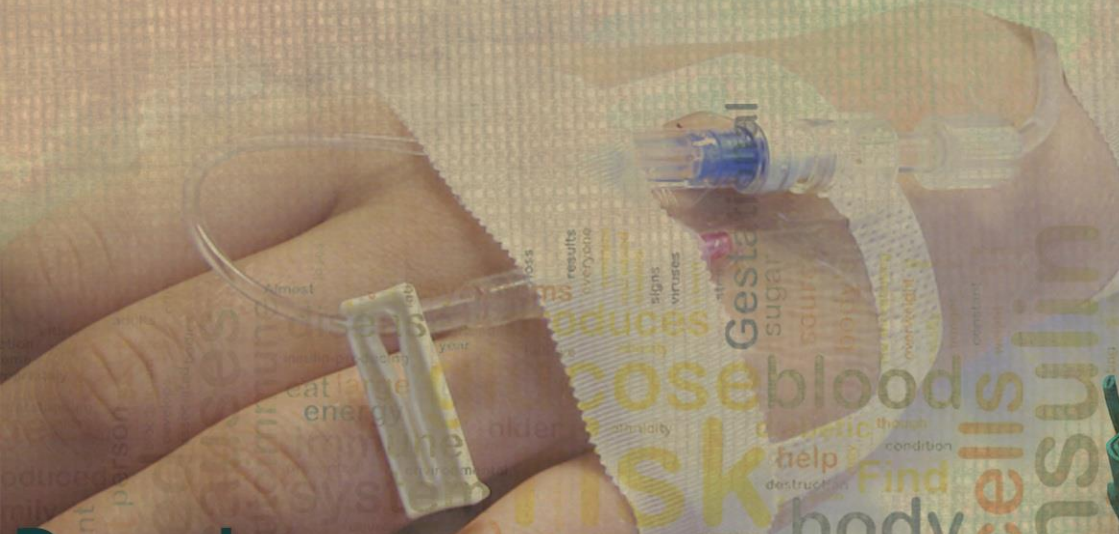
431 Teams
medical students

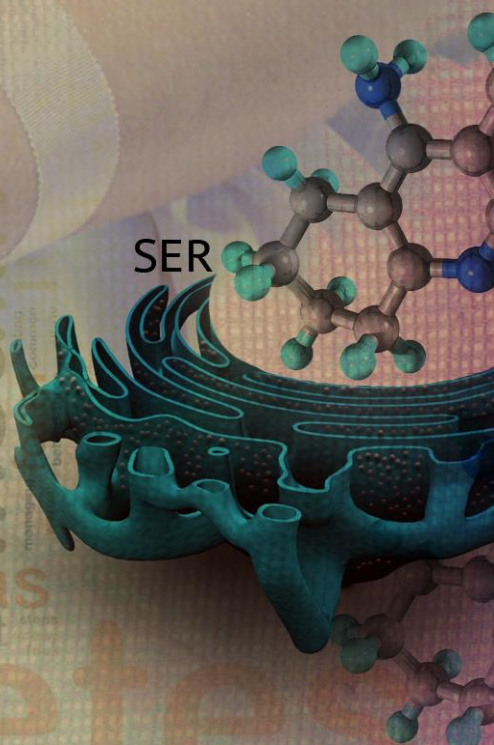
PT 431 Team Pharmacology

Endocrine block

Lecture 5

Pharmacology of Corticosteroids





Done by :

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Corticosterol are classes of steroid hormones that are produced in the adrenal cortex

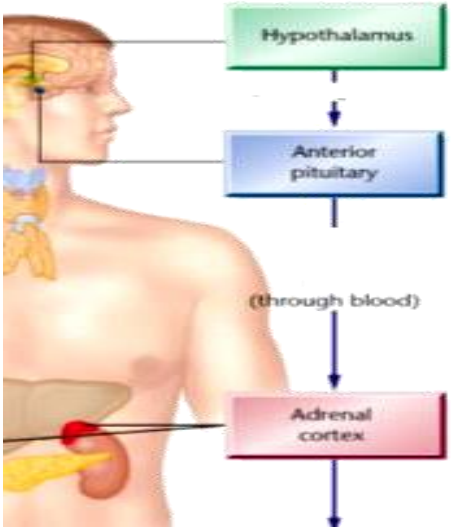
- **Glucocorticoids [GC]➔** Released from Zona Fasciculata ➔as Cortisol, Cortisone & Corticosterone ➔ Regulated by ACTH + cytokines (IL-1, IL-6, TNF), neuropeptides & catecholamines (stressors)

Control carbohydrate, fat & protein metabolism. They are also anti-inflammatory & immunosuppressants

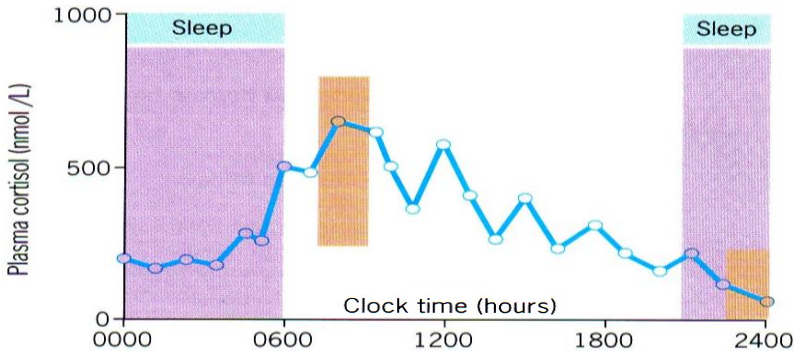
- **Mineralocorticoids [MC]➔** Released from Zona Glomeruloza ➔ as Aldosterone ➔ Regulated by angiotensin II, potassium, and ACTH. In addition, dopamine, atrial natriuretic peptide (ANP) and other neuropeptides

Control water & electrolyte homeostasis

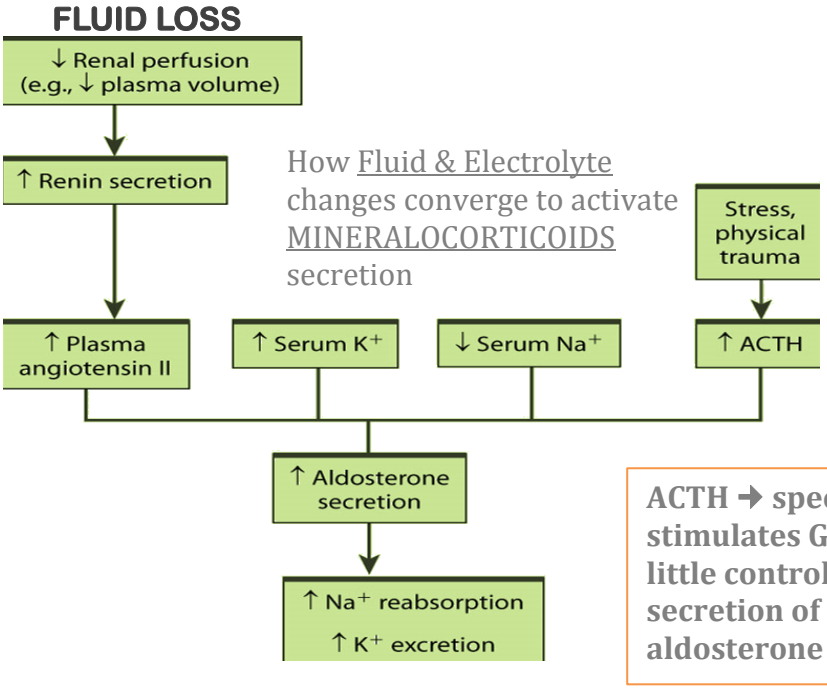
Glucocorticoids Regulation



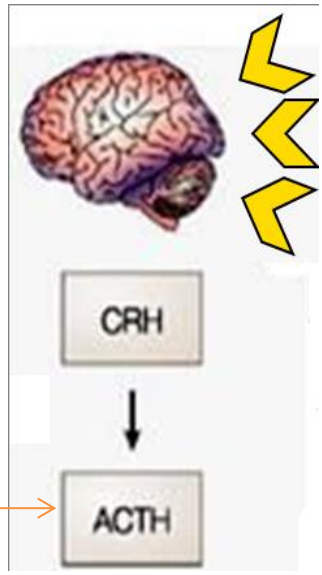
Circadian Pattern Of Cortisol Secretion



Mineralocorticoids Regulation



How Fluid & Electrolyte changes converge to activate MINERALOCORTICOIDS secretion



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

Dysregulation

Know the symptoms only

1) **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

2) **Deficiency of mineralocorticoids**, seldom alone ➜ Hyponatremia, hyper kalemia, acidosis & wasting + ↓ECF volume, hypotension & shock
3) Increased **production of glucocorticoids ➜ Cushing's syndrome**
4) Increased **production of mineralocorticoids ➜ Conn's syndrome**

Symptoms:

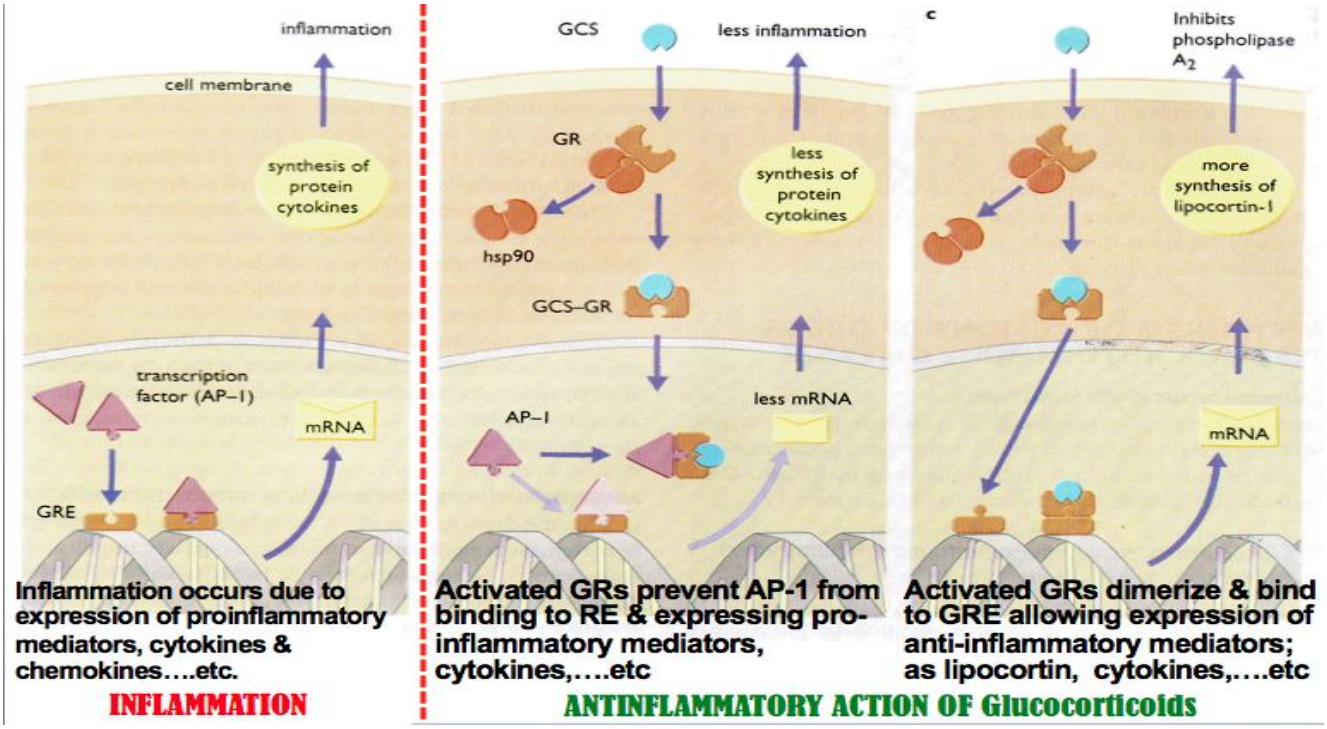
Hyperaldosteronism — Hypervolemia — Hypokalemia
Hypernatremia — Hypertension

GLUCOCORTICOIDS

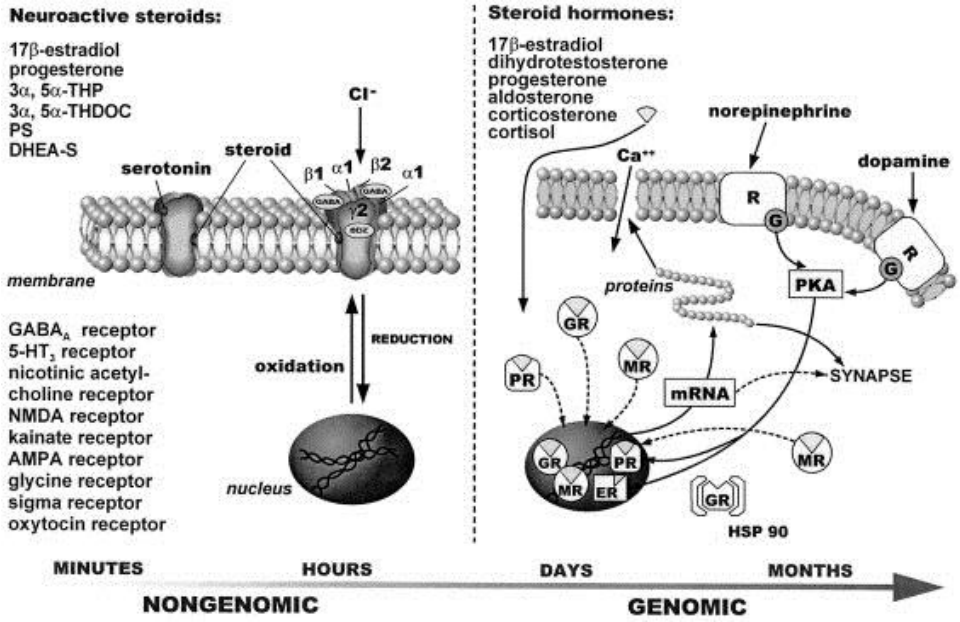
Mechanism of Action: Glucocorticoids Binds to G receptors → Cytosolic & membranous

1) **Cytosolic Glucocorticoids Receptors → mediates GENOMIC Action**

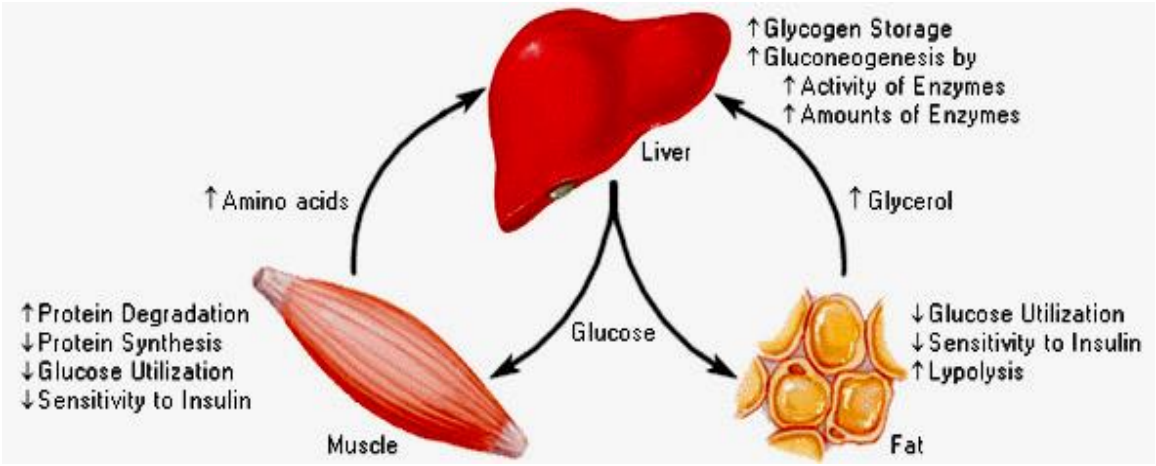
Expression of proteins (Anti-inflammatory Effects)	Repression of proteins (Pro-inflammatory Effects)
✶ Binding & Activation	✶ Binding & Activation
✶ Nuclear translocation	✶ Nuclear translocation
✶ Nuclear translocation	✶ Prevent other transcription factors (AP-1) from binding to their RE
✶ Gene Transcription	✶ No Gene Transcription
✶ mRNA Translation	✶ No mRNA Translation
✶ New Protein Formation: e.g. Lipocortin➜ Inhibit PLA_2 & COX-2	✶ No new Protein Formation e.g. No pro-inflammatory cytokines (IL-2)& chemokines



2) **Membranous Glucocorticoids Receptors ➔ mediates NON-GENOMIC Action** ➔ Cross talks with G Protein coupled receptors ➔ **alter Ca, cAMP,** their downstream kinases (PKA & PKC) ➔ rapidly exert anti-inflammatory effects & shut down pro-inflammatory effects ➔ **rapid process needs minutes to hours**



PHARMACOLOGICAL (PHYSIOLOGICAL) ACTION



1. On Metabolism:

CHO:

↓Glucose utilization.

↑Gluconeogenesis → hyperglycemia

Dr. Omnia said that this is physiology and she will not ask about it

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 strai

Fats: fat deposition on shoulders, face and abdomen.

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

2. **On Inflammatory And 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

1) **Absorption:** Most preparations are → effective orally. Parenteral forms are also available. Can get absorbed systemically when given at local sites (e.g. skin, respiratory tract, conjunctival sac, synovial spaces etc.)
2) **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

3) **Metabolism:** are metabolized by the liver
   Some preparations transform to active form in liver
   Cortisone → Hydrocortisone
   Prednisone → Prednisolone
4) **T ½ is** variable [short, intermediate & long acting]
5) **Excretion:** as soluble sulphates in the urine.

Classification According To T 1/2 & Method Of Administration

1. Systemic

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)

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2. Inhaler

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

N.B. Changes in basic cortisol molecule ➔compounds with

- ↓Mineralocorticoid activity.
- ↑Greater potency
- ↑Duration of action

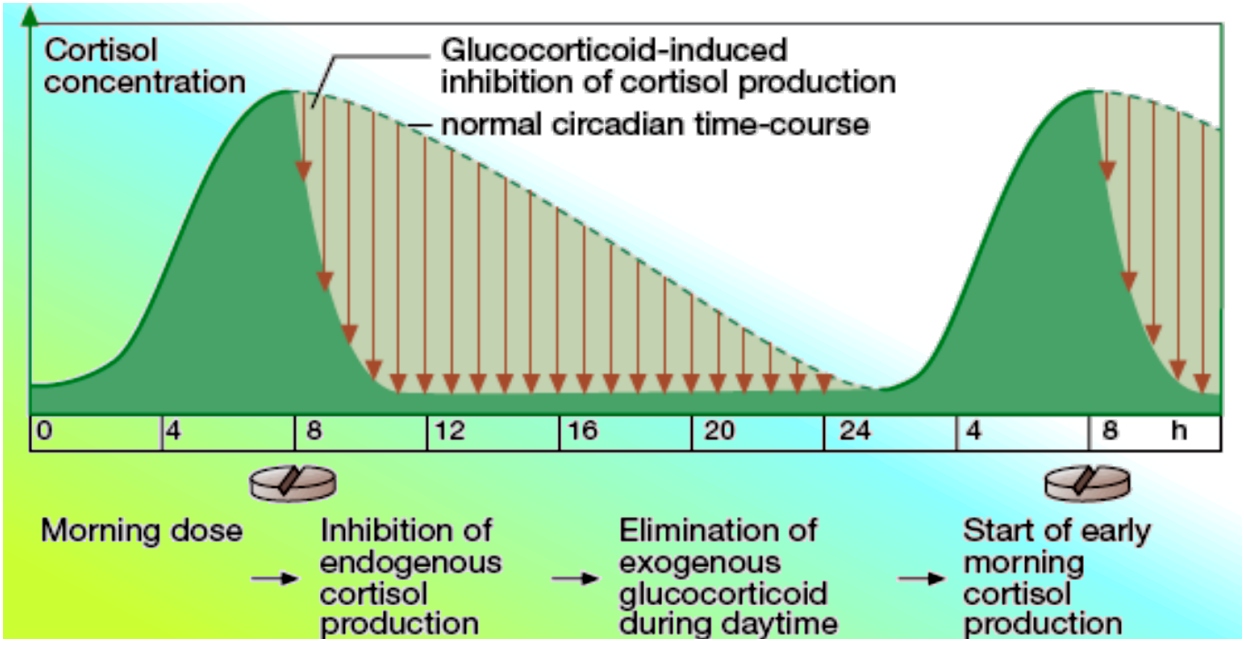
3. Topical

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 (Mometasone [cream]-Fluticasone) and it's used at night

Dosage Schedule

Time of administration of Glucocorticoids especially 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

A. Hormone Replacement Therapy:

1. Adrenal Insuffeciency:

i. **Acute (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

ii. **Chronic (Addison's Disease)**
- **Cortisol** (20-30 mg/day orally) + (**fludrocortisone** {mineralocorticoid} (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

B. Anti-Inflammatory & Immunosuppressant:

Prednisolone – Dexamethasone – Betamethasone → high anti-inflammatory and immunosupperession effect
- **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

C. Others:

These drugs cause no water retention and this is why we use them to treat intracranial pressure

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

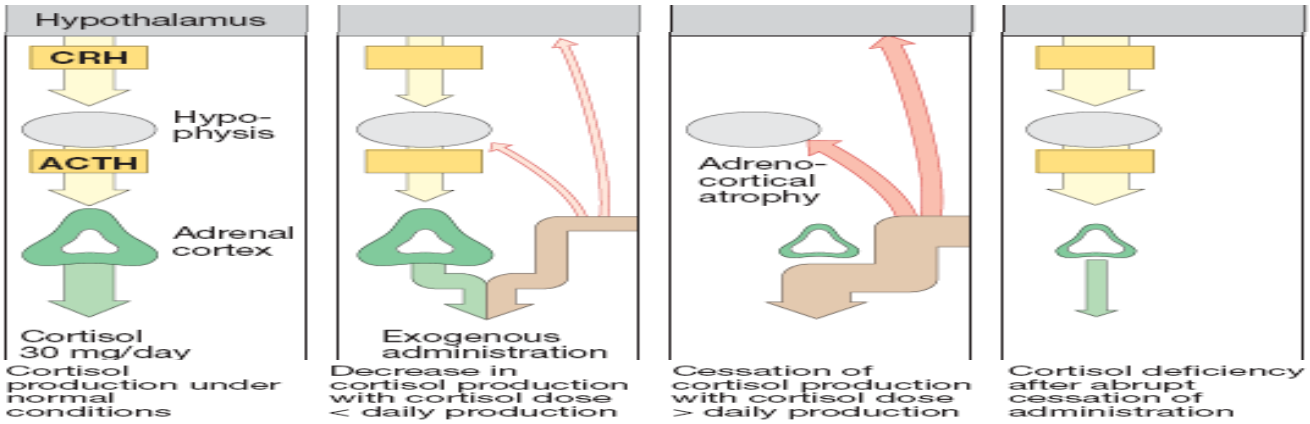
Adverse Drug Reactions

1. Suppression Of Hypothalamic Pituitary Adrenal Axis:

How to avoid?

Withdraw Corticosteroids Regimens

- If treatment is less than one week with low doses there is no fear of HPA suppression
- If the doses are high ↓ 2.5-5 mg prednisolone → at an interval of 2 - 3 days
- If treatment is for a longer period with higher doses
  Reduce half dose weekly until 25 mg prednisolone or equivalent is reached then reduce it by about 1mg every 3-7 days.



2. Iatrogenic Cushing's Syndrome

How to treat?

a. If possible slowly withdraw the drug to allow body to slowly resume its normal balance of ACTH & cortisol

b. If it's not possible to stop the drug because of underlying disease, treat concurrent symptom separately
   - Anti-diabetic for hyperglycemia
   - Bisphosphonates for osteoporosis
   - H_2 blocker or proton pump inhibitors for peptic ulcer

3. Other:

- **Hyperglycaemia**, 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
- **Effect on Skin;** acne, striae, hirsutism
- **Ocular toxicity;** glaucoma & cataract

- **Local Toxicity (topical Administration):**
  - Skin➔ infection, atrophy, bruising.
  - Eye ➔ viral infection, cataract, and 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 glucocorticoids and is **subjected to stress** (surgery) ➔ double the dose
- In children receiving ➔ take care of live attenuated vaccines (use killed vaccines if available or stop the drug temporarily until the effect of the vaccines takes place)
- In **pregnant women**; better avoid fluorinated glucocorticoids ➔ teratogenicity
- Newborns to mothers taking high dose GCs ➔ suppress HPA axis

MINERALOCORTICOIDS

e.g.: Aldosterone, Deoxycorticosterone, Fludrocortisonee

Mechanism:

Bind to mineralocorticoid receptors [MC R] ⇨ in MC responsive cells i.e. distal nephron
In MC responsive cells glucocorticoids are enzymatically destroyed⇨ so MC will bind to its receptor alone without any competition

> MC receptors have the same affinity for glucocorticoids which is present in much higher concentration than mineralocorticoids

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
   - Ksimporters ➔ ↑excretion of K & H

❖ Actions also on (distal convoluted and collecting tubules, colon, sweat & salivary glands)

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/ 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**

CORTICOSTEROID

Medications that inhibit adrenal steroid synthesis to ↓ GC:

Mitotane

Mechanism:

Inhibits 11 β-hydroxylase ➔ 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

Medications that compete with steroids on receptors to block MC actions:

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)

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)

CORTICOSTERIODS
C-Cushing's syndrome
O-osteoporosis
R-retardation of growth
T-thin skin n easy bruisability
I-infections in immunosuppression
C-cataract and glaucoma
O-odema
S-suppression of HPA axis
T-thinning and ulceration of gastric mucosa
E-Emotional disturbance
R-rise in BP and Na+ retention I-Increase in hair growth (hirsuitism)
O- others like hypokalemia
D- Delayed wound healing
S-stria

Questions

1. Which of the following is a pharmacologic effect of exogenous glucocorticoids?
(A) Increased muscle mass
(B) Hypoglycemia
(C) Inhibition of Leukortiene synthesis.
(D) Improved wound healing
(E) Increased excretion of salt and water.

2. A 34-yr-old woman with ulcerative colitis has required long-term treatment with pharmacologic does of a glucocorticoid agonist. Which of the following is a toxic effect associated with long-term glucocorticoid treatment?
(A) A " lupus-like" syndrome.
(B) Adrenal gland neoplasm
(C) Hepatotixicity
(D) Osteoporosis
(E) Precocious puberty in children.

3. A-46-yr-old male patient has Cushing's syndrome that is due to the presence of an adrenal tumor. Which of the following drugs would be expected to reduce the signs and symptoms of this man's disease?
(A) Betamethasone
(B) Cortisol
(C) Fludrocortisone
(D) Ketoconazole
(E) Triamcinolone 2

4. Which of the following best describes a glucocorticoid response element?
(A) A protein regulator that controls the interaction between an activated steroid receptor and DNA
(B) A short DNA sequence that binds tightly to RNA polymerase
(C) A small protein that binds to an unoccupied steroid receptor protein and prevents it from becoming denatured
(D) A specific nucleotide sequence that is recognized by a
Steroid hormone receptor-hormone complex
(E) The portion of the steroid receptor that binds to DNA

5. Glucocorticoids have proved useful in the treatment of which of the following medical conditions?
(A) Chemotherapy-induced vomiting
(B) Essential hypertension
(C) Hyperprolactinemia
(D) Parkinson's disease
(E) Type II diabetes

6.) A 56-yr-old woman with systemic lupus erythematous had been maintained on a moderate daily dose of prednisone for 9 mo. Her disease has finally gone into remission and she now wishes to gradually taper and then discontinue the prednisone. Gradual tapering of a glucocorticoid is required for recovery of which of the following?
(A) Depressed release of insulin from pancreatic B cells
(B) Hematopoiesis in the bone marrow.
(C) Normal osteoblast function.
(D) The control by vasopressin of water excretion.
E) The hypothalamic-pituitary-adrenal system.

7.) A 54-yr-old man with advanced tuberculosis has developed signs of severe acute adrenal insufficiency.Which of the following signs or symptoms is this patient most likely to exhibit?
(A) A moon face
(B) Dehydration
(C) Hyperglycemia
(D) Hypertension.
(E) Hyperthermia

Summary and Questions from 430 team work, so we thank them a lot.

- **Answer Key: 1:C - 2:D – 3:D – 4:D – 5:A – 6:E – 7:B**