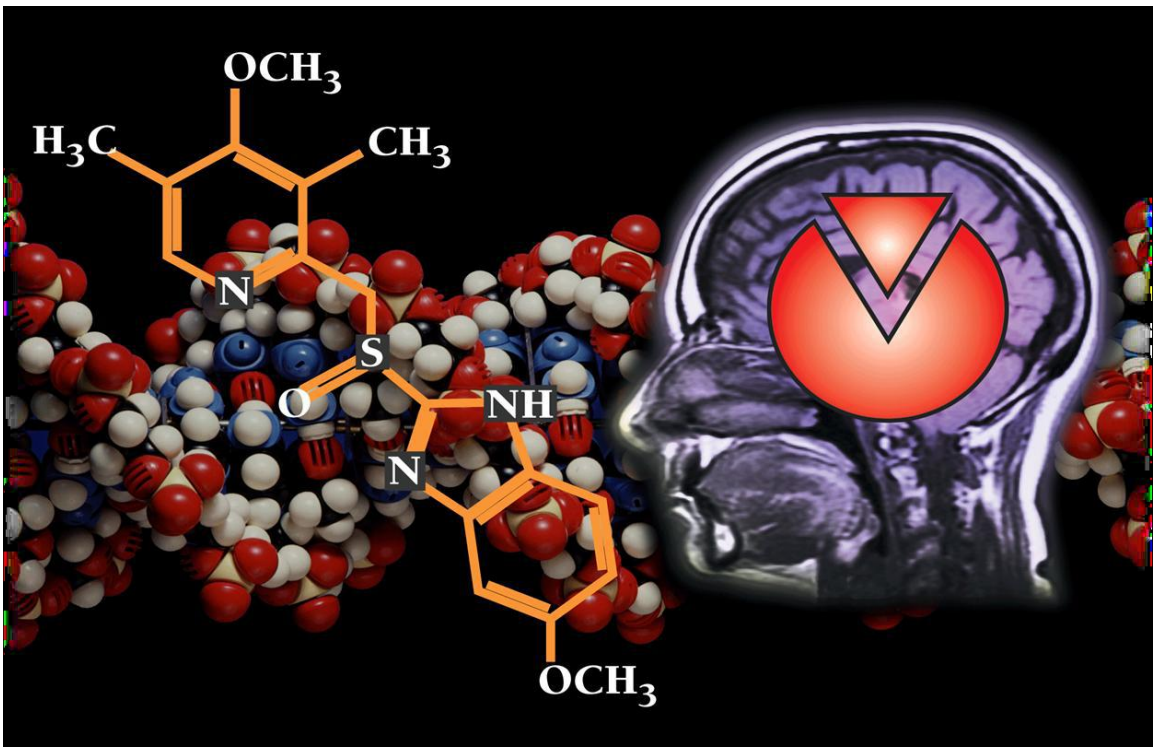
King Saud University
College Of Medicine
Pharmacology Team 430
Endocrine Block

Pharmacology of Corticosteroids



Note: first two pages is an introduction

Text in red is doctor's notes,

text in green and textboxes in thick blue margins are **additional info.**

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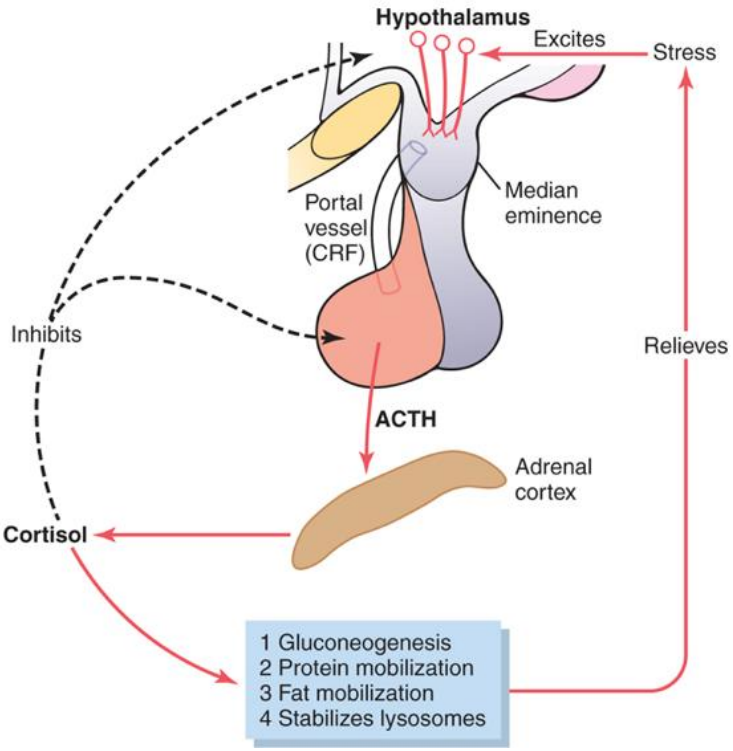
Physiology of Glucorticoids:

- **Glucorticoids** are a class of steroid hormones that are produced in **the zona fasiculata** of the adrenal cortex.
- The **zona fasiculata** mainly secretes **Cortisol** (also called hydrocortisone) and Corticosterone, with **95% of glucorticoid** effects being a result of cortisol activity.

Secretion and regulation:

- Secretions of the **zona fasiculata** and **zona retrularis** are controlled by **ACTH** from the anterior pituitary, which in turn is controlled by the hypothalamic hormone: corticotropin-releasing hormone (CRH).
- **Glucorticoids** have direct negative feedback effects on the **hypothalmus** and **anterior pitutary** to reduce the formation of both CRF and ACTH.



Effects of Glucorticoids:

Glucorticoids have different effects on different body processes that enable the body to cope with stress. They have a great number of effects that will be discussed later on, but the most important effects can be summarized as follows:

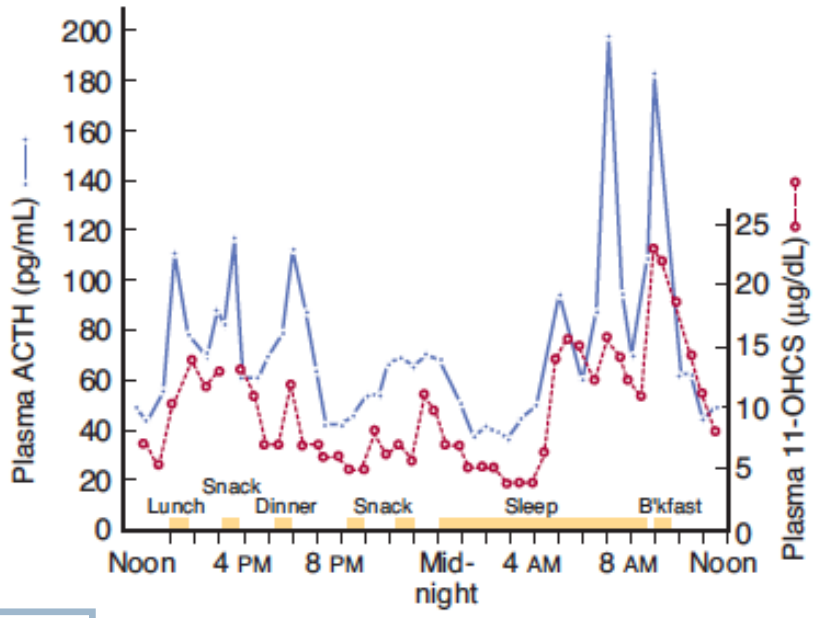
1. Control of carbohydrate, protein, and fat metabolism in a way that favors **gluconeogenesis and high blood glucose levels.**
2. Inhibition of immune and inflammatory responses.
3. Enhancement of vascular responsiveness to **catecholamine** to maintain blood pressure

Circadian (diurnal) Rhythm of Cortisol secretion:

- The secretory rates of **CRF, ACTH**, and **cortisol** are **high** in the early morning **but low in** the late evening.

- This effect results from a 24-hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion.

- Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made.

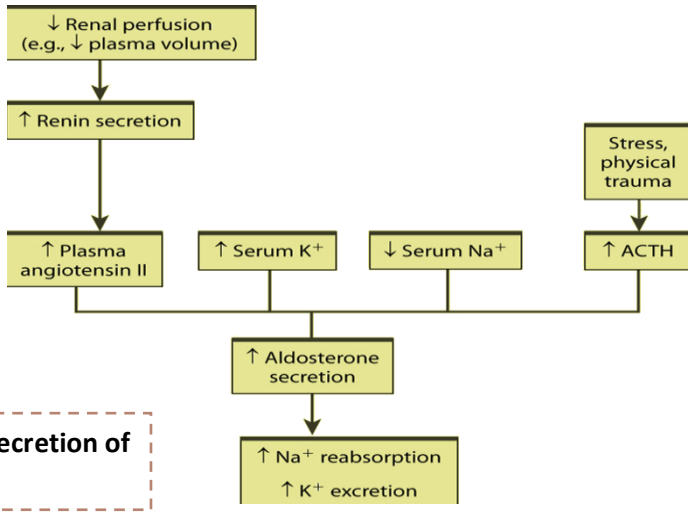


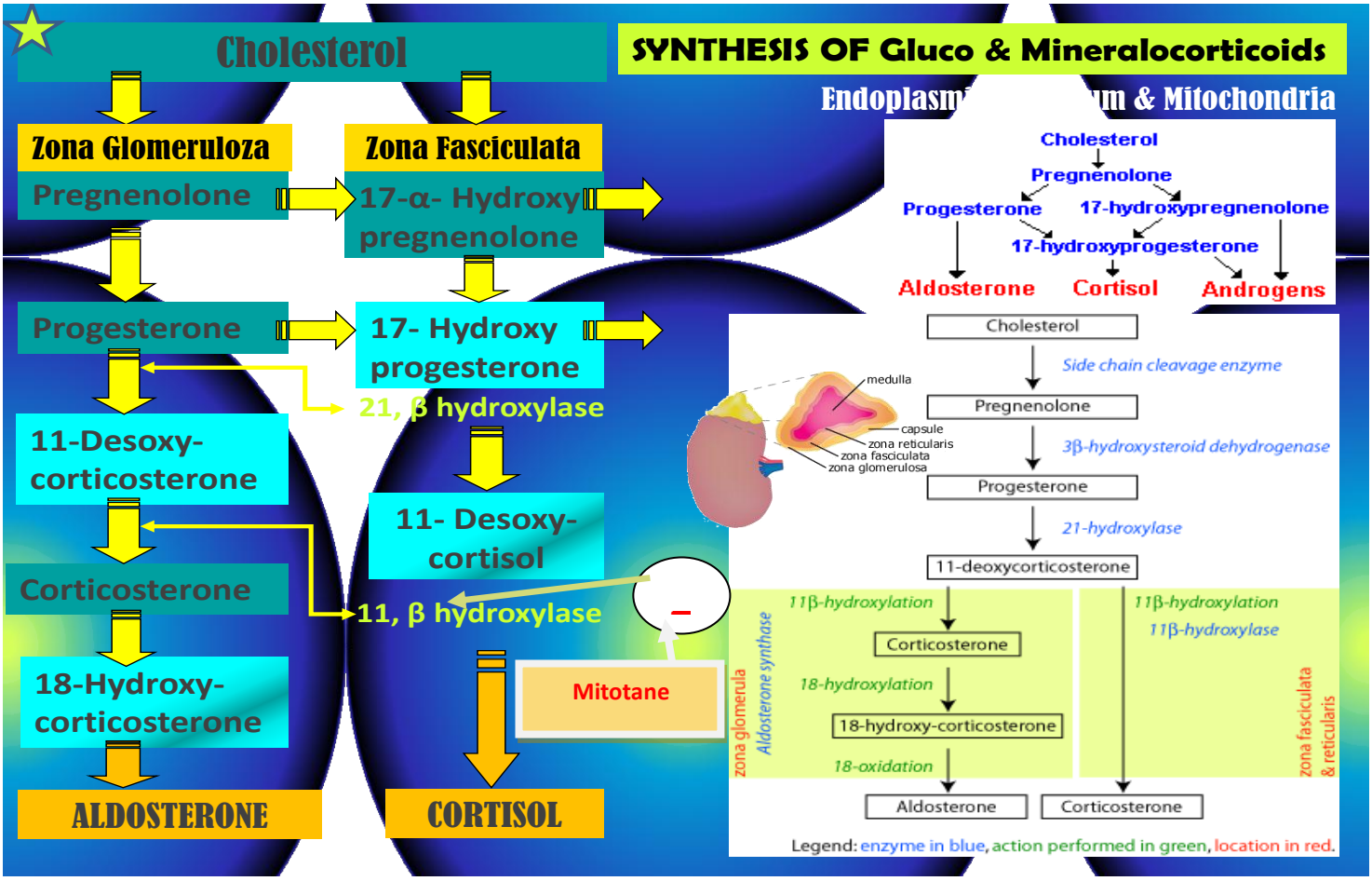
Note: When we give drug we have to mimic circadian rhythm because the low concentration of hormone at night stimulate the hypothalamus to secrete cortisol at morning and prevent it's suppression

Mineralocorticoids

- Mineralocorticoids ➜ **Released from <u>Zona Glomerulosa</u> ➜ as Aldosterone ➜**
- **Regulated by angiotensin II, potassium, and ACTH.**
- **In addition, dopamine, atrial natriuretic peptide (ANP) and other neuropeptides**
- **It Control water & electrolyte homeostasis**

Note: ACTH specifically stimulates GC & has little control over secretion of aldosterone .





Dysregulation of Corticosteroid

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

An increased production of glucocoticoids ➜ Cushing's syndrome

An increased production of mineralocorticoids ➜ Conn's syndrome (Hyperaldosteronism ,Hypernatremia ,Hypervolemia ,Hypertension,Hypokalemia ,Alkalosis)

Pharmacology of Exogenous Glucocorticoids:

Exogenous Glucocorticoids come in a variety of preparations with different potencies. Here are a few examples:

Prednisone, Prednisolone, Methylprednisolone, Triamcinolone, Dexamethasone, Betamethasone, Beclomethasone, Fluticasone, Budesonide, and Mometasone.

Mechanism of action:

Glucorticoids exert their effects by binding either to:

A. Cytosolic receptor

B. Membranous (present on the cellular membrane).

The **genomic mechanism** is relatively slow and takes **hours to days** to take effect, while the **non-genomic** takes only **minutes to hours.**

Essentially all these steroids use one or both mechanisms to produce their effects, but the example we use here is how these steroids produce their **anti-Inflammatory** and **immune suppressive effects.** They achieve this by the following actions:

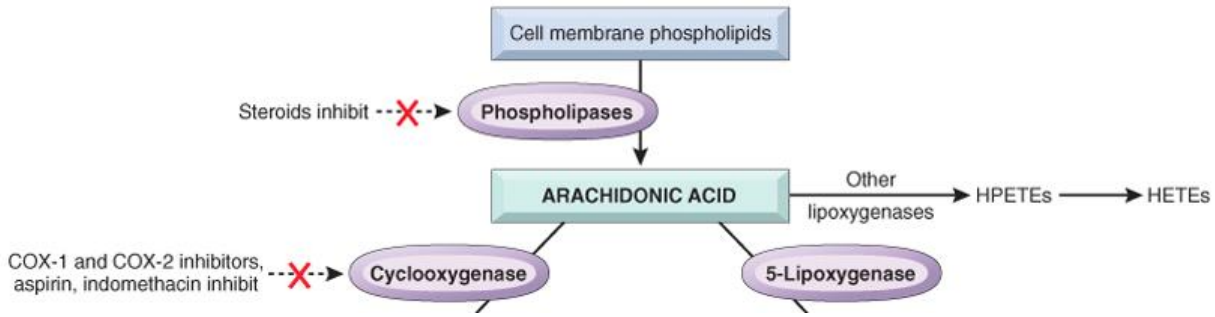
A. Cytosolic receptor binding (genomic effect):

These effects depend on an **increase** or **decrease** in genetic expression of **proteins** to give **stimulatory** or **inhibitory** effects. These are classified as follows:

Inducing Protein Expression having Anti-Inflammatory effect:

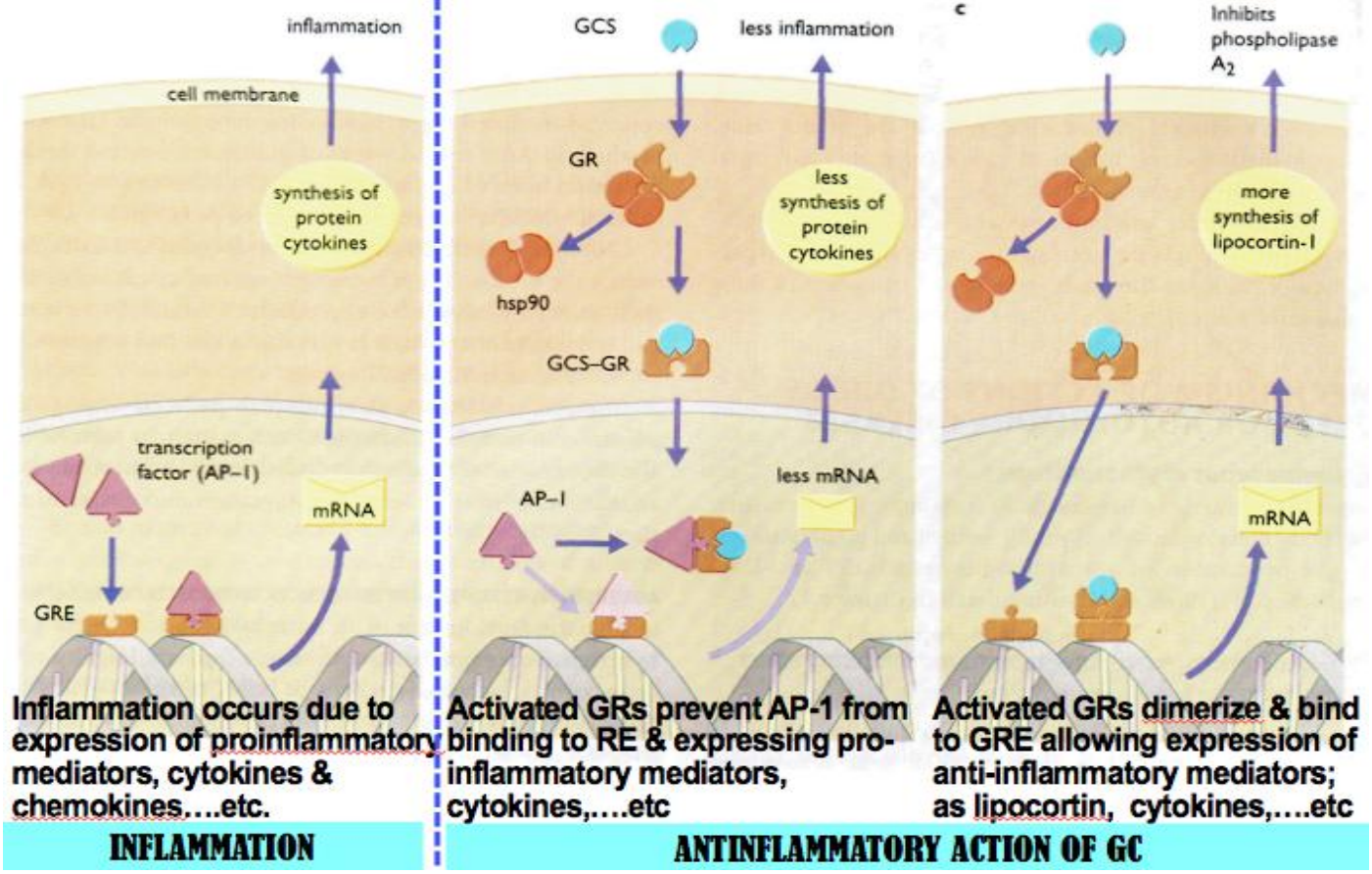
Binding of the activated cytosolic receptor to the glucocorticoid response element (GRE) on the regulatory region of the gene causes an increase in **antinflamatory protein (e.g. lipocotrin) transcription and production.**

Lipocortin causes these **antinflamatory** effects by inhibiting the actions of **phospholipase A_2**, which reduces the amount of **Archidonic Acid** metabolites (e.g. prostaglandins and leukotrines) that are necessary for inflammation.



Repressing Protein Expression:

In contrast to the previous mechanism, The **Steroid Receptor Complex** (steroid bound to the activated receptor) in this case inhibits other transcription proteins (e.g. AP-1) from binding to their specific genes (response elements) to translate inflammatory mediators (e.g. IL-2; other cytokines and chemokines) and thus greatly suppressing the inflammatory and immune reaction.



Explanation of MOA: The glucocorticoid dissociates from the binding plasma protein (usually cortisol binding globulin CBG) and diffuses into the cell. The hormone then binds to its cytoplasmic receptor that is bounded to a group of proteins, most importantly being heat shock protein 90 (HSP 90). The hormone causes these HSP 90 and the other proteins to dissociate from the receptor complex, and then allow the hormone receptor complex to enter the cell nucleus. Once inside the nucleus the steroid receptor complex interacts with the cell's DNA through promoters by increasing transcription of mRNA to be translated and that to produce the affecting proteins that bring up the physiological response. Another action of the steroid receptor complex is to prevent other transcription factors (e.g. Ap-1) to act on their response elements, and thus inhibit the expression of pro inflammatory mediators

B. Membranous receptor binding (non-genomic effects):

Steroids act on membrane bound receptors to utilize second messenger mechanisms to **cause rapid responses (in mins – hrs)**

cross talks with G protein 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 or physiological effects of Glucorticoids:

1-Effects on metabolism:

A) Effects on carbohydrate metabolism:

i. **Stimulate gluconeogenesis** (formation of carbohydrate from proteins and some other substances) by the liver through inducing the enzymes responsible for **gluconeogenesis and mobilization substrates** (amino acids, free fatty acids, and other) to the liver to be used.

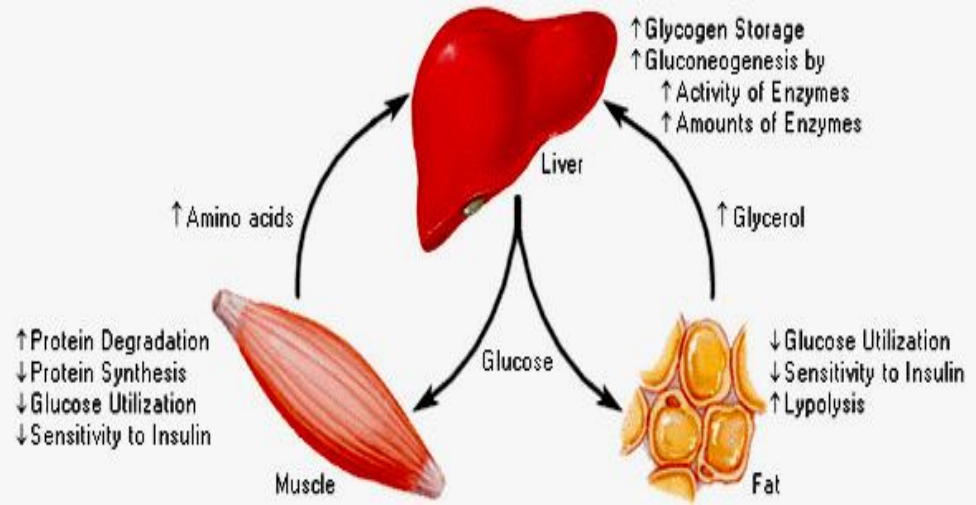
ii. Mild decrease the rate of **glucose utilization** by cells (insulin resistance)

iii. Increases glycogen storage for future access by the body through epinephrine and glucagon.

B) Effects on protein:

-Increased catabolism and decreased anabolism in **extra hepatic** tissues to increase plasma amino acid concentration for gluconeogensis

- **Increased protein anabolism** in the **liver.**
- Negative nitrogen balance with muscle wasting and subsequent increase in **uric acid** production.
- **Osteoporosis**
- Retardation (Slowing) of growth in children
- **Skin atrophy** and **capillary fragility** that causes easy bruising and the appearance of stria throughout the body because of fibroblasts and collagen synthesis inhibition.



C) Effects on lipids and fatty acids:

- It promotes **lipolysis** to increase plasma free fatty acids concentration.
- **fat deposition on shoulders, face and abdomen.**

2. Effects on immune and inflammatory response:

1. Glucocorticoids **reduce** vascular permeability with **vasoconstriction** so there is reduced edema. They cause these effects by inhibiting mast cell granule release, especially histamine.
2. **Decrease** the release and synthesis of **inflammatory mediators** largely through inhibiting the actions of **phospholipase A2** and subsequently **Aracadonic Acid** metabolites (**prostaglandins and leukotrienes).**
3. Decrease antigen – antibody binding causing a decrease in mast degranulation and transmitter release.
4. Glucotricoids d**ecrease the infiltration** and activity of inflammatory cells (eosinophils, macrophages, lymphocytes, etc.) by decreasing the formation and release of **cytokines and chemokines**.
5. Decrease complement formation and activation.

- There is also a decrease in lymphocyte count, which reduces the availability of cells to participate in inflammation.

3. Effects on Ca^{2+} metabolism:

Increase urinary **excretion of Calcium and decrease absorption** from intestine (antivitamin D action).

4. Effects on Hypothalamic-Pituitary-Adrenal Axis:

Glucocorticoids have a suppressive effect on the hypothalamus (to release CRH) and the pituitary (to release ACTH).

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

5. Other effects:

Euphoria or psychotic states. This effects may occur due to CNS electrolyte changes.

Pharmacokinetics:

Absorption:

Hydrocortisone & its synthetic analogues are effective **orally,** while parentral forms are also available.

Can get absorbed systemically when given at local sites (e.g. skin, respiratory tract, conjunctival sac, synovial spaces etc.). This means that corticosteroids can have some mild systemic effects even if they are administered at specific locations. These systemic effects are markedly reduced with fluorinated preparations and have been made a requirement for topical treatment.

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, while 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 like:

Cortisone →Hydrocortisone

Prednisone→ Prednisolone

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

Excretion; as soluble sulphates in the urine.

Classification of Glucocorticoids according $t_{1/2}$		
Drug	**Anti Inflammatory Effect**	**Na retention**
Short Acting Preparations ($t_{1/2}$ <12hors)		
Cortisol (for emergency)	1	1.0
Cortisone	0.8	0.8
Intermediate Acting Preparations ($t_{1/2}$ = 12 -36h)		
Prednisolone	4	0.8
Triamcinolone	5	0
Long Acting Preparations ($t_{1/2}$ >36)		
Dexamethasone (Fluorinated)	25	0
Betamethasone (Fluorinated)	25	0

- **You have to know:**
- ❖ which drugs that have more (water retention)
- ❖ The only preparation used in emergency situations is **cortisol**
- ❖ The more potent immunosuppressive effect of the drug, the less mineralocorticoid effect that drug has.
- ❖ You must know which preparations are short acting, which are intermediately acting, and which are long acting (without memorizing numbers)

Classification according to potency & method of administration of topical preparations	
Topical Drug	Potency
Beclomethasone (Cream)	Potent
Triamcinolone actinide(Ointment)	Potent
Mometasone(Cream & Ointment)	Moderate
Fluticasone (Cream)	Moderate
Hydrocortsione acetate(Ointment)	Mild

You have to memorize just 5 drugs :

Potent which are not preferable:
Beclomethasone , Triamcinolone actinide

Moderate: Mometasone and Fluticasone

Mild: Hydrocortisone acetate

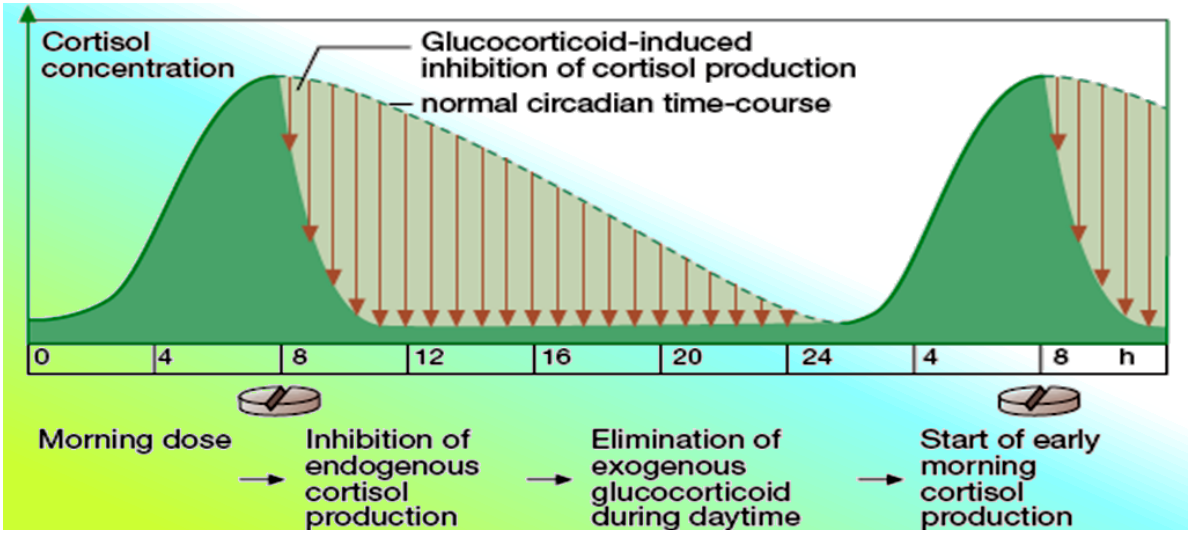
Note:

- You must know the two preparations that are used in the inhaler form are **fluticasone** and **budesonide**, and that they are used because they undergo very little first-pass metabolism that will cause almost no effect because of rapid deactivation by liver.
- Topical drugs can be used in the face (which is thin –very sensitive –so we have to put in our consideration many things when we use them on the face):
- the cream is the optimal preparation ,don't use ointment because it's more potent and work strongly
- use only mild –moderate topical steroid
- take it at night because the photosensitivity(when the pt exposure to sun ,red and brown patches appear in his skin)

Dosage Schedule:

- Time of administration of GCs, especially on prolonged use, should follow natural circadian rhythm i.e. person should take it in the early morning.
- A regimen of alternate-day administration of the adrenocortical steroid may be useful. This schedule allows the HPA axis to recover/function on the days the hormone is not taken.

- This dosage schedule is used to minimize hypothalamo-pituitary-adrenal axis impairment.



Recovery of the HPA axis is aided if there is no exogenous glucocorticoid present during the nocturnal (night) surge in ACTH secretion. This can be achieved by giving glucocorticoid in the morning. Giving ACTH to stimulate adrenal recovery is of no value as the pituitary remains

Indications:

A-Hormone replacement therapy:

1- Adrenal Insufficiency:

Adrenal 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

In treatment of chronic Addison disease we usually give combination of fludrocortisone (which is mineralocorticoid)and Dexamethasone(which is glucocorticoid) then the pt continue to be treated with only **Dexamethasone**

2 - 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.

3- Cushing Syndrome:

In Diagnoses ➔ **Dexamethasone suppression test**

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

B- Immunosuppressant and Antinflmatory Indication:

- **Severe allergic reactions** (an immune reaction) e.g. serum sickness, angioneurotic edema (angioedema)... etc.

Note: serum sickness is a type of hypersensitivity, immune complex hypersensitivity (type III) that developes as a result of exposure to antibodies and proteins derived from animals. When the antiserum is given, the human immune system can mistake the proteins present for harmful antigens. The body produces antibodies, which combine with these proteins to form immune complexes. These complexes can cause more reactions, and cause the symptoms

- **Diseases of allergic origin** (an immune disease after sensitization); bronchial asthma, rhinitis, conjunctivitis, eczema, and many other atopic & proliferative skin diseases
- **Autoimmune disorders**; rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythrematosus, nephrotic syndrome.
- **Organ transplantation**; e.g. kidney, cardiac, bone marrow

Corticosteroids are used to prevent transplant rejection. This is a very important use for corticosteroids as they decrease antigen presentation from the grafted tissue, and interfere with the sensitization of Cytotoxic T lymphocytes, and thus decrease the likelihood of rejection.

- **Blood dyscrasias**; hemolytic anemia, thrombocytopenic purpura, agranulocytosis ... etc. Because a lot of blood dyscrasias have an autoimmune component, corticosteroids have very beneficial effects. Even though corticosteroids may cause agranulocytosis, the treatment benefits of corticosteroids outweigh the possible side effects of agranulcytosis.
- **Acute gout** (resistant) to other drugs

Note: Prednisolone, Dexamethasone, and Betamethasone are the most potent immunosuppressants and antinflamatory corticosteroids.

C- Other indications: Dexamethasone & betamethasone are used

1. **Raised intracranial pressure**, to minimize cerebral edema
2. **In neoplastic diseases:**
   With cytotoxic drugs ➔ as in Hodgkin's disease, acute lymphocytic leukaemia
   Pry or 2ndry neoplasms in the brain & postoperative to brain surgery➔ ➔edema
3. **As antiemetic regimens:** to prevent and cure emesis of chemotherapy. These effects are not well understood.
4. **Suppress excess ACTH production**

Dexamethasone, and Betamethasone we use it to treat the raising in intracranial pressure because they cause no water retention

Adverse Reactions of Corticosteroids:

- The adverse effects of corticosteroids depend greatly on **dosage and duration** of therapy.

- When glucocorticoids are used for **short periods** (< 2 weeks), it is unusual to see serious adverse effects even with moderately large doses, but the risk increases with *prolonged use and increase dosing.*

- Adverse effects of **corticosteroids** can be related to one of the three effects:
  1) **Inhibition** of the **hypothalmic-Pitutary-Adrenal Axis.**
  2) **Iatrogenic Cushing Syndrome**
  3) **Other effects**

1) Inhibition of the hypothalmic-Pitutary-Adrenal Axis (HPA):

- If treatment is less than one week with mild to moderately high doses: there **should be no fear of HPA suppression.**
- If doses are high: 2.5-5 mg prednisolone should be reduced at an interval **of 2-3 days.**
- If treatment is for **long and with high doses**: reduce **half the dose every week until** 25 mg prednisolone or equivalent is reached, then reduce by about 1mg every 3-7 days.

Notes: If the patient has experienced HPA suppression, abrupt removal of the corticosteroids may cause: A. the disease treated to reappear (sometimes with an increase in intensity) or B. acute adrenal insufficiency syndrome (adrenal crisis) that can be lethal. These outcomes coupled with the possibility of psychologic dependence on the drug, means the dose must be tapered according to the individual, possibly through trial and error. The patient must be monitored carefully.

2) Iatrogenic Cushing Syndrome:

- Most patients who are given daily doses of 100 mg of hydrocortisone or more (or the equivalent amount of synthetic steroid) for longer than 2 weeks undergo a series of changes that have been termed **iatrogenic Cushing's syndrome.**

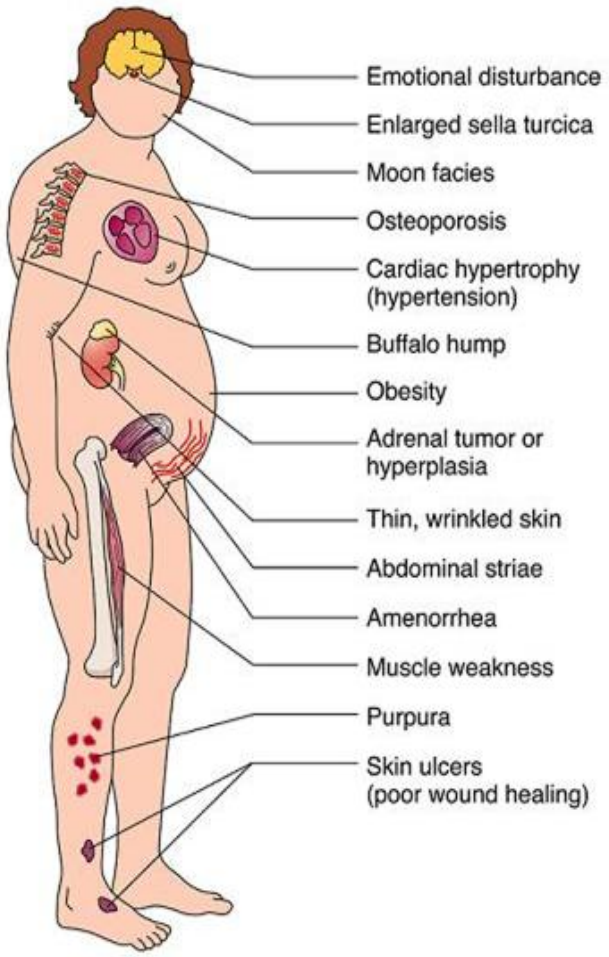
- These effects are shown in the graph:

- If possible, there should be **slow withdraw of corticosteroids** to allow body to slowly resume its normal balance of ACTH & cortisol secretion.

- If it is not possible to stop corticosteroid treatment because of underlying disease,

- Concurrent symptoms are treated separately:

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



3) Other adverse effects: usually with the systemic preparations

- **Hyperglycemia , glycosuria, diabetes mellitus** (esp. with fluorinated preparations) Glycosuria happens because renal tubules reach their threshold for reabsorption, causing glucose to be excreted. This excreted glucose drags water and causes increased urine output and polyuria

- **Growth retardation** with premature closure of epiphysis, which causes short stature.

- **Muscle wasting** and **negative nitrogen balance** (esp. fluorinated preparations) This is due to the decreased protein synthesis and increased protein catabolism in extrahepatic tissues.

- **Fat redistribution & abnormal deposition.** The exact mechanism for this specific redistribution is not known, but this may be due to the increased appetite that happens with increased and the high levels of insulin which have a lipogenic effect.

- **Hypertension and Na^+ retention**. This may be due to the following mechanisms:

A) The mineralocorticoid effect of glucorticoids
B) The increased levels of angiotensinogen and angiotensin II
C) The permissive vascular effects they have on catecholamines

- **Hypokalaemia** due to the mineralocorticoid effect of glucocorticoids.

- **Osteoporosis** because of –ve on effects on osteoblasts / +ve effects on osteoclasts and negative Ca2+ balance. These combined effects cause vertebral compression and fractures.

- **Avascular necrosis of head of femur.** This effect almost only happens with excessive levels exogenous corticosteroids.
- **Menstrual irregularities** due to the disruption of LH secretion by the anterior pituitary.
- **Psychiatric disorders; depression, and euphoria.** How corticosteroids bring up these neurological effects is not well understood.
- **Impairment of defense mechanism→** serious infections, flare of dormant T.B or activate a carrier state of hepatitis. This may cause an infection even when life attenuated vaccines are given.
- **Delayed wound healing** due to inhibition of fibroblasts that leads to decreased collagen and connective tissue synthesis.
- **Peptic ulcer specially if with NSAIDs.** It maybe not well established that corticosteroids cause peptic ulcers, but they at least synergistically with NSAIDS to increase the risk of peptic ulcer development.
- **Effects on skin: striae, acne, and hirsutism.** Striae develops because of connective tissue and fat deposition.
- **Ocular toxicity:** glaucoma & cataract. (Glucocorticoids raise intra-ocular pressure)

Local Toxicity: (with topical administration)

- **Skin→** infection, atrophy, bruising.
- **Eye →** viral infection, cataract, glaucoma.
- **Inhalation →** fungal infection, hoarseness
- **Intrarticular** (Situated between two joint surfaces)→ infection, necrosis
- These are local effect s and happen at the site of topical administration, rather than the systemic effects that are seen with systemic administrations like oral or paraenteral forms.

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

Preactions:

- Patients receiving GCs for adrenal insufficiency and are subjected to major stress (e.g. surgery) ➔ should have their doses doubled
- In children receiving ➔ take care of live attenuated vaccines. Killed vaccines should be used if available, but if not: glucocorticoids should be stopped temporarily, until the effect of the vaccines takes place.
- In pregnant women; better avoid fluorinated GCs ➔ teratogenicity (only fluorinated perprations have a slight teratogenic effect. Other preparations are very safe even with mega doses)
- Newborns to mothers taking high dose GCs ➔ -ve HPA axis (glucorticoids may slightly pass through to the baby to cause a slight suppression of HPA, These effects happen especially within the first trimester)

MINERALOCORTICOIDS

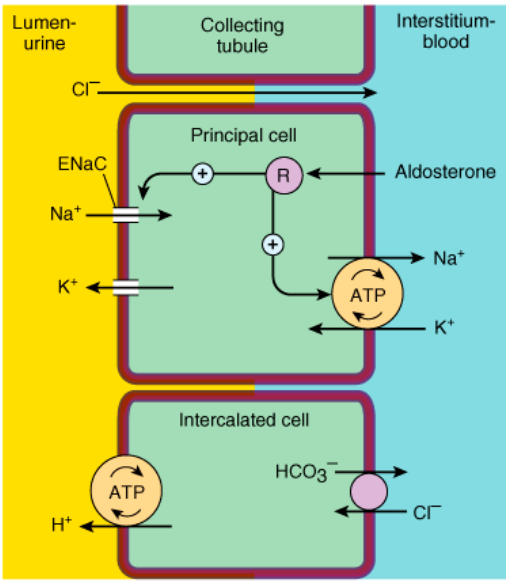
E.g: (Aldosterone, Deoxycorticosterone, Fludrocortisone)

MOA: by two different pathways

They act by binding to **mineralocorticoid receptors (MCR's)**

These receptors have the same affinity for glucocorticoids, which is present in much higher concentrations in the extracellular fluid than mineralocorticoid. (So these MCR's will be bound mainly to glucocorticoids).

In mineralocorticoid responsive cells i.e. distal nephron, glucocorticoids are enzymatically destroyed in MC responsive cells ⇨ so mineralocorticoid will bind to their receptors alone without any competition from glucocorticoids.



1-In Cytosolic MCR's → mediates GENOMIC Action → Expression of proteins

- **Na/k ATPase pumps** → ↑ Na retention
- **Na channels** (epithelial sodium channel (ENaC)). → ↑ Na reuptake from lumen
- **K simporters** → ↑ excretion of K & H

This genomic occurs In **distal convoluted and collecting tubules of the kidney, in the colon,and in sweat & saivary gland)**

2. Membranous glucocorticoid receptors (GCR) mediates NON-GENOMIC Action

- **Interact with G protein coupled receptors & channels to mediate rapid adaptive changes to fluid depletion**

Effects/uses/preparation

Net effect:

- **Sodium retintion → osmotic effect → water follows → expansion of extracellular fluid**
- **↑Renal excretion of potassium &↓ intracellular potassium**

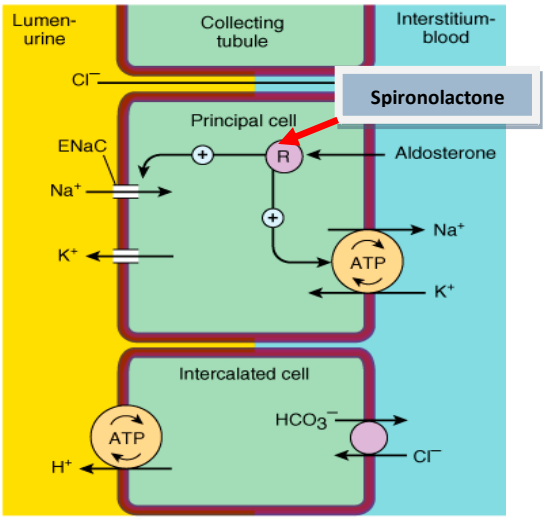
In excess amounts of mineralocorticoids → hypertension, atherosclerosis, fibrosis → vascular & cardiac remodeling → cerebral hemorrhage / stroke & or cardiomyopathy

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

Corticosteroid antagonists

1-Medications that compete with steroids on receptors to block mineralocorticoids : SPIRONOLACTONE

- Is a competitive aldosterone receptor antagonist ➔
- Is a K^+ sparing diuretic (weak, slow onset & prolonged effect)



Used in: hypertension (alternation with others), in heart failure, and In Hyperaldosteronism (Conn's)

2-Medications that inhibit adrenal steroid synthesis to ↓ GC : MITOTANE

Inhibits 11 b-hydroxylase which will:

Decrease 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

Summary

- The **main regulator of glucocorticoid is ACTH** secreted by hypothalamus –pituitary axis **however the fluid and electrolytes are the main regulator of mineralocorticoid**
- Steroid has two mechanism the **rapid one which acts on the membranous receptors** and the **long process which act in cystolic receptors**
- The genomic action of steroid which **express anti-inflammatory proteins e.g. lipocortin** which inhibit the PLA2 and COX2 **and inhibit proteins (pro inflammatory proteins AP-1 transcription factor** from binding to the responsive element in the DNA)
- Corticosteroid transported by binding reversibly to CBG **– and the glucocorticoid bind more than mineralocorticoid -.**
- **The first choice in the emergency situation is cortisol (hydrocortisone IV) but it has water retention side effects however dexamethasone and betamethasone are the drugs of choice for long term usage and for treating intracranial pressure because they have no water retention side effect**
- We can use **fluticasone** and **budesonide as inhalers for treating asthmatic patient**
- **Topical drugs should be mild-moderate creams and used at night**
- We use corticosteroids in neoplastic disease (eg: it's effective in cancer induced vomiting)
- The main ADRs of corticosteroid is the suppression of HPA axis and to avoid this we give the patient large doses at the beginning then we reduce the dosage gradually in basic amount each week
- In treatment of Iatrogenic cushing's syndrome we slowly withdrawal the drug but if not possible to stop because the underlying disease we treat the symptoms
- Precaution :If Patients receiving GCs and **subjected to stress→ double the dose , should not be used with children receiving live attenuated vaccines , In pregnant women; better avoid fluorinated GCs**
- **The mineral corticosteroid bind in MC R which is in MC responsive cells i.e distal nephron**(these cells destroy GC and allow MC to works more)
- **The mineralocorticoids drug of choice in replacement thereby is fludrocortisone**
- **GC antagonist is MITOTANE** which Inhibits 11 b-hydroxylase Used in Cushing syndrome and it's Safe in pregnancy
- **MC antagonist is SPIRNOLACTONE** , Used in: hypertension (alternation with others), in heart failure, and In Hyperaldosteronism (Conn's)