CORTICOSTEROIDS

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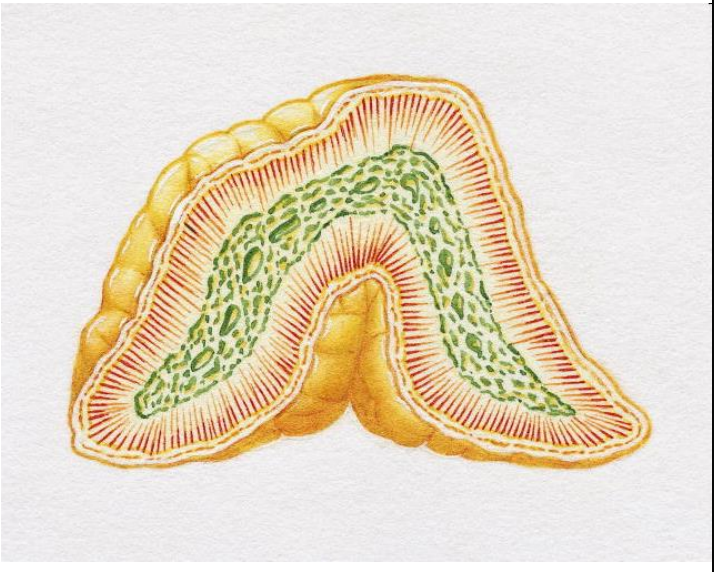
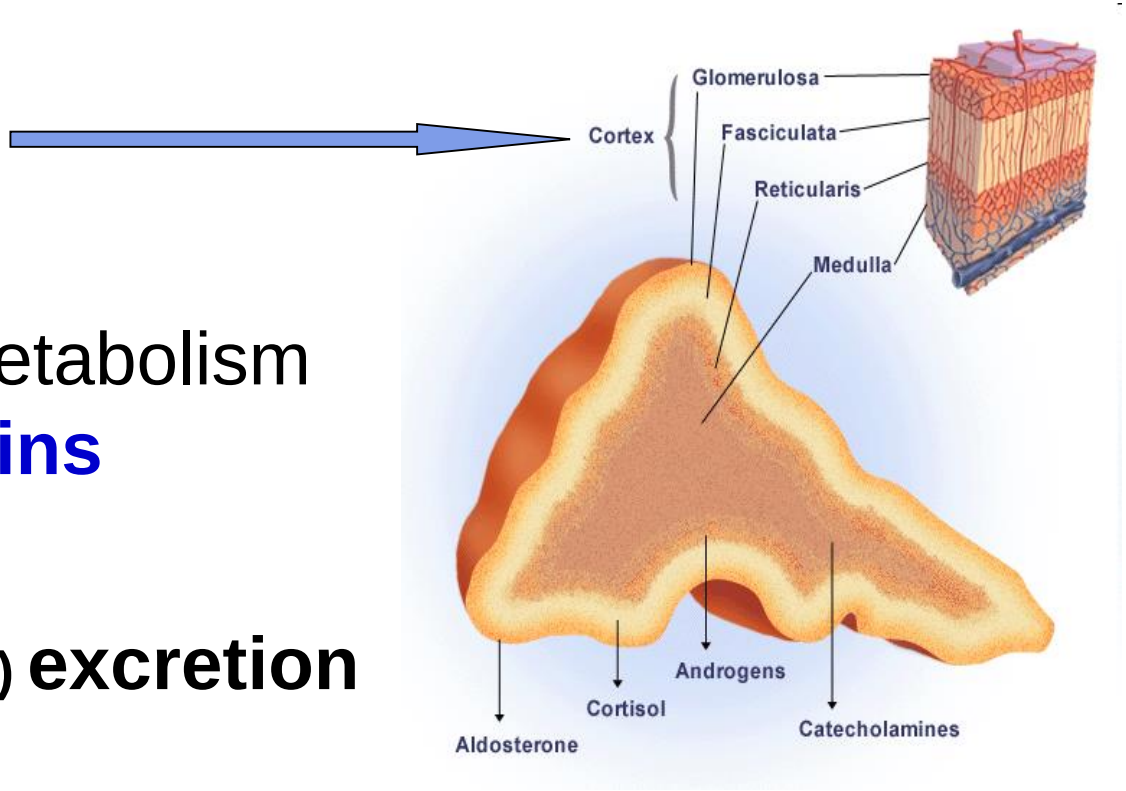


CORTICOSTEROIDS

- Synthesised in **adrenal cortex**

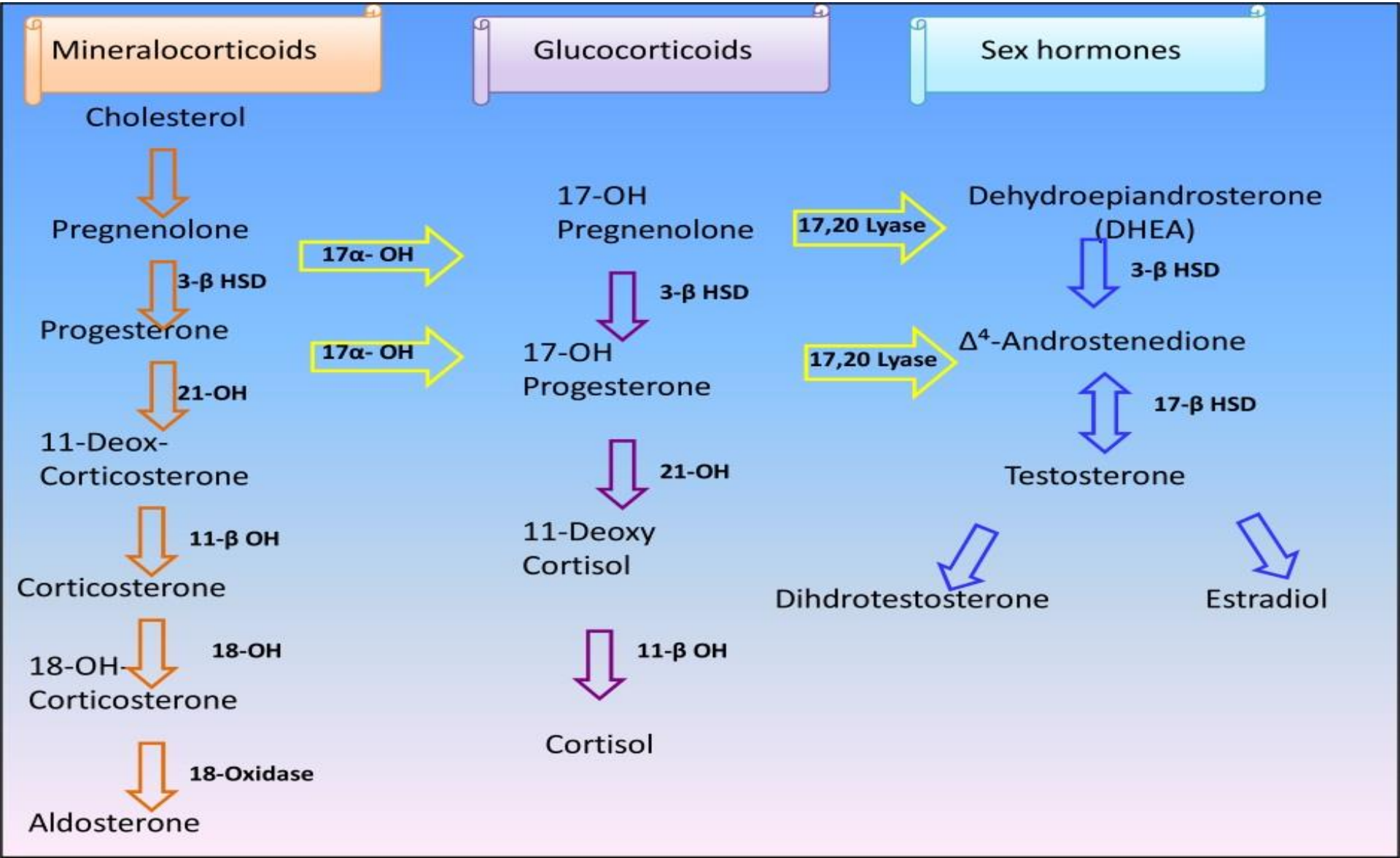


- Influence mainly metabolism of **glycids & proteins**
- Regulate **salt (water) excretion**

www.mmi.mcgill.ca/mmimediasampler2002/

Corticosteroids

Synthesis



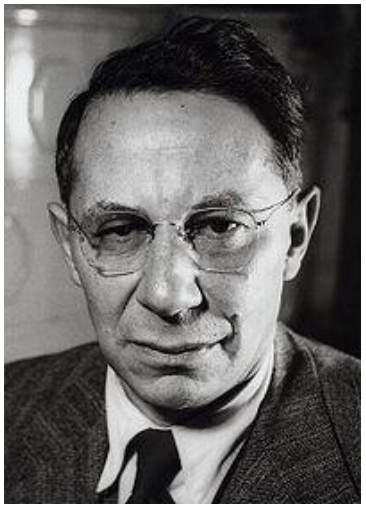
History of corticosteroids

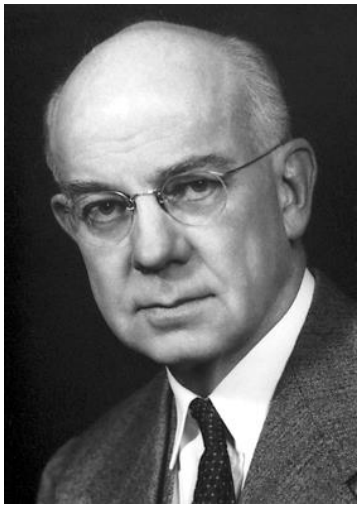
- Tadeusz **Reichstein**

  (1897-1996)
- Philip Showalter **Hench**

  (1896 - 1965)
- Edward Calvin **Kendall**

  (1886-1972)



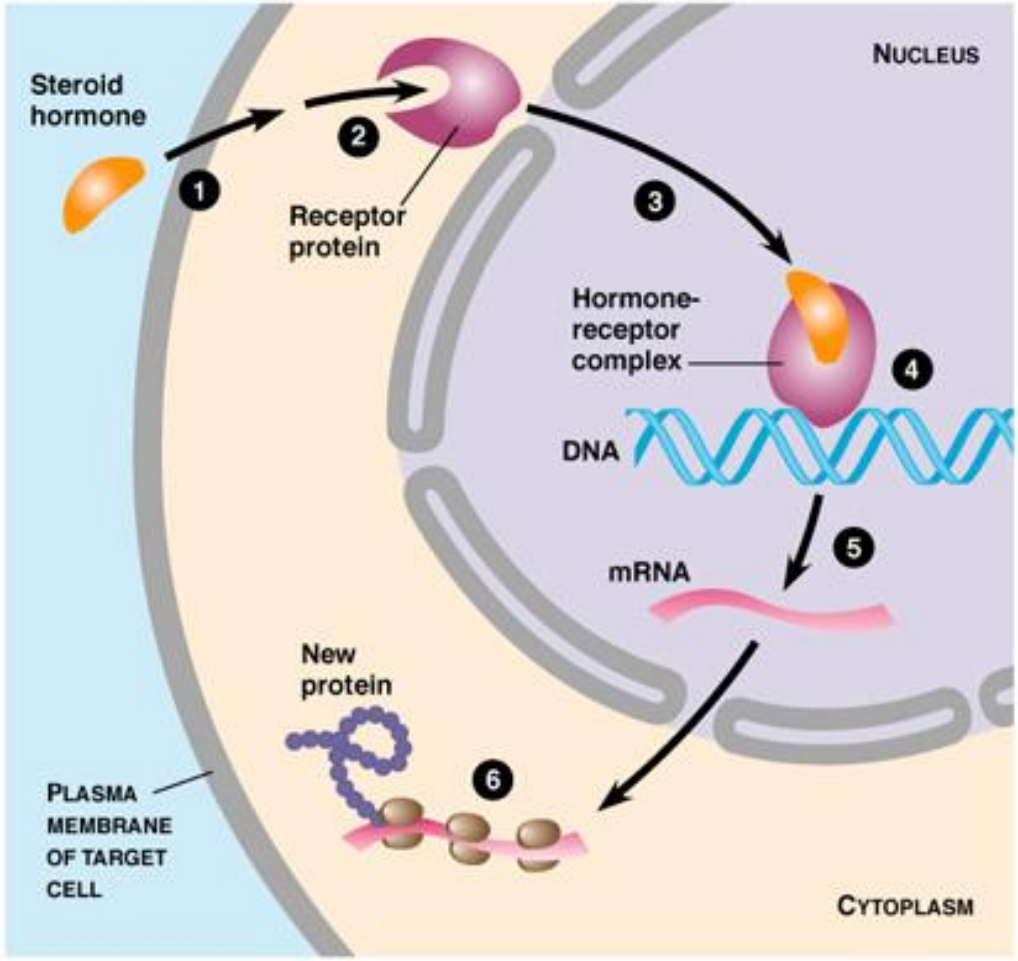


- **Nobel Prize for Physiology & Medicine in 1950**

  (for their work on hormones of the adrenal cortex & the isolation of *cortisone)*

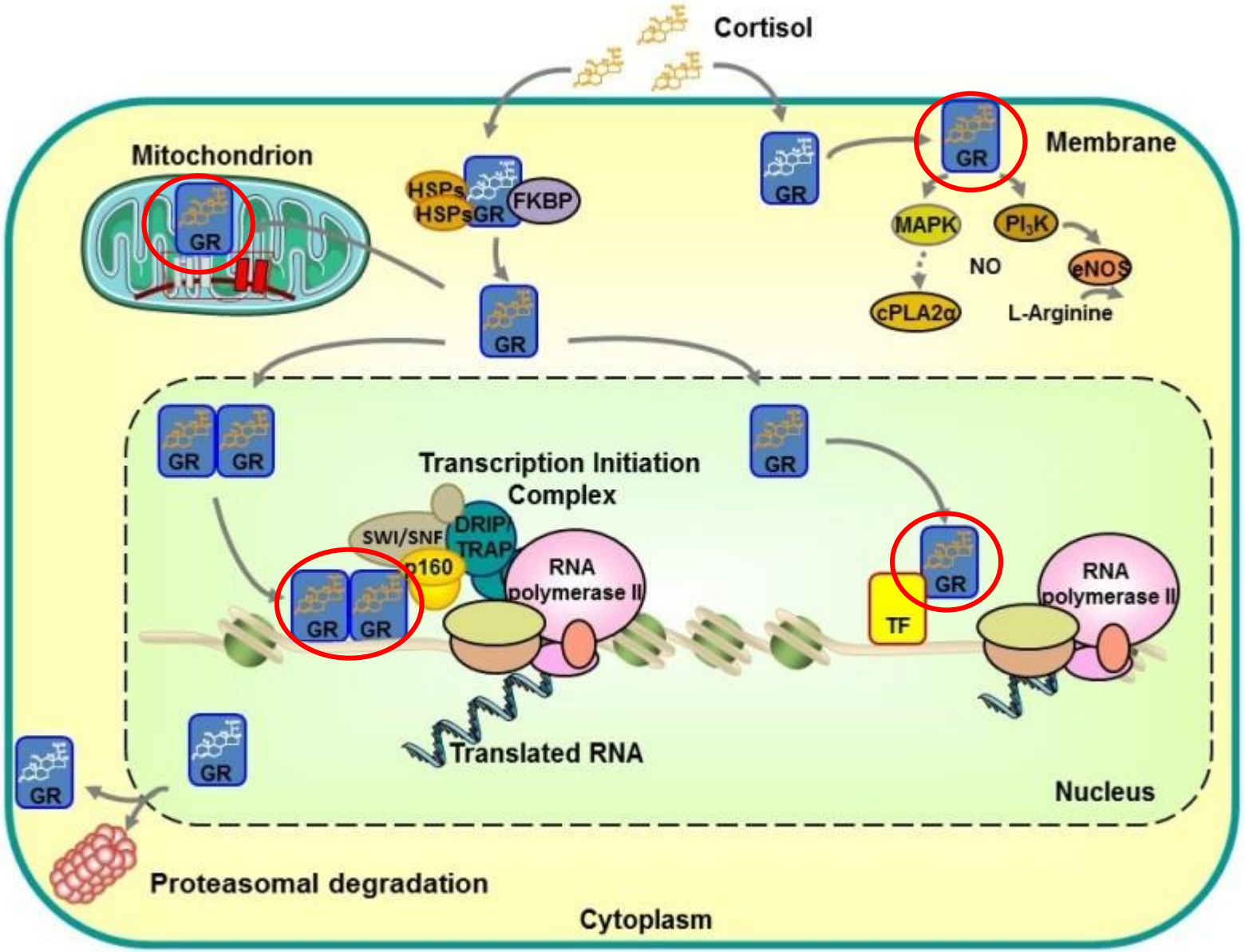
Glucocorticoids - GC
Cellular delivery

- Protein bound - 90% of GC (to Corticosteroid Binding Globulin - CBG):
  - receptors for CBG-steroid complex (on cell surface)
  - CBG "delivers drug to the cells"
  - binding restricts volume of distribution
  - active transport of bound steroid into cell



GC actions

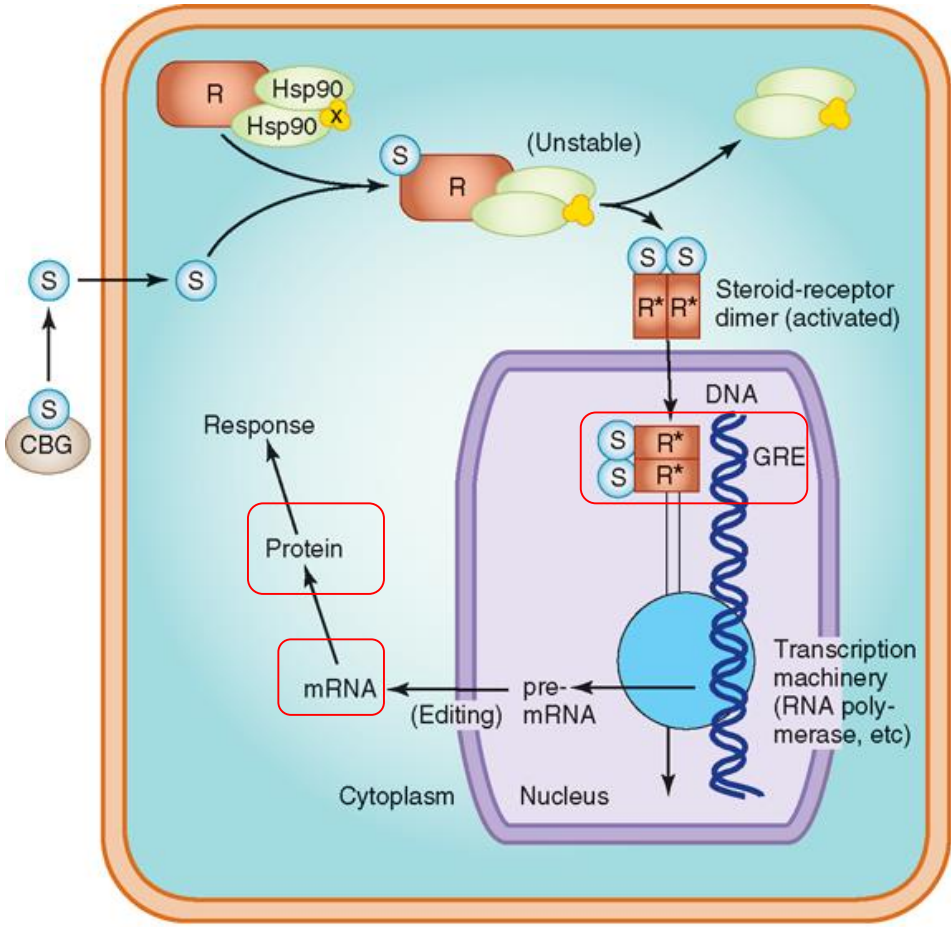
Genomic, nongenomic, mitochondrial



GC

Genomic effects – GRE-mediated

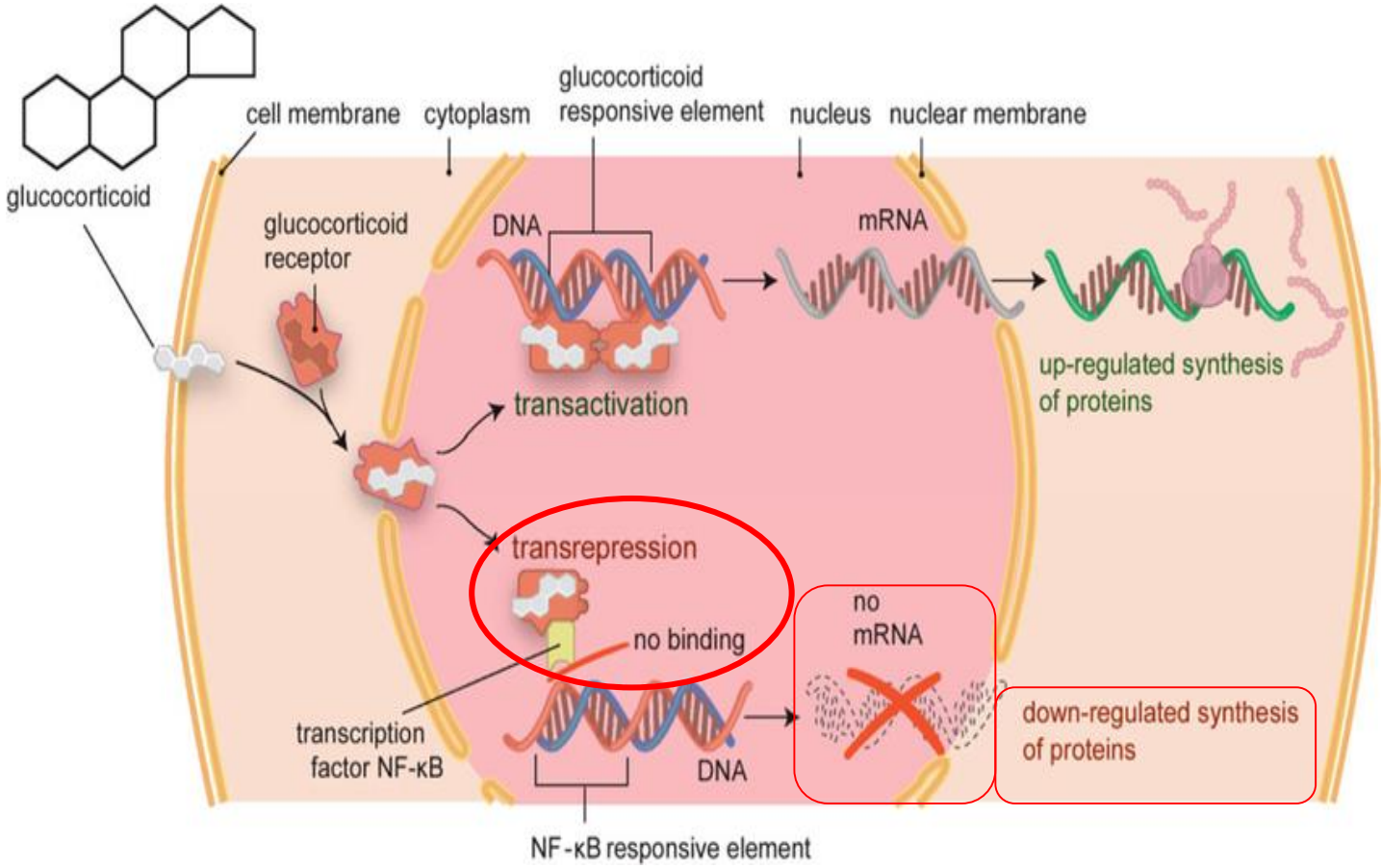
- Binding of GC to human GC receptor (GR) in cytoplasm (complex dissociation)
- Active transport of dimer (to nucleus)
- Binding of dimer to regulated gene sequences - GRE (cell type determines which sequences)
- A variety of proteins may be produced (depending on specific genes activated)
- ⇑ or ⇓ in DNA transcription



GC

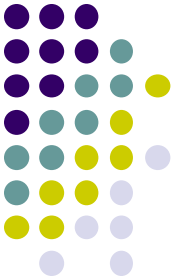
Genomic effects – GRE-independent

- The ligand-activated GR can also modulate gene expression independently of binding to GREs directly interacting with other transcription factors (TF), such as:
  - activator protein-1 (AP-1)
  - NF-κB
  - P53
  - signal transducers & activators of transcription (STATs)



GC

Examples of GRE-independent effects

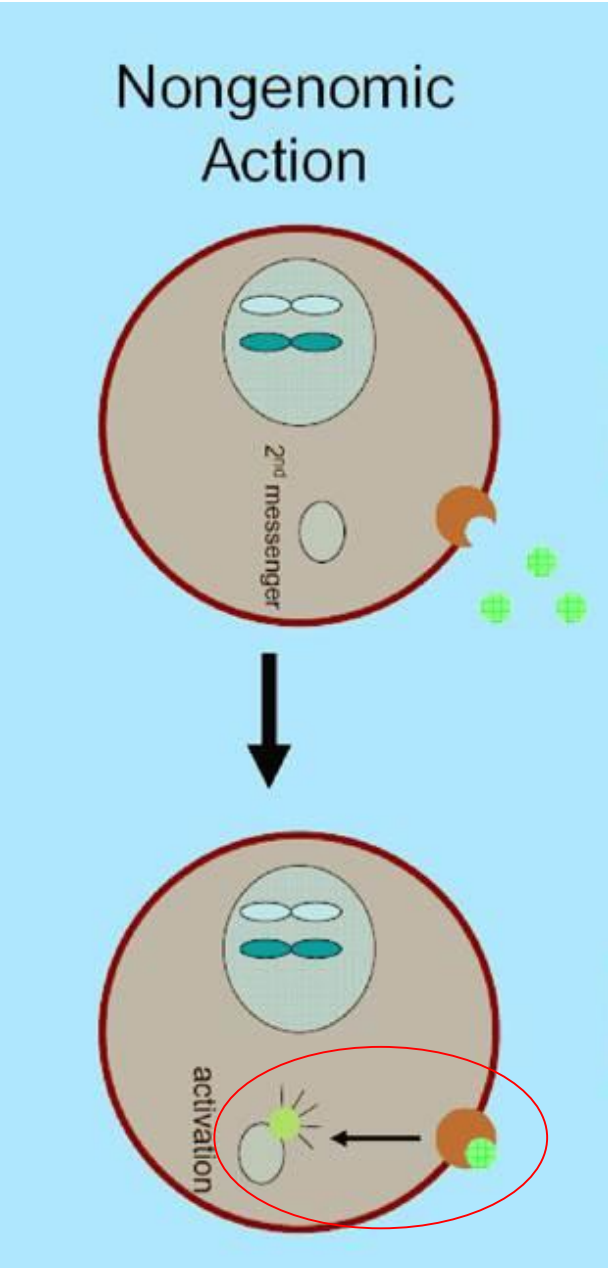


- Suppression of transactivation of other TF through protein-protein interactions may be particularly important in suppression of:
  - **immune function &**
  - **inflammation by GC**
- Most of the effects of GC on the immune system may be mediated by the interaction between:
  - GR & NF-κB,
  - GR & AP-1
  - GR & STATs

GC

Nongenomic effects

- Further to genomic actions, GC also signal within seconds or minutes
- These effects are termed as "nongenomic" (since they do not require GR transcriptional activity)
- Most of the nongenomic GC actions are triggered by membrane-bound GR (mGR), which induces the activity of kinase signaling pathways, e. g.:
  - the mitogen-activated protein kinase (MAPK)
  - the phosphatidylinositol 3-kinase (PI_3K)



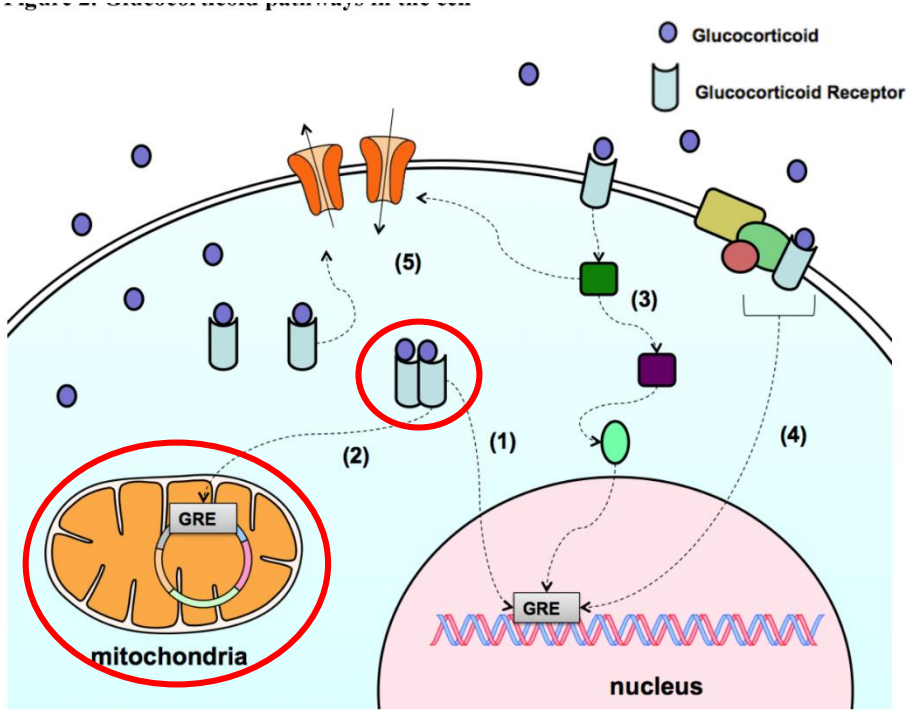
GC
Examples of nongenomic effects

- Some representative **examples of nongenomic actions** are:

- the immediate suppression of ACTH release from the anterior lobe of pituitary by GC
- the ⇑ frequency of excitatory post-synaptic potentials in the hippocampus
- the cardioprotective role of GC through NO-mediated vasorelaxation in patients with MI or stroke
- some immunomodulatory GC effects via disruption of T-cell receptor signaling

GC
Mitochondrial effects

- In addition to genomic & nongenomic actions, GC exert some effects through mitochondrial GR (granted that many regulatory sites of the mitochondrial genome have functional GREs)
- ligand-activated GR translocates from the cytoplasm to mitochondrion & influences substantially mitochondrial gene expression



GC

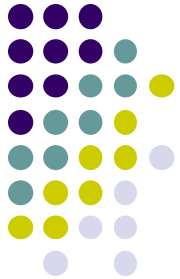
Examples of mitochondrial effects

- Many mitochondrial RNA-processing enzymes or TF are expressed under the control of nuclear GR (suggesting a dynamic interrelation between glucocorticoids, mitochondria and the nucleus)

- Importantly, the mitochondrial GR has been early recognized as a potent therapeutic target, because of its involvement in the programmed cell death (apoptosis) of malignant cells

- Indeed, synthetic GC are the **cornerstone** of several therapeutic protocols of **hematologic malignancies**

GC
Potency & duration



- **Strength of binding** (steroid to CBG, steroid to receptor, steroid-receptor to DNA) **determines potency** & **duration**

(PK of circulating GC have little effect on potency or duration):

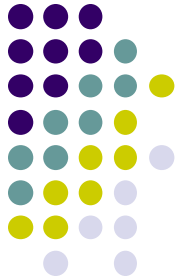
- **potency** is primarily determined by the GC base

(the ester may control the amount of drug released into the circulatory system which would also influence the magnitude of effect)

- **duration** is controlled by the base UNLESS the base is attached to an ester that makes it "long-acting„

(even then, the base will have some effect - e.g. *dexamethasone acetate* injection will have a longer duration of effect than *prednisolone acetate*)

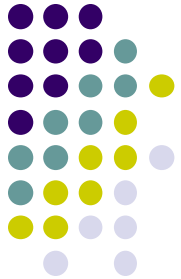
GC
Ultimate activity



- Ultimate activity of GC depends on the nature & quantity of the proteins produced:

  - PK of the new protein (amount produced & half-life) ultimately determines the potency & duration of the response
  - proteins may interact with each other & with DNA to alter binding

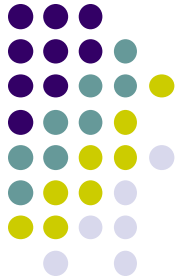
GC
PK



- Very good GIT resorption
- Oral; i. v.; i. m.; local application
- Metabolised in liver *(cortisol* - 70%)
- There, cortisol is reduced, oxidized, or hydroxylated, & the products of these reactions are made water soluble by conjugation with sulfate or glucuronic acid to facilitate their excretion in urine
- Cortisol is inactivated mainly by reduction (reduction reactions can also result in "regeneration" of *cortisol* from its inactive metabolite, *cortisone*)
- Metabolic activation of:
  - *prednisone, methylprednisone* ⇨ *prednisolone, methylprednisolone*
- Synthetic corticoid elimination ⇨ strictly renal

GC products

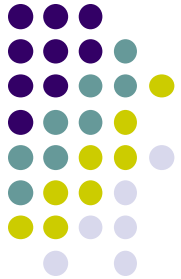
Esters & dosage forms



Selection of a GC ester is based on the route of administration & the desired duration & potency of effect:

- Oral
  - the ester is irrelevant
  - all are separated from the base in the GIT
  - the base drugs are well absorbed

GC products
Injection forms



- IM, SC, Intralesional
  - rapidly absorbed products can be used as substitutes for oral preparations (their absorption & duration are roughly equivalent to the oral base products & salts)
  - slowly absorbed (Depot) products are designed to provide either low concentrations of GC for extended periods of time or high concentrations in a local area (e.g. tumor or joint injections...)
- IV
  - water soluble salts reach sites of action 1/2 - 1 hour faster than oral but are otherwise similar in potency
  - this is the most appropriate route of administration for "EXTREME-DOSE" GC therapy (e.g. CNS trauma, shock, etc.)

GC
Substances

- **Short-acting:**
  - *cortisone*
  - *hydrocortisone*
- **Intermediate-acting:**
  - *methylprednisolone*
  - *prednisone*
  - *triamcinolone*
- **Long-acting:**
  - *betamethasone*
  - *dexamethasone*

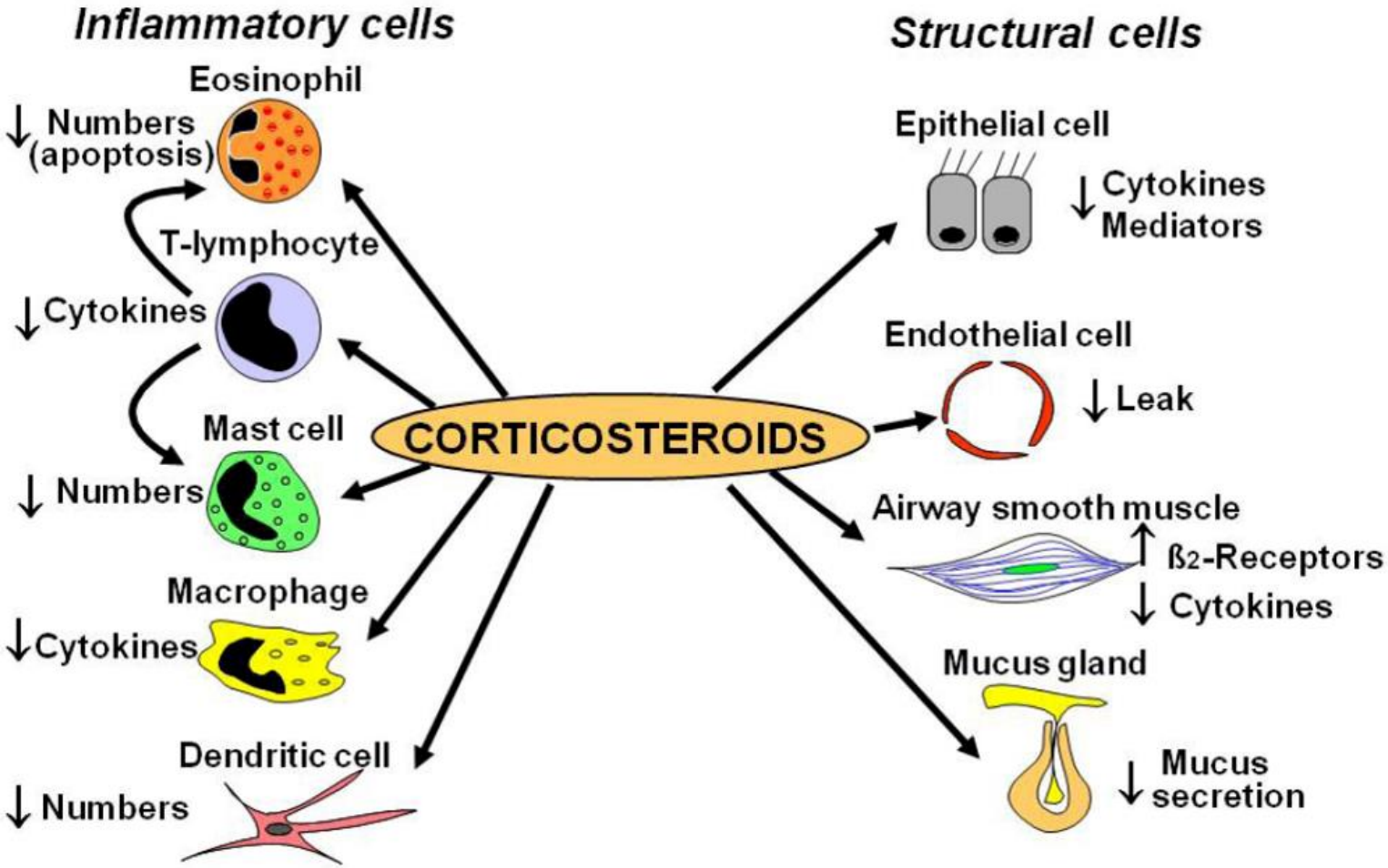
- ***Cortisone*** is a precursor that could be converted to ***cortisol***
- ***Cortisol*** ***(hydrocortisone)*** is the active form
- **...many others**

CNS	Euphoria & behavioral changes Maintenance of alpha rhythm Lower seizure threshold
GIT	⇓ Ca^{2+} & iron absorption Facilitation of fat absorption ⇑ acid, pepsin & trypsin Structural alteration of mucin
Skeletal muscle	Weakness (excess & deficiency) Muscle atrophy (chronic excess) ⇓ glucose uptake & utilization
Skin	Atrophy & thinning (chronic excess) Calcinosis cutis
Hematopoietic system	Involution of lymphoid tissue ⇓ in peripheral lymphocytes, monocytes, eosinophils ⇑ in peripheral neutrophils, platelets, RBCs ⇓ clotting time ⇓ phagocyte competence
Fat	⇓ glucose uptake & utilization

CVS	Positive inotropic effect ⇑ BP (⇑ blood volume)
Kidney	⇑ reabsorption of water, Na^+, Cl^- ⇑ excretion of K^+, Ca^{2+} ⇑ extracellular fluid
Bone	⇓ of collagen synthesis by fibroblasts Acceleration of bone resorption Antagonism of vitamin D
Liver	⇑ glykogenolysis & glukoneogenesis
Reproductive system	Teratogenesis during early pregnancy
Cells	"Stabilization" of liposomal membranes ⇓ of macrophage response to migration inhibition factor Lymphocyte sensitization blocked Cellular response to inflammatory mediators blocked ⇓ of fibroblast proliferation

GC main clinically useful effects

Inflammation, immunity, allergy



GC

Anti-inflammatory & anti-immunity therapy

- GC - potently interrupt events triggered at the cell membrane (PLC, etc.):
  - ⇓ of inflammatory & immunity mediator synthesis (e.g. PG, LT)
- GC - potently ⇓ cell mediated immunity (antigen recognition, cell migration, etc.):
  - ⇓ of immune cell proliferation & function (e.g. phagocytosis)

GC are NOT effective inhibitors of antibody synthesis

GC

Antiinflammatory & immunosuppressive effects

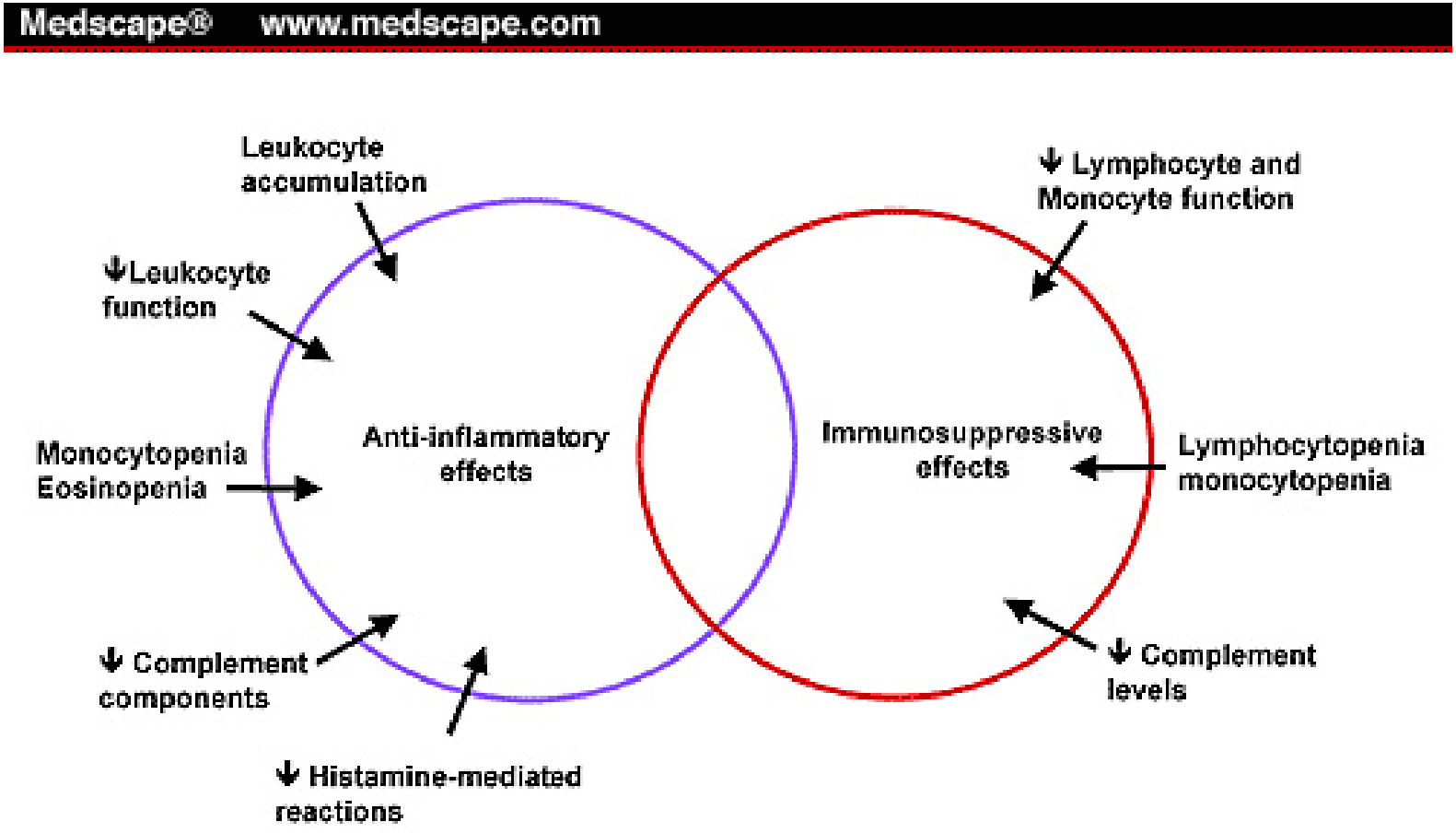
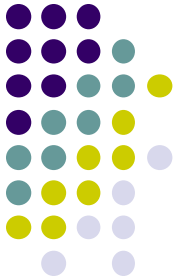


Figure 2. Anti-inflammatory and immunosuppressive effects of corticosteroids.

Antiinflammatory effects of GC

Cells & tissues



Effect on eosinofils

- ↓ gene transcription for adhesive factors & cytokines
- ↓ circulatory eosinophils
- ↓ production in bone marrow
- ↓ accumulation of eosinophils

Lymphocytes & macrophages

- ↓ lymphocyte & macrophage proliferation & activity
- ↓ T-helper effects; ↓ T-cell proliferation

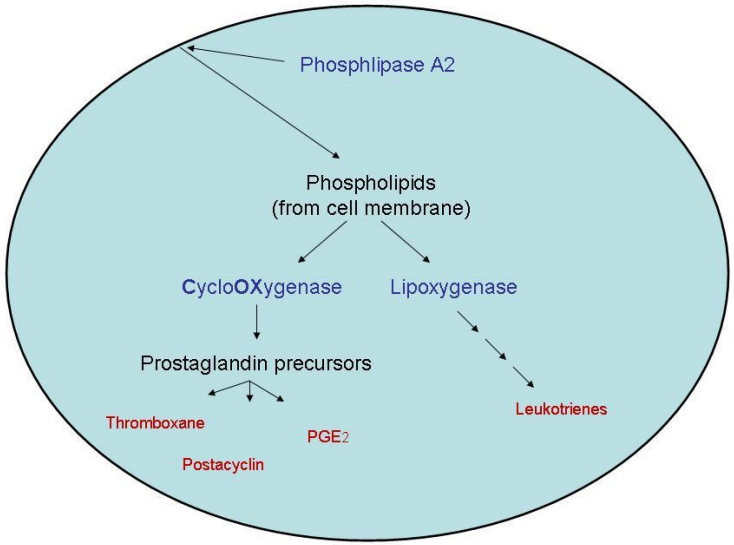
Reduction of mucosal edema

- ↑ synthesis & sensitivity of β-adrenergic receptors

Antiinflammatory effects of GC
Mediators

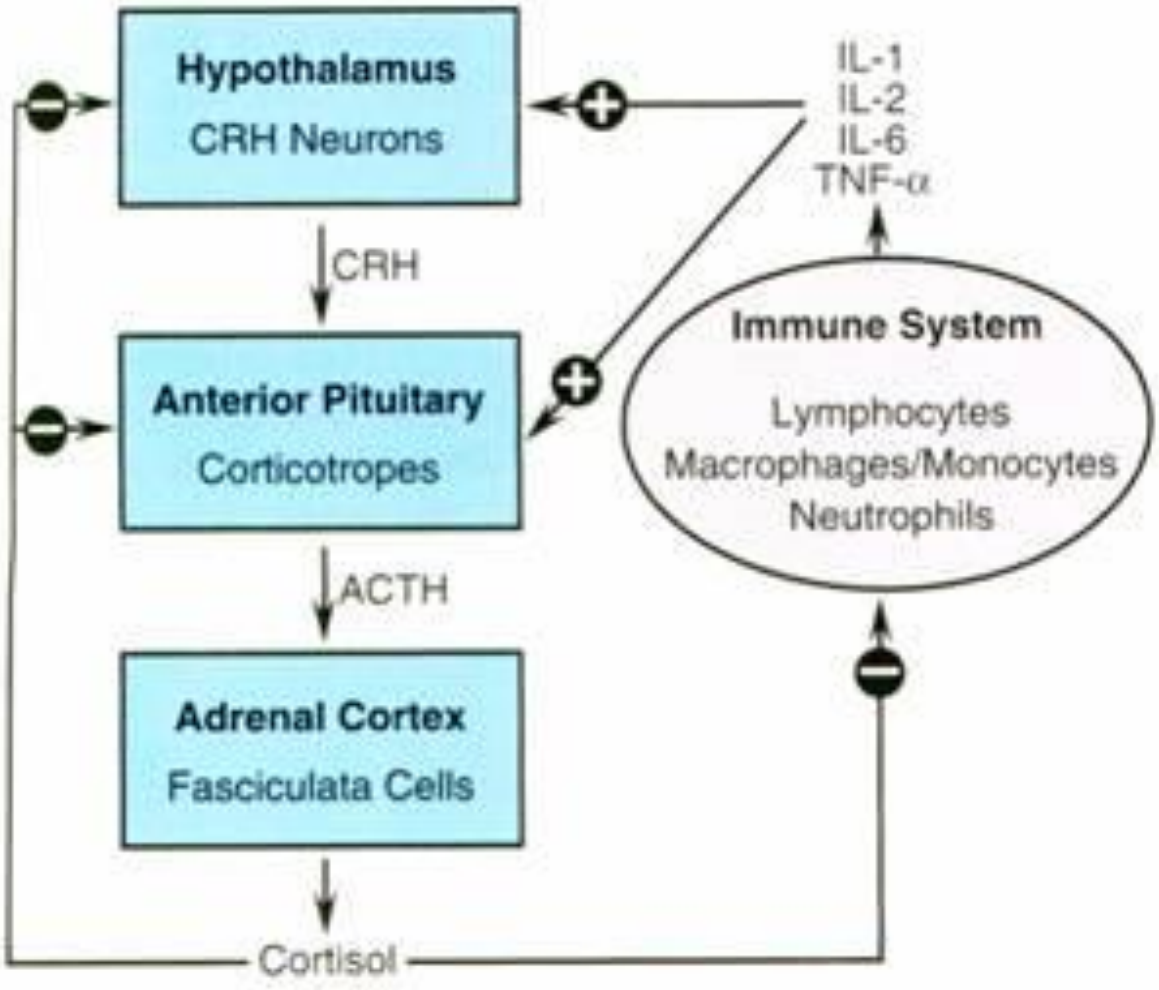
Effect on inflammatory mediators

- ↓ production of eikosanoids; ↓ PLA2, ↓ COX expression
- ↓ IL production (1,2,3,4,5,6,8), TNFα
- ↓ complement concentration in plasma
- ↓ NO production
- ↓ histamine release

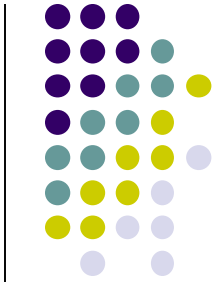


GC

Immune system regulation



GC reduce inflammation



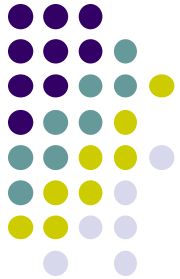
Dosing

- Approximately 4x replacement dose
- Usually 1 mg/kg *prednisone* or *prednisolone*
- Various "protocols" lead to success

Discontinuing therapy

- Abrupt discontinuation possible if GC therapy < 2 weeks duration:
- taper off if GC therapy > 2 weeks duration
- rate of taper should be proportional to duration of prior therapy (the longer the original therapy, the slower the rate of dose reduction)

GC inhibit immunologic responses



Dosing

- Approximately 16x replacement dose (daily)
- Usually initiate with 4 mg/kg *prednisone* or *prednisolone* daily in 2 doses (2 mg/kg q12 h)
  - avoids relatively remote potential for acute adverse effects
  - possibly reduces initial efficacy (vs one single daily dose)
  - acute "psychosis" POSSIBLE with these doses (especially in one 4 mg/kg daily dose)

Reducing dose rates

- Goal - to "acheive the lowest dose that will control the disease"
- Disease break may require returning to original remission doses (or higher)

Dosing examples of GC

Dosage & schedule

- **Low dosage for replacement therapy**

  Addison's disease, anteriorhypopituitarism , post subtotal bilateral adrenalectomy

  cortisone12.5～25 mg/d, or hydrocortisone 10～20 mg/d.

- **Universal dosage for long term therapy**

  inflammations, rheumatoid arthritis, lymphoma, lymphoblastic leukemia

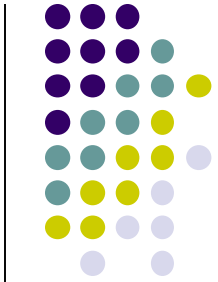
  Started with prednisone 10～20 mg, 3/d; gradually decreased to the maintenance dose after obtained the initial effect.

- **High dosage for implosive therapy**

  Serious infections: hydrocortisone i.v.d. 200-300 mg, ≥1 g/d.

  Shocks: hydrocortisone v.d. 1 g, 4-6 g/d.

Alternate day therapy
Anti-inflammatory or anti-immunologic



- Administration of a single dose of an intermediate-acting GC on alternate days (in a dose equivalent to that being employed over a 48 h period):

- any patient who is dosed with GC for longer than 14 days
- **greater risk** of disease "breakthrough„
- greater reduction in side effects than can be acheived by dose reduction alone (does NOT eliminate side effects, merely minimizes them)
- **useful** for *prednisone, prednisolone, methylprednisolone* (**inappropriate** for *dexamethasone, betamethasone*)

GC

Intravenous use

Shock:

- *Methylprednisolone sodium succinate*
- *Dexamethasone Na phosphate*

Spinal cord trauma:

- *Methylprednisolone sodium succinate*

Glucocorticoids - Indications

- As hormone replacement therapy – in deficiency syndromes like Addisonian states (physiological replacement doses)
- For HPA axis suppression, in Congenital Adrenal Hyperplasia (physiological doses are sufficient)
- Anti Inflammatory activity / Immunosuppressive action (5- 20 times of physiological doses)

Common therapeutic uses of glucocorticoids

- **Respiratory disease**
- Asthma,COPD,sarcoidosis,hayfever,prevention and treatment of ARDS.

- **Cardiac disease**
- Post-myocardial infarction syndrome

- **Renal**
- Some nephrotic syndromes, some glomerulonephritides

- **GI disease**
- Ulcerative colitis
- Crohn's disease
- Autoimmune hepatitis

- **Rheumatological disease**
- SLE,polymyalgia rheumatica, cranial arteritis,juvenile idiopathic arthritis, vasculitides,rheumatoid arthritis

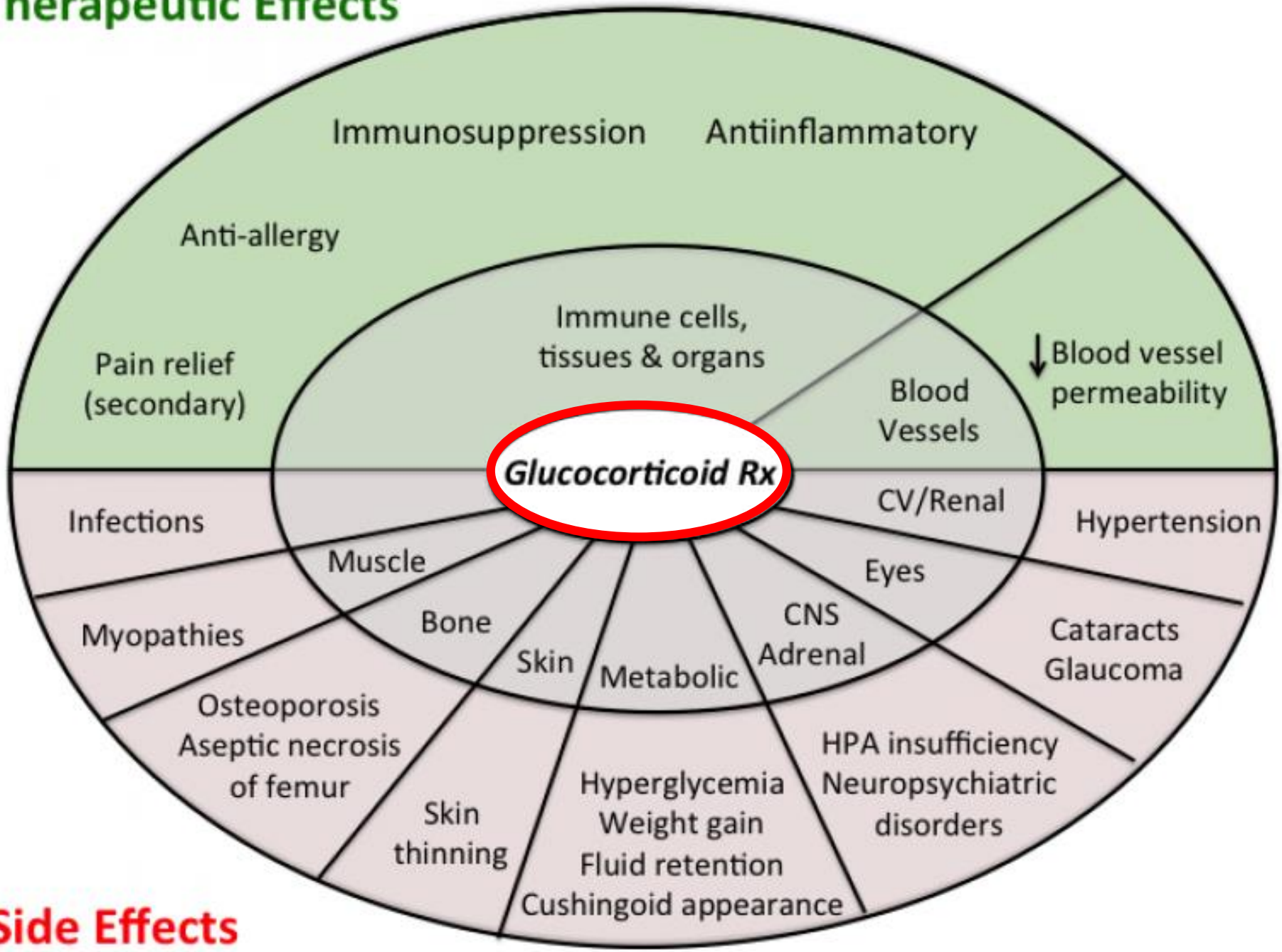
- **Neurological disease**
- Cerebral oedema

- **Skin disease**
- Pemphigus,eczema

- **Tumours**
- Hodgkin's lymphoma, other lymphomas

- **Transplantation**
- Immunosuppression

- **THE MOST COMMON INDICATION FOR STEROID USE IS AS AN ANTI-INFLAMMATORY DRUG**


Therapeutic Effects
Immunosuppression
Antiinflammatory
Anti-allergy
Pain relief
(secondary)
Immune cells,
tissues & organs
Blood
Vessels
↓Blood vessel
permeability
Glucocorticoid Rx
Infections
Muscle
Bone
Skin
Metabolic
CNS
Adrenal
Eyes
CV/Renal
Hypertension
Myopathies
Osteoporosis
Aseptic necrosis
of femur
Skin
thinning
Hyperglycemia
Weight gain
Fluid retention
Cushingoid appearance
HPA insufficiency
Neuropsychiatric
disorders
Cataracts
Glaucoma
Side Effects

GC SE
Summary

Adverse effects

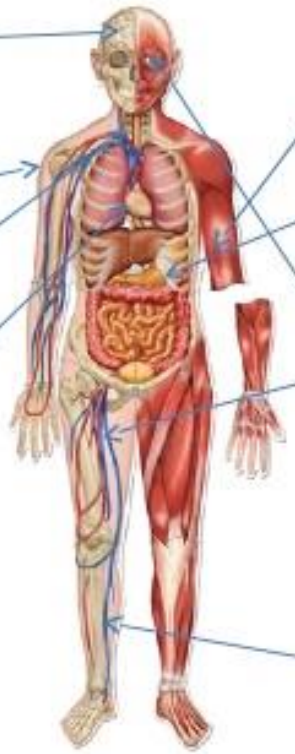
- Occur with prolonged use of high doses
- Cushing's disease

Psychiatric
- Sleep disturbance/activation
- Mood disturbance
- Psychosis

Skin/soft tissue
- Cushingoid appearance
- Abdominal striae
- Acne
- Hirsutism
- Oedema

Neurologic
- Neuropathy
- Pseudomotor cerebri

Cardiovascular
- Hypertension



MSK
- Osteoporosis
- Asceptic necrosis of bone
- Myopathy

Endocrine
- Diabetes mellitus
- Adrenal cortex suppression

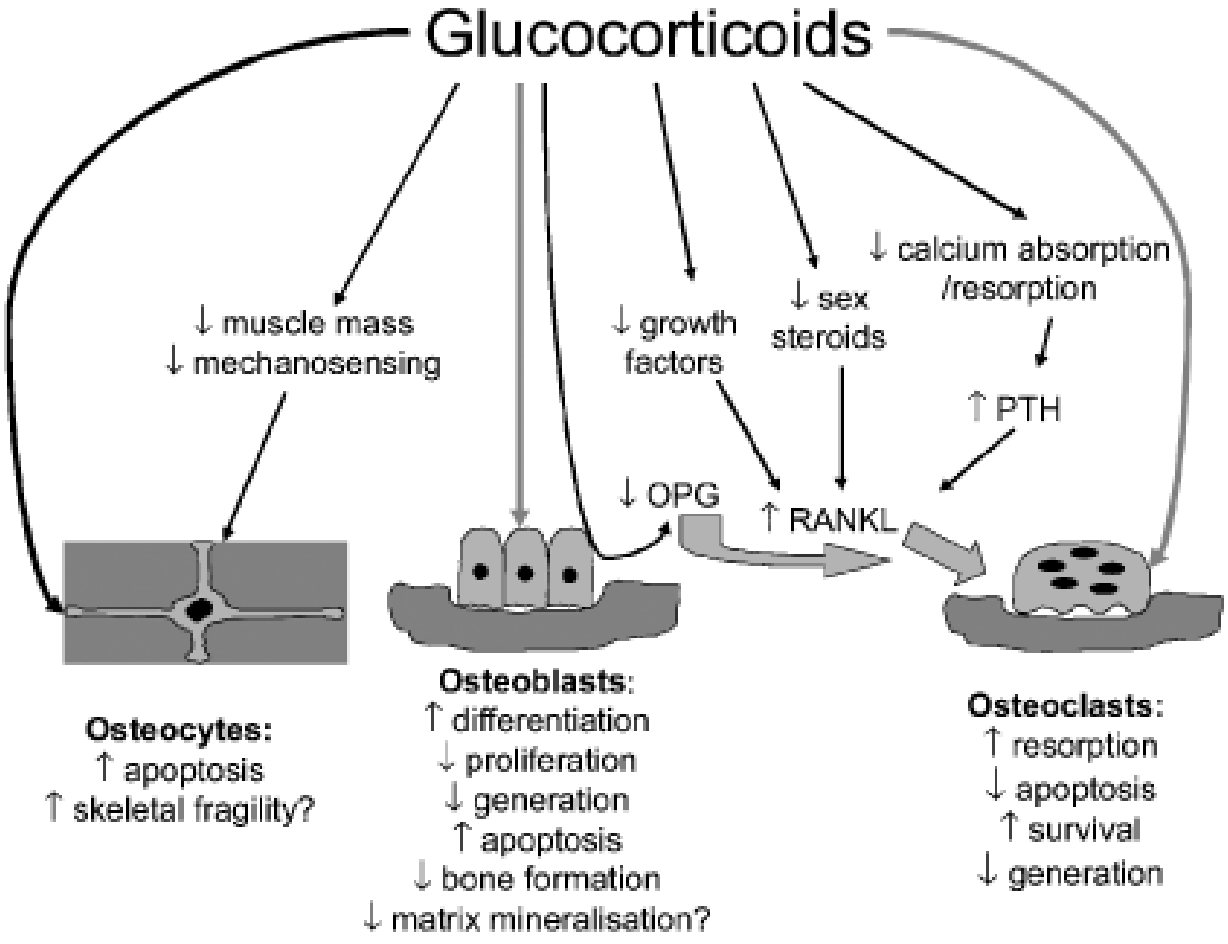
Immunologic
- Lymphocytopenia
- Immunosuppression
- False-negative skin test

Opthalmic
- Cataract
- Narrow-angle glaucoma

Developmental
- Growth retardation

GC-induced osteoporosis

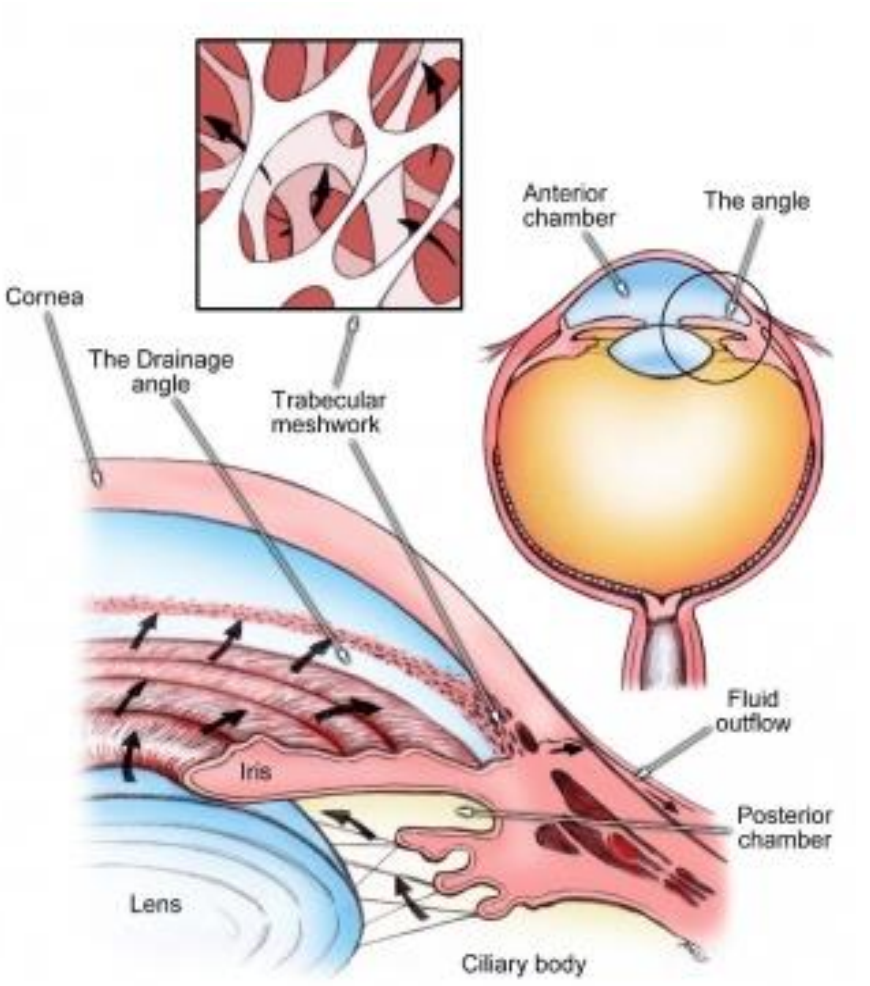
MOA



GC-induced glaucoma
MOA

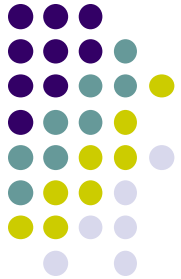
- Steroid administration alters **trabecular meshwork** cell morphology by different mechanisms resulting in:

  - reduction in facility of aqueous outflow
  - intraocular pression elevation



GC

SE can result in



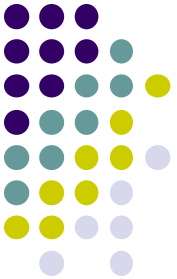
- ⇑ infective diseases susceptibility
- Spreading infection in inadequate use
- Wound healing prolongation
- Petic ulcer induction
- Because of hypothalamo-hypophyseal-suprarenal axis supression (starts after 2 weeks of use)

sudden therapy termination should be fatal

(taper regimen for discontinuation > 2 weeks)

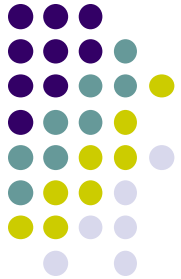
GC

Therapeutic principles



- Define relative contraindications
- Eliminate infection
- Choose optimal cortisonoid
- Apply the lowest effective dose possible
- Treat the shortest time possible
- ⇓ progressively the dose as soon as possible
- Never suddenly terminate the therapy
- Check body weight, BP, glycosuria & kaliemia
- Protein diet with sufficient calcium intake
- ⇓ NaCl intake
- In high steroid doses add KCl

GC
General summary



- All GC act by the same basic mechanism
- Cells control the specific response by controlling specific DNA sequences or protein interactions (anti-inflammatory & anti-immunologic activity cannot be separated from metabolic SE)
- Differences between GC are potency, duration of action of the base & PK behavior of the salts
- The salt (form) of a GC does not affect the duration of action (if the drug is given orally)
- Inj. replacements for oral GC (given daily or on alternate days) include bases for injection
- Alternate day therapy limits the toxicity of GC (metabolic & adrenal axis) while efficacy is maintained

GC antagonist

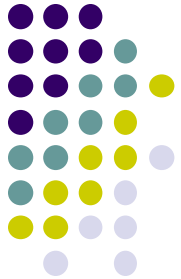
- ***Mifepristone***:
  - **GC** &
  - **progesterone** receptor antagonist

- **Indication:**
  - medical abortion in combination with ***misoprostol***

- **SE:**
  - vaginal bleeding
  - abdominal pain
  - GI upset
  - diarrhea
  - headache

Mineralocorticoids

Pharmacologic effect

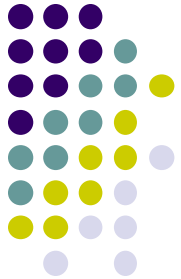


ALDOSTERONE

- Physiologic regulation is influenced by 3 principal factors:
  - **ACTH**
  - **renin-angiotensin system**
  - **plasma K^+ concentrations**

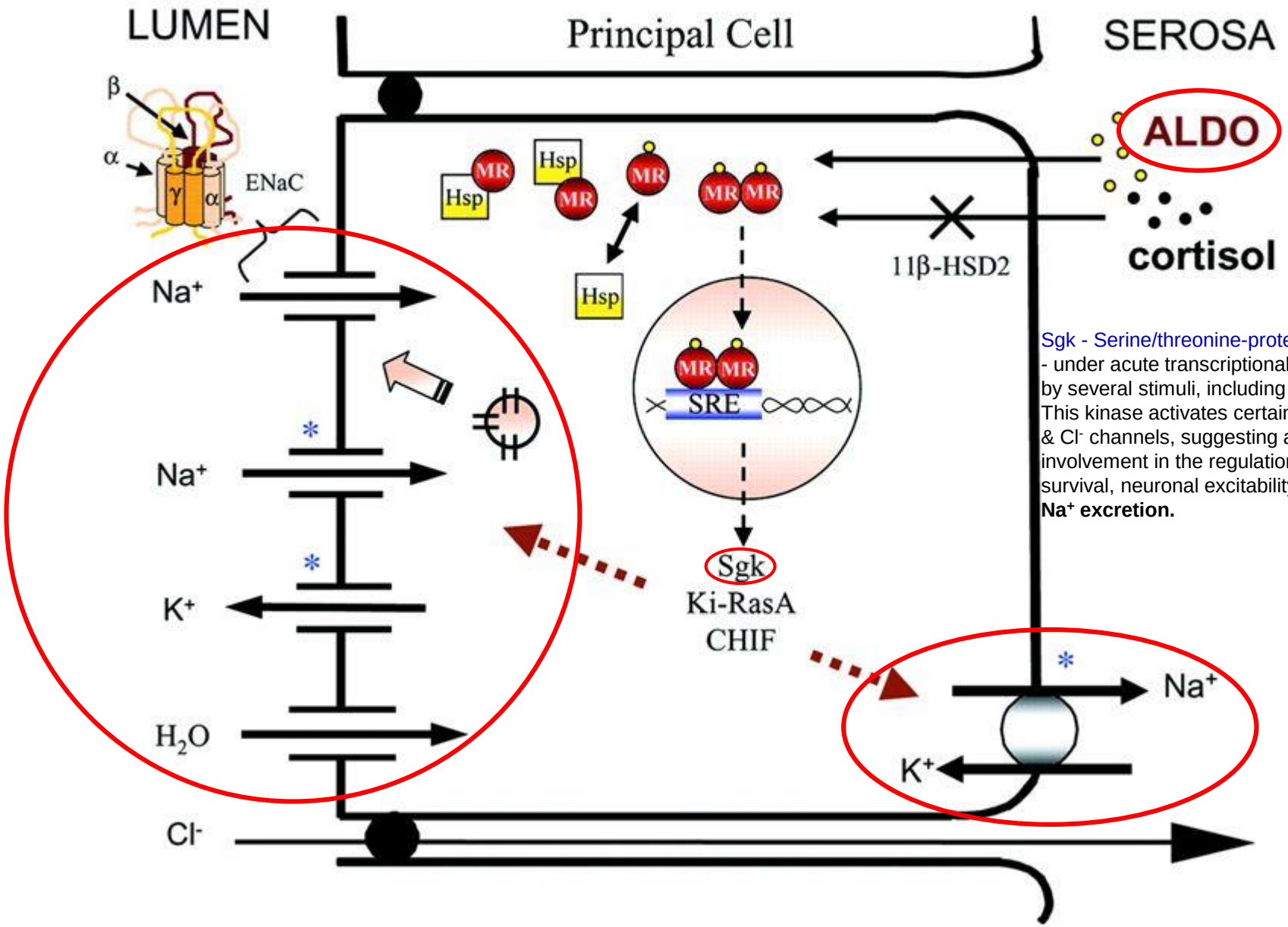
- ⇓ BP or volume of extracellular fluid ⇨ ⇑ renin release in kidneys ⇨ which by means of angiotensin II induces aldosterone secretion ⇨ ⇑ Na^+ & water retention & by feedback reaction ⇓ renin release

Aldosterone
MOA



- Acts on the nuclear mineralocorticoid receptors
- The principal cells - the distal tubule & the collecting duct of the kidney nephron
- It upregulates & activates the basolateral Na^+/K^+ pumps, which:
  - pumps 3 Na^+ ions out of the cell (into the interstitial fluid)
  - 2 K^+ ions into the cell from the interstitial fluid
- This creates a concentration gradient which results in:
  - reabsorption of Na^+ ions & water into the blood &
  - secreting K^+ ions into the urine (lumen of collecting duct)

Aldosterone Action



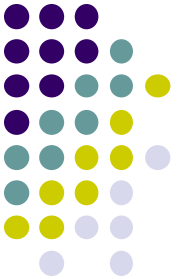
Sgk - Serine/threonine-protein kinase - under acute transcriptional control by several stimuli, including GC
This kinase activates certain K^+, Na^+, & Cl^- channels, suggesting an involvement in the regulation of cell survival, neuronal excitability & **renal Na^+ excretion.**

Aldosterone

Pathology

- **⇑ production of aldosterone could be:**
  - **primary** (adrenal adenoma or hyperplasia)
  - **secondary** (due to malignant hypertension, renal artery constriction, pregnancy, liver cirrhosis, nephrotic edema, congestive heart disease)
- **Antagonist - *spironolactone***

Spironolactone
Pharmacology & SE

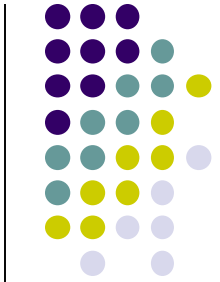


- **Blocks aldosterone receptors in kidneys**
- Prevents Na^+ reabsorption in the distal tubules
- Does not ⇑ K^+ loss
- **Potassium-sparing diuretic agent**

- Anti-androgen SE (gynecomastia)
- Hyperkalemia (in combination with ACE inhibitors)

Mineralocorticoids & steroid synthesis inhibitors

Therapeutic overview

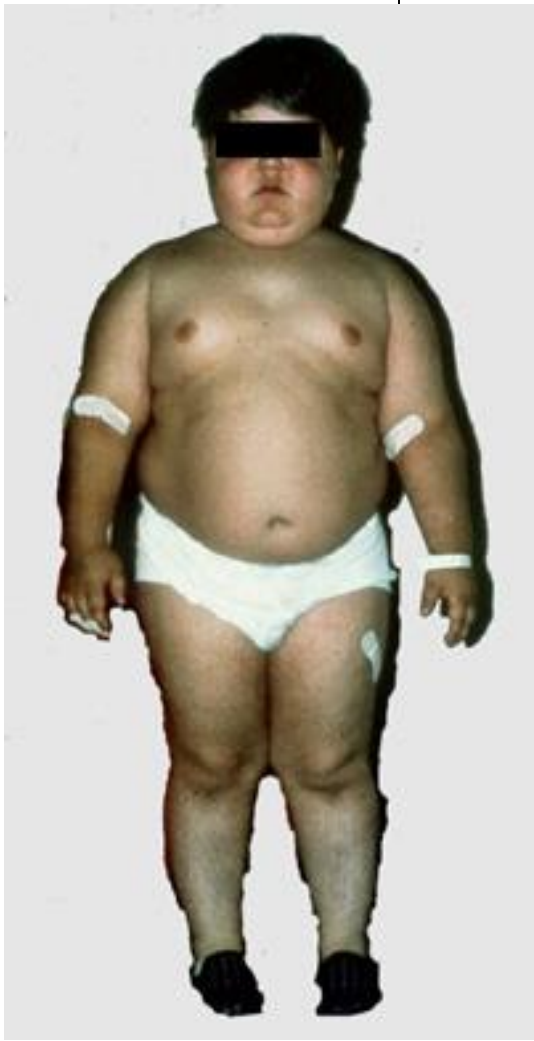


- **Hypoaldosteronism (Addison´s disease)**
  - ***fludrocortisone –*** replacement therapy
- **Adrenal hyperfunction**
  - *metyrapone, ketoconazol*

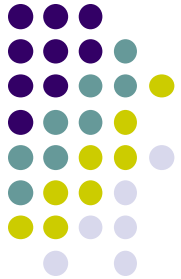
Metyrapone
Effect & clinical use

- ***Metyrapone*** - blocks **cortisol synthesis** by reversibly ⇓ steroid 11β-hydroxylase

- Can be used in:
  - diagnosis of **adrenal insufficiency**
  - occasionally in the treatment of **Cushing´s syndrome**



Ketoconazole
Effect & clinical use



- Imidazole antifungal drug by blocking the synthesis of **ergosterol** in fungi (plant sterol)
- In humans it ⇓ the conversion of **cholesterol to steroid hormones** (cortisol & testosterone)

- **Indications:**
  - suppression of **GC synthesis** in the treatment of Cushing´s syndrome
  - second-line treatment for certain forms of advanced prostate cancer