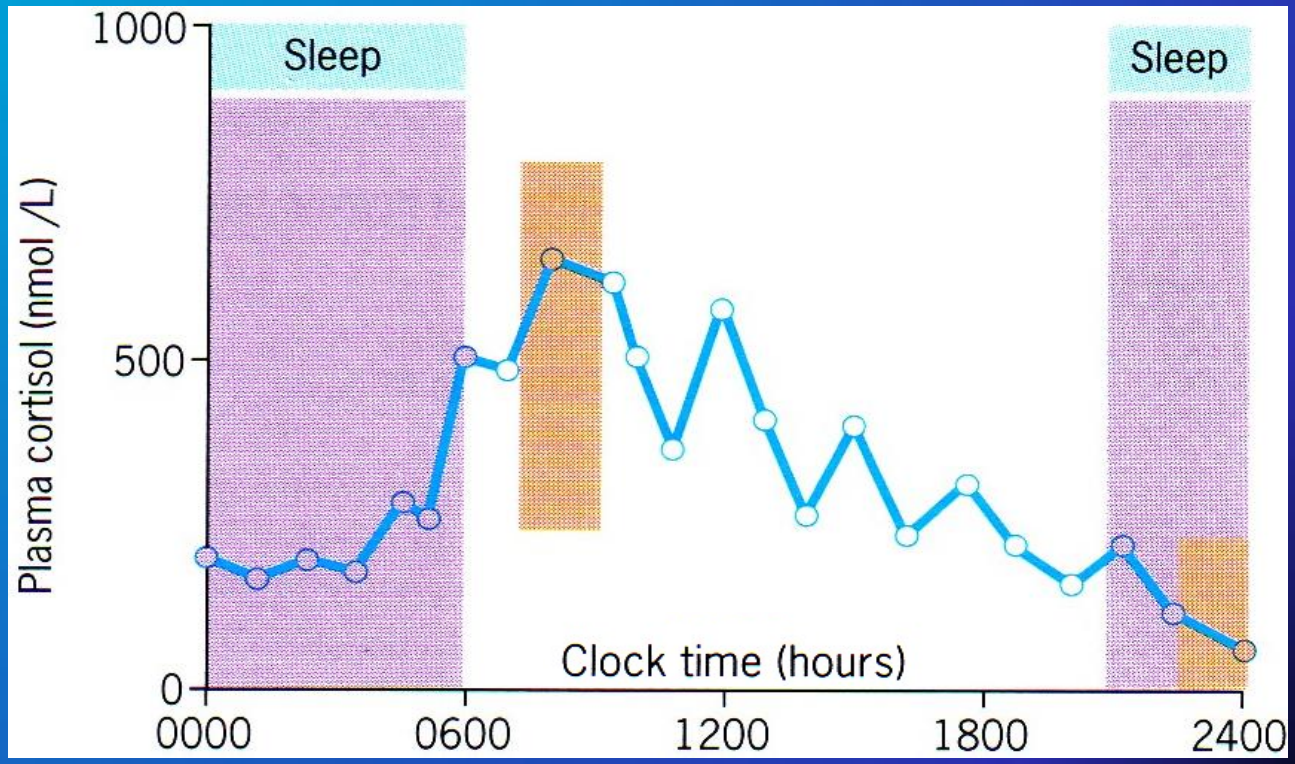
Control water & electrolyte homeostasis



Glucocorticoids



CIRCADIAN pattern of CORTISOL secretion



REGULATION

Mineralocorticoids

FLUID LOSS

↓ Renal perfusion (e.g., ↓ plasma volume)

↑ Renin secretion

↑ Plasma angiotensin II

↑ Serum K^+

↓ Serum Na^+

Stress, physical trauma

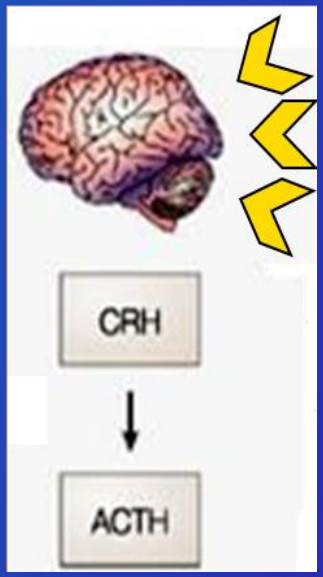
↑ ACTH

↑ Aldosterone secretion

↑ Na^+ reabsorption

↑ K^+ excretion

How Fluid & Electrolyte changes converge to activate MINERALOCORTICOIDS secretion



ACTH → specifically stimulates GC & has little control over secretion of aldosterone

DYSREGULATION

Deficiency in corticosteroids → [Addison's disease]

Hyponatremia, hyperkalemia, hypoglycemia, progressive weakness & fatigue, low blood pressure, depression, anorexia & loss of weight, skin hyperpigmentation

If subjected to stresses → [Addisonian Crisis] → ↑↑ symptoms →

+ fever, confusion sever vomiting, diarrhea, abdominal pain & shock

Deficiency of mineralocorticoids, seldom alone → Hyponatremia, hyper kalemia, acidosis & wasting + ↓ ECF volume, hypotension & shock .

Increased production of glucocorticoids → Cushing's syndrome

Increased production of mineralocorticoids → Conn's syndrome

Hyperaldosteronism
Hypernatremia
Hypervolemia
Hypertension
Hypokalemia

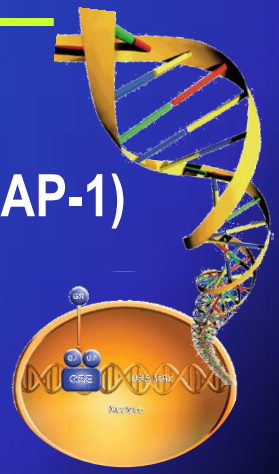
PHARMACOLOGY OF EXOGENOUS GLUCOCORTICOIDS

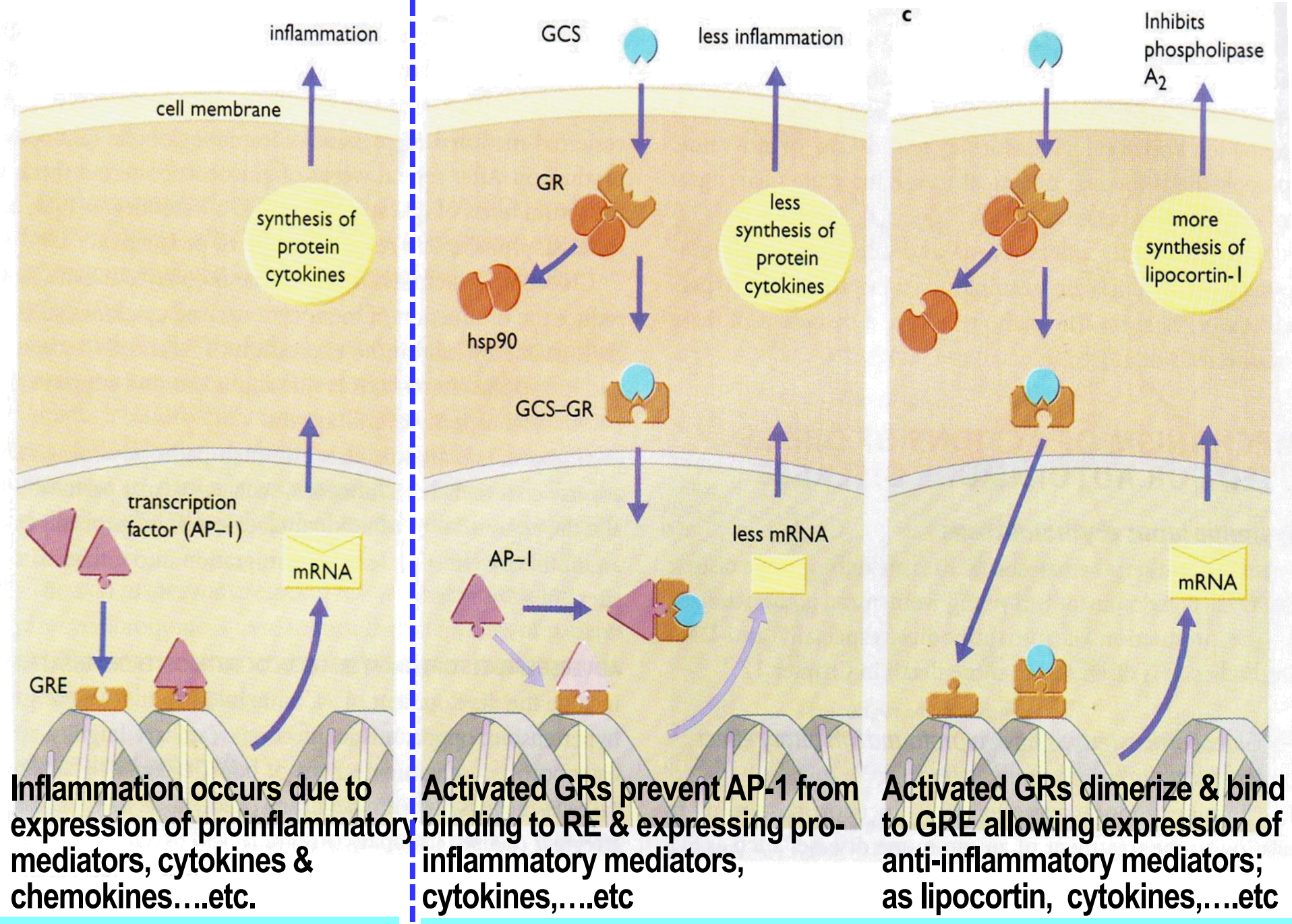
Cortisol, Cortisone, Hydrocortisone, Prednisone, Prednisolone, Methylprednisolone, Triamcinolone, Dexamethasone, Betamethasone, Beclomethasone, Fluticasone, Budesonide, Mometasone, …etc.

MECHANISM GC binds to GRs ⇄ In the cytosol / On cell membrane

1. Cytosolic GC R → mediates **GENOMIC Action** → slow process needs → hrs-days

Expression of proteins → Anti-inflammatory Effects	**Repression of proteins → Pro-inflammatory Effects**
✶Binding & Activation ✶Nuclear translocation ✶Dimerization on GRE ✶Gene Transcription ✶mRNA Translation ✶New Protein Formation e.g. Lipocortin → –ve PLA_2 -ve COX-2	✶Binding & Activation ✶Nuclear translocation ✶Prevent other transcription factors (AP-1) from binding to their RE ✶No Gene Transcription ✶No mRNA Translation ✶No new Protein Formation e.g. No proinflammatory cytokines (IL-2)& chemokines





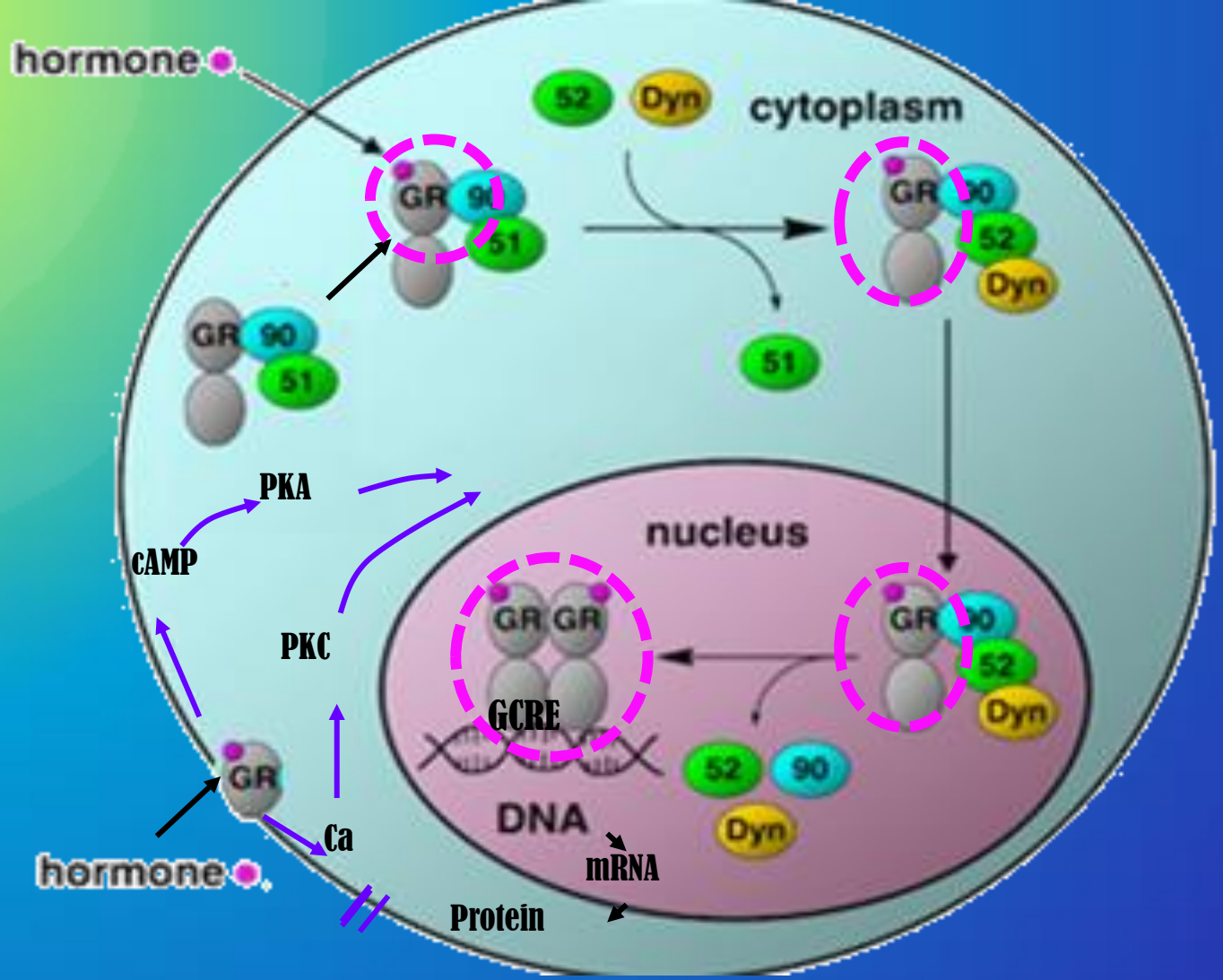
Inflammation occurs due to expression of proinflammatory mediators, cytokines & chemokines….etc.

Activated GRs prevent AP-1 from binding to RE & expressing pro-inflammatory mediators, cytokines,….etc

Activated GRs dimerize & bind to GRE allowing expression of anti-inflammatory mediators; as lipocortin, cytokines,….etc

INFLAMMATION

ANTINFLAMMATORY ACTION OF GC

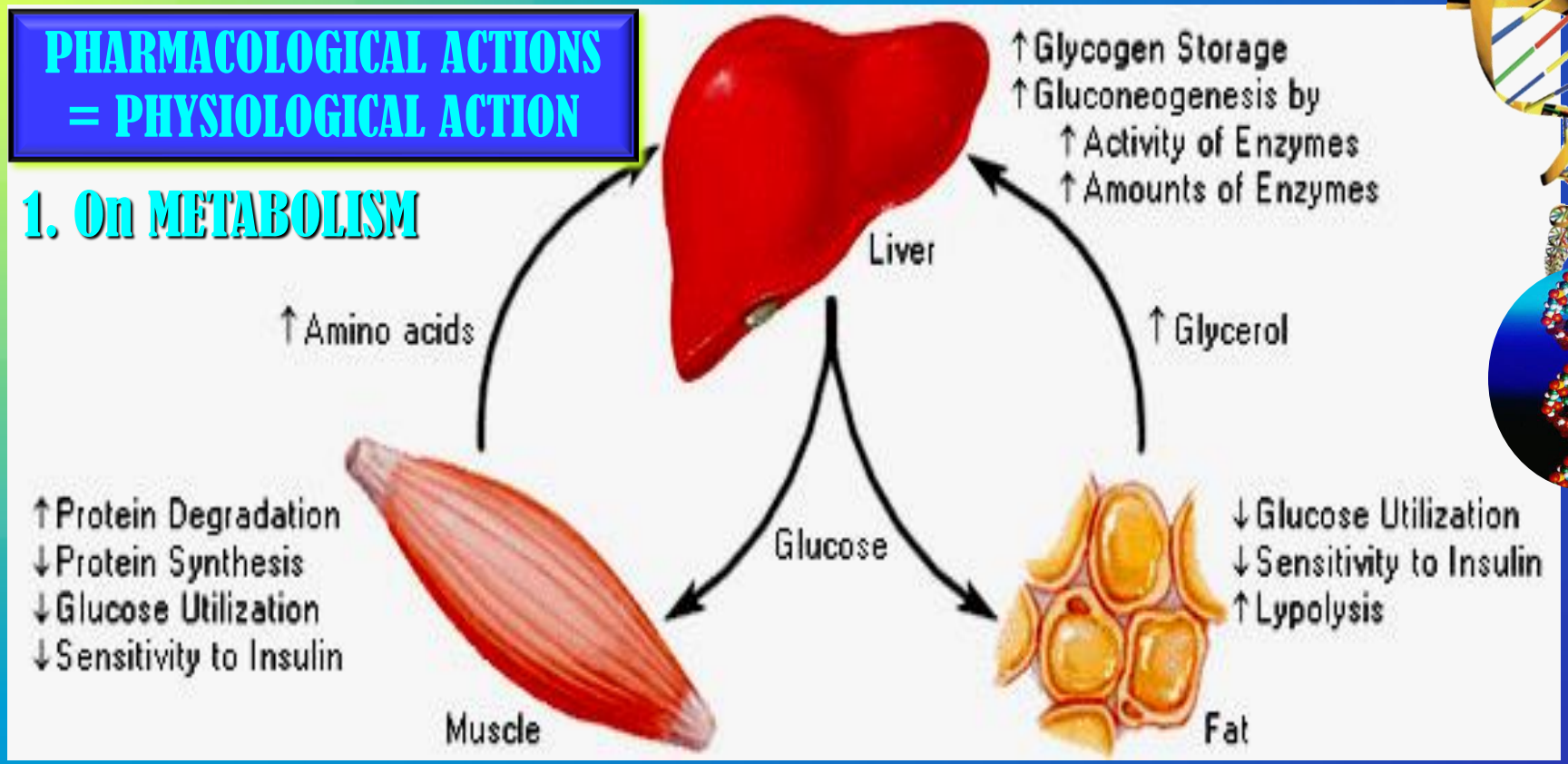


2. Membranous GC R ➔ mediates **NON-GENOMIC Action**

➔ cross talks with GP coupled receptors ➔ alter Ca, cAMP, their downstream kinases (PKA & PKC) ➔ rapidly exert anti-inflammatory effects & shut down proinflammatory effects ➔ **rapid process needs minutes-hrs**

PHARMACOLOGICAL ACTIONS = PHYSIOLOGICAL ACTION

1. On METABOLISM



CHO:
↓glucose utilization.
↑gluconeogenesis →hyperglycaemia

Fats: fat deposition on shoulders, face and abdomen.

Proteins: ↓ anabolism & ↑ catabolism leading to:
Negative nitrogen balance with muscle wasting + ↑ uric a. production
Osteoporosis.
Retardation of growth in children.
Skin atrophy + capillary fragility → bruising and stria.

Calcium metabolism: ↑ urinary excretion & ↓ absorption from intestine (antivitamin D action).

2. On INFLAMMATORY & IMMUNE RESPONSE

↓vascular permeability; so → ↓ edema & redundancy of soft tissues
↓ release & synthesis of inflammatory mediators; so -ve PLA2 → -ve AA & LTs pathways….
↓antigen antibody reaction→↓ mast cell degranulation & transmitter release
↓infiltration & activity of inflammatory cells (eosinophilic, lymphocytic, …etc) by → ↓cytokines & chemokine production
↓ Complement formation

3. ON HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Occurs with high doses & long periods of treatment.
Sudden withdrawal of corticosteroids→
produce a state of adrenocortical insufficiency

4. Others

Euphoria or psychotic states: may occur (probably due to CNS electrolyte changes).

PHARMACOKINETICS

- **Absorption;** Most preparations are ➔ effective orally.
  Parentral forms are also available.
  Can get absorbed systemically when given at local sites (e.g. skin, respiratory tract, conjunctival sac, synovial spaces etc.)

- **Distribution;** 90% or more of cortisol in plasma is transported by reversible binding to Corticosteroids Binding Globulin (CBG) & to albumin
  * Corticosteroids compete with each other on CBG;
    Glucocorticoids bind with high affinity
    Mineralocorticoids bind with low affinity
  * Only the unbound free form is active & can enter cells by diffusion

- **Metabolism;** are metabolized by the liver
  * Some preparations transform to active form in liver
    - ▶ Cortisone ➔ Hydrocortisone
    - ▶ Prednisone ➔ Prednisolone

- t ½ is variable [short, intermediate & long acting]

Excretion; as soluble sulphates in the urine.

CLASSIFICATION ACCORDING TO $t_{1/2}$ & METHOD OF ADMINISTRATION

SYSTEMIC Drugs	Anti-inflam.	Na retention	Preparations & doses
Short Acting Preparations (t1/2 < 12 h)			
Cortisol	1	1.0	5 mg tablet 100 mg/vial (IM/IV) **EMERGENCY** Topical; enema
Cortisone	0.8	0.8	5 mg tablet / *not in liver disease* 25 mg/vial (IM)
Intermediate Acting Preparations ($t_{1/2}$ = 12 -36 h)			
Prednisone	4	0.8	2.5, 5, 10, 20, 50 mg tablet
Prednisolone	5	0.3	5, 10 mg tablet 20 mg/vial (IM, intrarticular)
Methyl- "	5	0	0.5, 1.0 gm (IM / slow IV)
Triamcinolone	5	0	4 mg Tab., 10,40 mg/ml (IM & intrarticular)
Long Acting Preparations (t1/2 > 36 h)			
Dexamethasone *[Fluorinated]*	25	0	0.5 mg tab. 4mg/ml inj (IM / IV)
Betamethasone *[Fluorinated]*	25	0	0.5, 1 mg tab. 4mg/ml inj (IM / IV)

CLASSIFICATION ACCORDING TO $t_{1/2}$ & METHOD OF ADMINISTRATION

N.B.

Changes in basic cortisol molecule → compounds with

- ↓ mineralocorticoid activity.
- ↑ greater potency
- ↑ duration of action

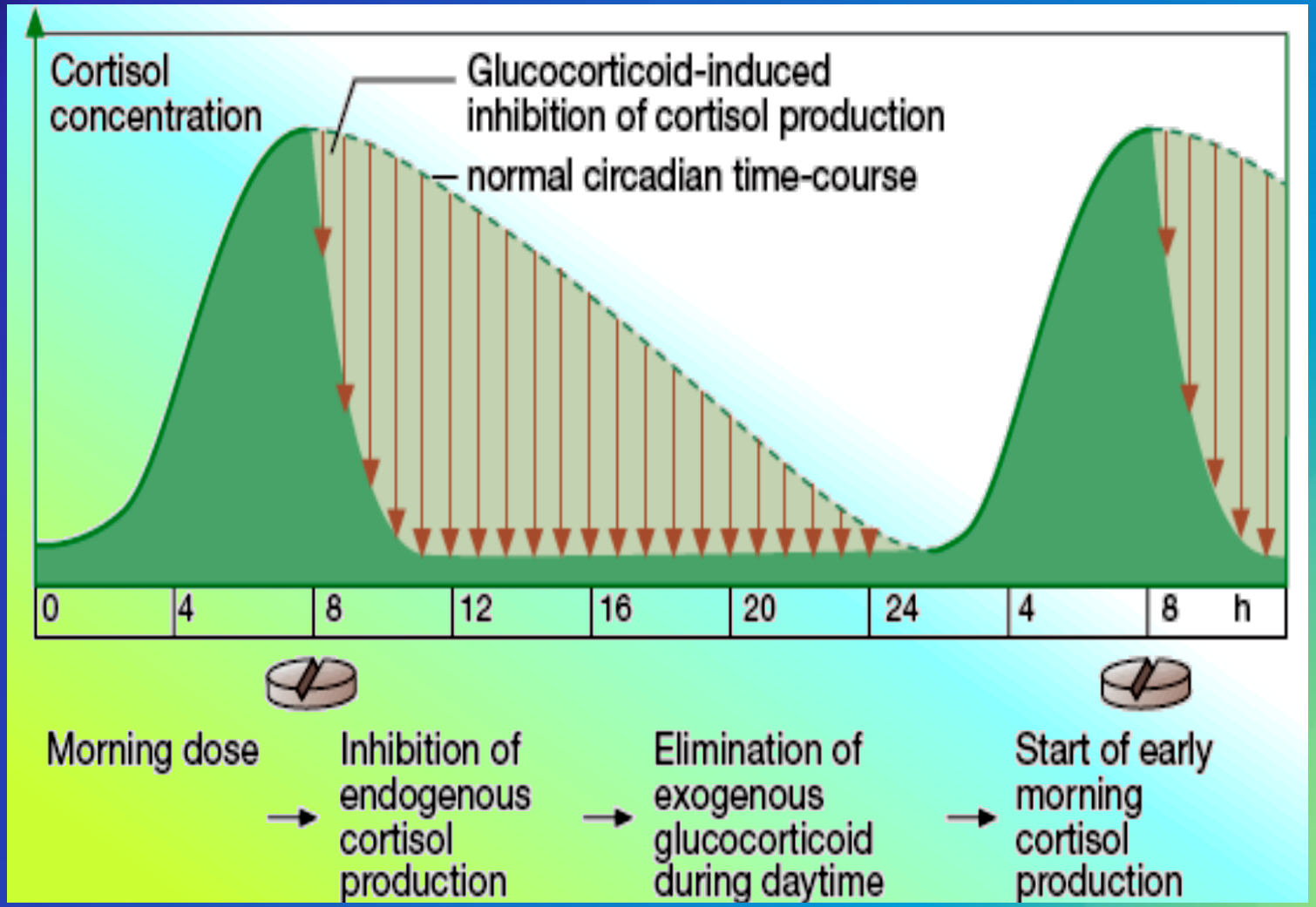
INHALANT DRUGS	Administration Forms
Beclomethasone	50,100,200 mcg/md inhaler
Fluticasone	25, 50 mcg/md inhaler
Budesonide	100,200 mcg/md inhaler

TOPICAL DRUGS	Preparation	Potency
Beclomethasone	0.025 % cream	Potent
Betamethasone	0.025 & 0.12 % cream, ointment	Potent
Triamcinolone actonide	0.1 % ointment	Potent
Fluocinolone actonide	0.025% ointment	Moderate
Mometasone	0.1 % cream, ointment	Moderate
Fluticasone	0.05 % cream	Moderate
Hydrocortisone acetate	2.5 % ointment	Moderate
Hydrocortisone acetate	0.1 – 1.0% ointment	Mild

N.B. Mild-moderate topical steroids are applied on the face as creams only

Dosage Schedule

Time of administration of GCs➔ specially on prolonged use ➔follows natural circadian rhythm i.e. early morning ➔ to minimize hypothalamo-pituitary-adrenal axis impairment. Better if administered on alternate days



INDICATIONS → HORMONE REPLACEMENT THERAPY

1. ADRENAL INSUFFECIENCY

ACUTE & Chronic

Addisonian Crisis

Emergency situation

- Parental **Cortisol (hydrocortisone)** → 100 mg IV / every 6-8 hrs until patient is stable. Dose → gradually reduced → reach maintenance dosage in 5 dys
- Fluids and electrolytes should be corrected.
- Treatment of precipitating factors.

Addison's Disease

- **Cortisol** (20-30 mg/day orally) + **(fludrocortisone** (0.1 mg orally)
- **Dexamethasone** could be given on prolonged use
- Doses must be increased in stress to prevent development of Addisonian crisis
- Doses should follow circadian rhythm

2. CUSHING'S SYNDROME

In Diagnoses → **Dexamethasone suppression test**

In Treatment → **Cortisol;** Temporally administred **AFTER** surgical removal of pituitary / adrenal / corticosteroid secreting tumors

INDICATIONS → I. ANTI-INFLAMMATORY & IMMUNOSUPPRESSANT

Prednisolone
Dexamethasone
Betamethasone

- **Severe allergic reactions** e.g. serum sickness, angioneurotic edema... etc.
- **Diseases of allergic origin**; bronchial asthma, rhinitis, conjunctivitis, eczema & many other atopic & proliferative skin diseases
- **Autoimmune disorders**; rheumatoid arthritis, inflammatory bowel disease systemic lupus erythrematosus, nephrotic syndrome,…
- **Organ transplantation**; kidney, cardiac, bone marrow (↓rejection)
- **Blood dyscrasias**; hemolytic anemia, thrombocytopenic purpura, agranulocytosis ... etc.
- **Acute gout** (resistant) to other drugs

> Anti-inflammatory & Immuno-suppression

INDICATIONS → II. OTHERS

Dexamethasone
Betamethasone
If water retention is undesirable

- Raised intracranial pressure
- In neoplastic diseases
  - With cytotoxic drugs → as in Hodgkin's disease, acute lymphocytic leukaemia
  - P^{ry} or 2^{ndry} neoplasms in the brain & postoperative to brain surgery → ↓edema
  - In antiemetic regimens →prevent / cure emesis of chemotherapy
- Suppress excess ACTH production

---

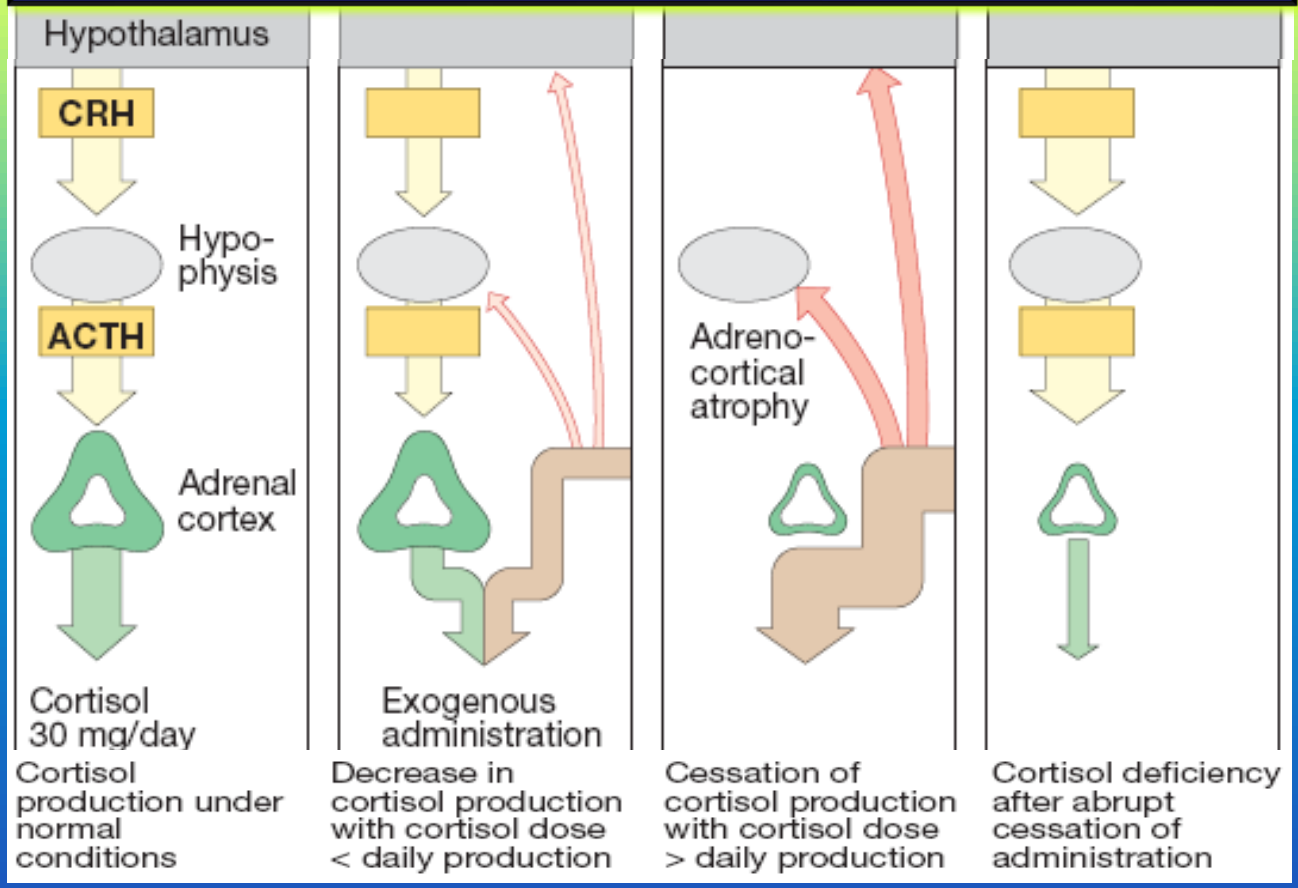
dose & time related

ADRs

1. ↓ HYPOTHALAMIC PITUITARY ADRNAL AXIS
2. IATROGENIC CUSHING's SYNDOME
3. Others

1. ADRs

SUPPRESSION OF HYPOTHALAMIC PITUITARY ADRNAL AXIS



HOW TO AVOID →

Withdraw Corticosteroids Regimens

- If < than 1 w. & not used in big doses no fear.

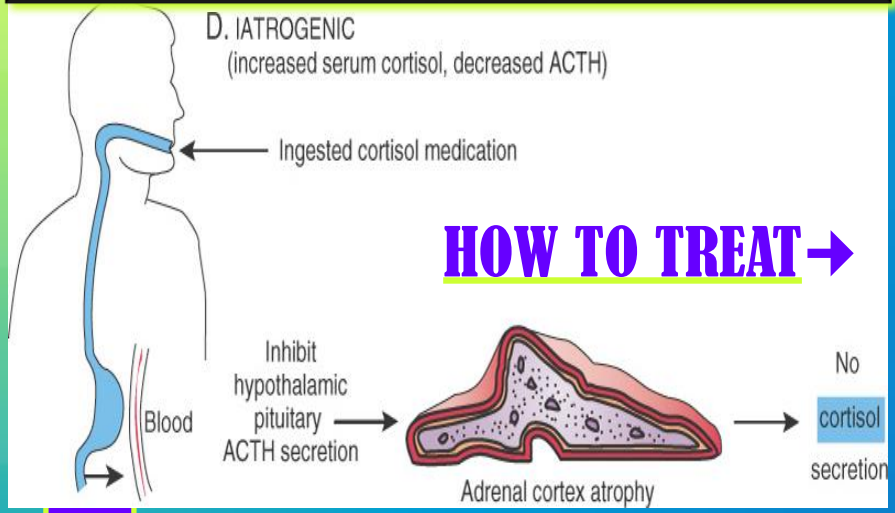
If big dose you may ↓ 2.5-5 mg prednisolone → at an interval of 2-3 days

- If longer periods & high dose

↓ halve dose weekly until 25 mg prednisolone or equival-ent is reached

Then ↓ by about 1mg every 3-7 days.

IATROGENIC CUSHING'S SYNDOME

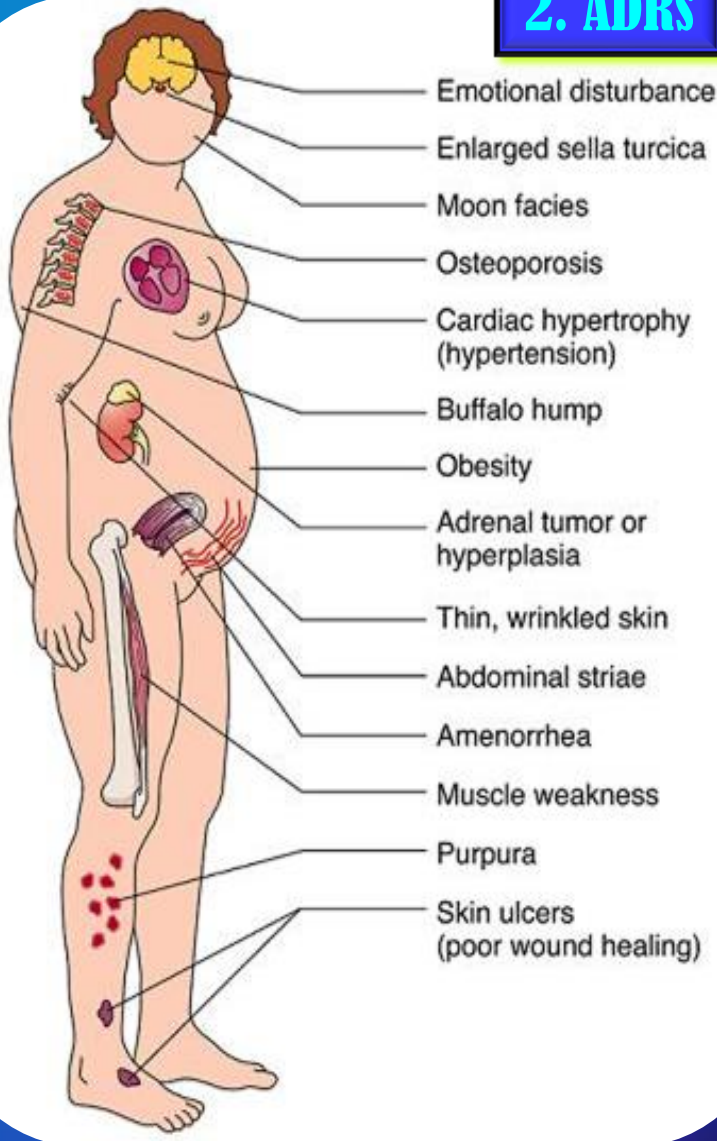


If possible → slow withdraw to allow body to slowly resume its normal balance of ACTH & cortisol

If not possible to stop because of underlying disease → ↓ treat concurrent symptom separately

- * Antidiabetic for hyperglycaemia
- * Bisphosphonates for osteoporosis
- * H_2 blocker or proton pump inhibitors for peptic ulcer

2. ADRs



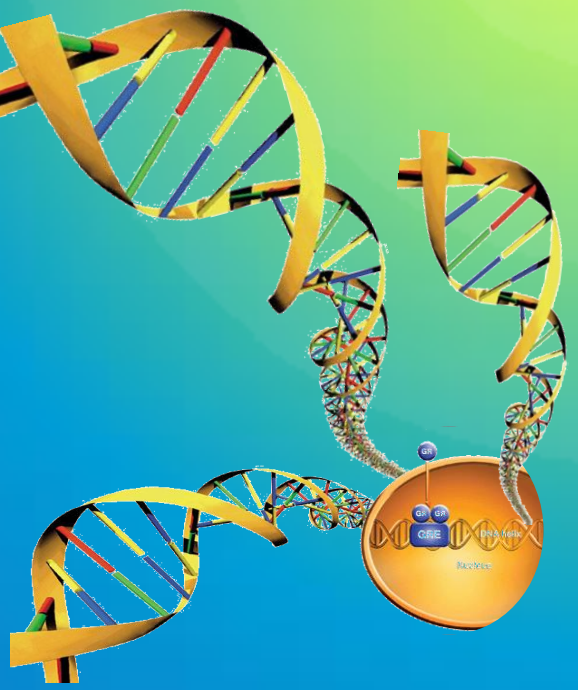
3. ADRs

- Hyperglycemia , glycosuria, diabetes mellitus > fluorinated preparations
- Growth retardation → premature closure of epiphysis →short stature
- Muscle wasting →-ve nitrogen balance > fluorinated preparations
- Fat redistribution & abnormal deposition
- Hypertension, oedema, Na retention
- Hypokalaemia
- Osteoporosis → -ve of osteoblasts / +ve osteoclasts & ↓ Ca absorption, ↑ Ca excretion → vertebral compression & fractures
- Avascular necrosis of head of femur ? Coagulation / apoptosis?
- Menstrual irregularities
- Psychiatric disorders; depression, euphoria,…
- Impairment of defense mechanism→ serious infections, flare of dormant T.B., activate hepatitis, ↑ reaction to live vaccines
- Delayed wound healing
- Peptic ulcer specially if with NSAIDs
- Skin, acne, striae, hirsutism
- Ocular toxicity →glaucoma & cataract

Local Toxicity

3. ADRs

- Skin → infection, atrophy, bruising.
- Eye → viral infection, cataract, glaucoma.
- Inhalation → fungal infection, hoarseness
- Intrarticular → infection, necrosis



CONTRAINDICATIONS

- Diabetes mellitus.
- Hypertension or heart failure
- History of mental disorders or Epilepsy.
- Osteoporosis
- Peptic ulcer
- Presence of infection or Tuberculosis → requires chemotherapy before administration

Precautions

- Patients receiving GCs and is subjected to stress → double the dose
- In children receiving → take care of live attenuated vaccines
- In pregnant women; better avoid fluorinated GCs → teratogenicity
- Neo-born to mothers taking high dose GCs → -ve HPA axis

PHARMACOLOGY OF MINERALOCORTICOIDS

MECHANISM ⇦ Aldosterone, Deoxycorticosterone, Fludrocortisone

Bind to mineralocorticoid receptors [MC R] ⇨ Binds GC > MC

⇨ in MC responsive cells i.e. distal nephron

GC is destroyed, enzymatically in MC responsive cells ⇨ so MC will bind to its receptor alone without any competition from GC.

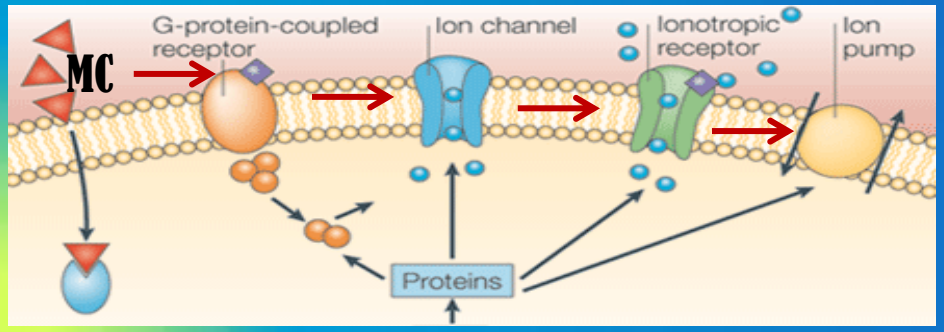
1. Cytosolic MC R ➔ mediates GENOMIC Action ➔ Expression of proteins

   In distal & collecting tubules

   - Na pumps ➔ ↑ Na retention
   - Na channels ➔ ↑ Na reuptake from lumen
   - K simporters ➔ ↑ excretion of K & H

N.B. Actions also on (colon, sweat & salivary glands)

2. Membranous GC R ➔ mediates NON-GENOMIC Action



Interact with GP coupled receptors & channels to mediate rapid adaptive changes to fluid depletion

MINERALOCORTICOIDS

EFFECTS / USES/ PREPARATIONS

Net effect is to conserve body sodium → osmotic effect → water follows → expansion of extracellular fluid
↑renal excretion of potassium &↓ intracellular potassium

In excess → hypertension, atherosclerosis , fibrosis → vascular & cardiac remodeling → cerebral hemorrhage / stroke & or cardiomyopathy

SYSTEMIC Drugs	Anti-inflam.	Na retention	Preparations & doses
Aldosterone	0.3	3000	Natural / Not used clinical
Deoxycortone sterone[DOCA]	0	100	2.5 mg sublinual, ineffective orally ? Inactive in liver
Fludrocortisone	10	150	100mcg oral tablets / duration of 36-72hrs / Drug of Choice in Replacement Therapy

PHARMACOLOGY OF CORTICOSTEROID ANTAGONIST

Medications that inhibit adrenal steroid synthesis to ↓ GC

MITOTANE

-ve 11 β-hydroxylase
↓Corticosteroid production → ↓ its peripheral metabolism & plasma & urine levels
Used in Cushing syndrome; whether iatrogenic, or to alleviate severe symptoms till removal by surgery
Safe in pregnancy

Medications that compete with steroids on receptors to block MC actions

SPIRONOLACTONE

Is a competitive aldosterone antagonist →
Is a K^+ sparing diuretic (weak, slow onset & prolonged effect)
Used in hypertension (alternation with others), in heart failure
In Hyperaldosteronism (Conn's)

CORTICOSTEROIDS

GOOD LUCK