9. Glucocorticoids? / Corticosteroids.

Mineralocorticoids

- Adrenal gland ← cortex → steroidal hormones
  ← medulla → adrenaline, nor-adrenaline

- Mineralocorticoid → Zona glomerulosa
  Glucocorticoid → fasciculata
  Adrenaline → reticularis

- Rate of secretion 10mg daily → Hydrocortisone } 3 AM – 8 AM
  0.125 mg daily → Aldosterone } sleep time

Pharmacodynamics

Glucocorticoid actions.

1. CARB MET – ↑ uptake & utilisation of glucose
   ↑ G. neogenesis

   MOA: Translocation of GLUT 4 to deeper sites.
   Induction of gluconeogenic enzymes

   Effect: Hyperglycemia – resistant to insulin

2. PROTEIN METABOLISM – ↓ protein breakdown
   – Amino A. mobilization
   – Excess urea produced – Negative N_2 balance
   – loss of bone matrix (osteoporosis)

   Clinical effect: ↑ catabolism
   ↓ anabolism.

3. FAT METABOLISM

- Lipolysis occurs → redistribution of body fat that is deposited over face, neck, shoulder → moon face, buffalo hump, fish mouth thin limbs → cushing syndrome.

4. CALCIUM MET

- Inhibition of Ca metabolism
- Enchancement of Ca^+ excretion

} neg cal balance

- Effected : Osteoporosis

5. H_2O EXCRETION

- Enhances secretary activity of renal tubules
- Glucocor have weak mineralocasticoid action, causes Na^+ & H_2O retention, ↑ K^+ excretion
- Thus prolonged use can cause edema & H.T

. CVS .

- Glucocorticoids have Na^+ & H_2O retention property, exert a permissive effect on pressor action of adrenaline & angiotensin.
- On chronic administration, these drugs may cause CCF worsening & H.T (↑ tone of muscle ↑ contraction ✓ H.T)

7. Skeletal muscle - Corticosteroids are req for normal func of skeletal muscle

Muscle weakness in both Hypocorticism & Hypercorticism

- Hypocorticism : due to inadequate circulation
- Hypercorticism : due to hypokalemia

8. CNS
- Mild euphoria
- ↑ motor activity
- insomnia
- anxiety.

NCA
☆ 2 drugs causes peptic ulcer
- Corticosteroids
- NSAID's.

9. GI - ↑ gastric acid sec & pepsin ↓ peptic ulcer.

10. BLOOD CELLS

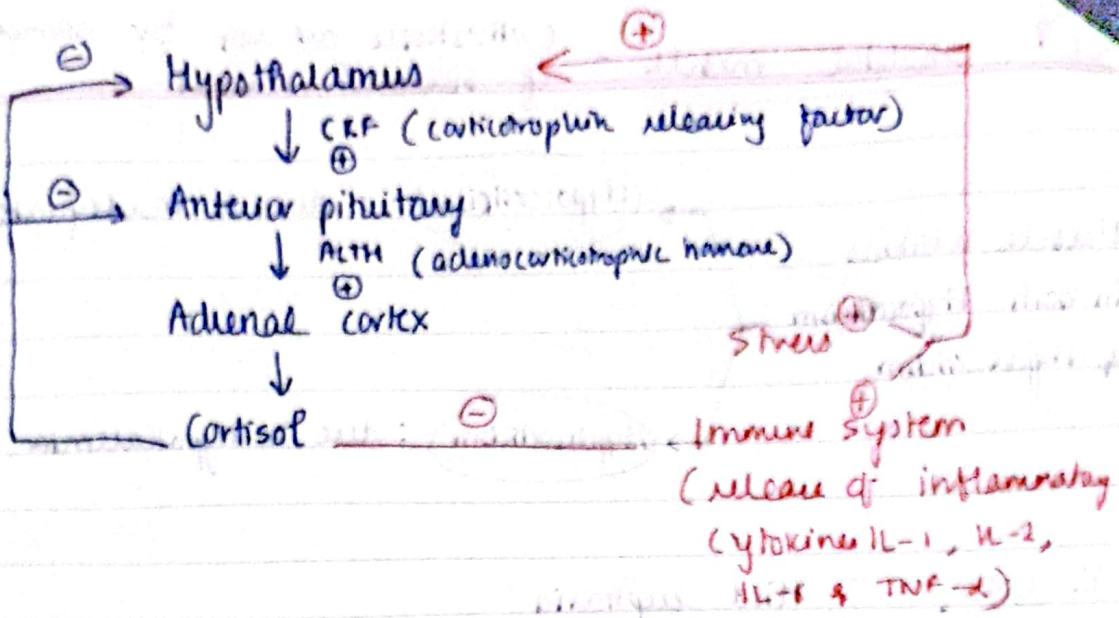
- ↓ in count of all blood cells like
- RBC
- lymphocyte
- Eosinophils
- Basophils
- Neutrophils
- Platets

11. LYMPHOID TISSUE

- They have lytic response in malignant lymphatic cells.

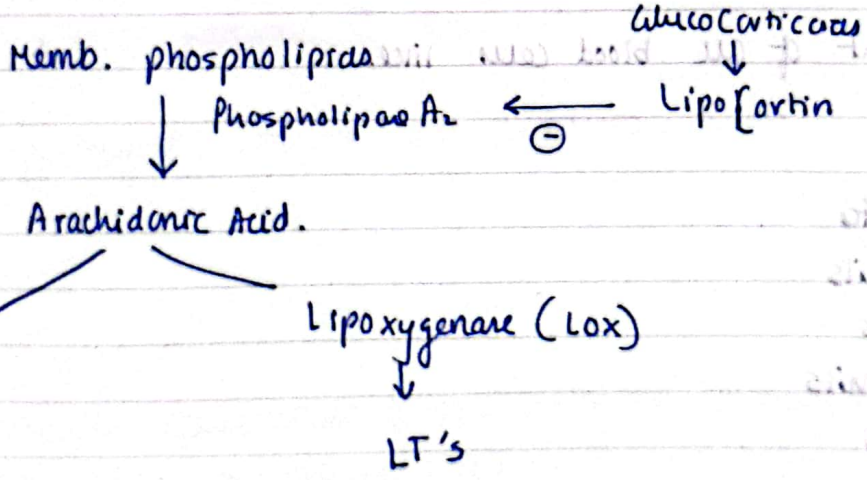
Limits: LYMPHOMA.

HYPOTHALAMO - PITUITARY AXIS



12. INFLAMMATORY RESPONSE

- They have very potent Anti-I response.
- They prevent / supress all the inflammatory mediators thus ↓↓ the clinical feature of inflammation such as heat, redness, pain, swelling.

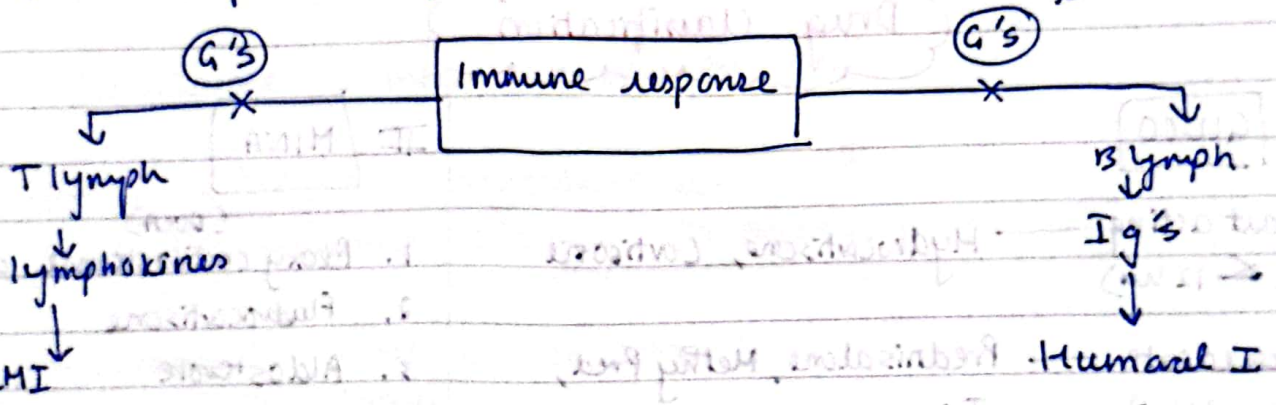


Explaination: - G's induce a protein called lipocortin which inhibits phospholipase A2 : hence PG's & LT's.

- Production of cytokines like (IL-1, IL-6, TNF-α) which is necessary for initiating inflammation is inhibited.
- Chemotaxis is supressed.
- They stabilized lysosomal membrane & prevent release of inflammatory mediators
- G's inhibit expression of various molecules on endothelial cells, thus inhibiting leucocyte migration to site of injury.

13. IMMUNE RESPONSE

- Supress all sorts of hypersensitivity reactions
- Greate supression of CMI (cell mediated immunity)



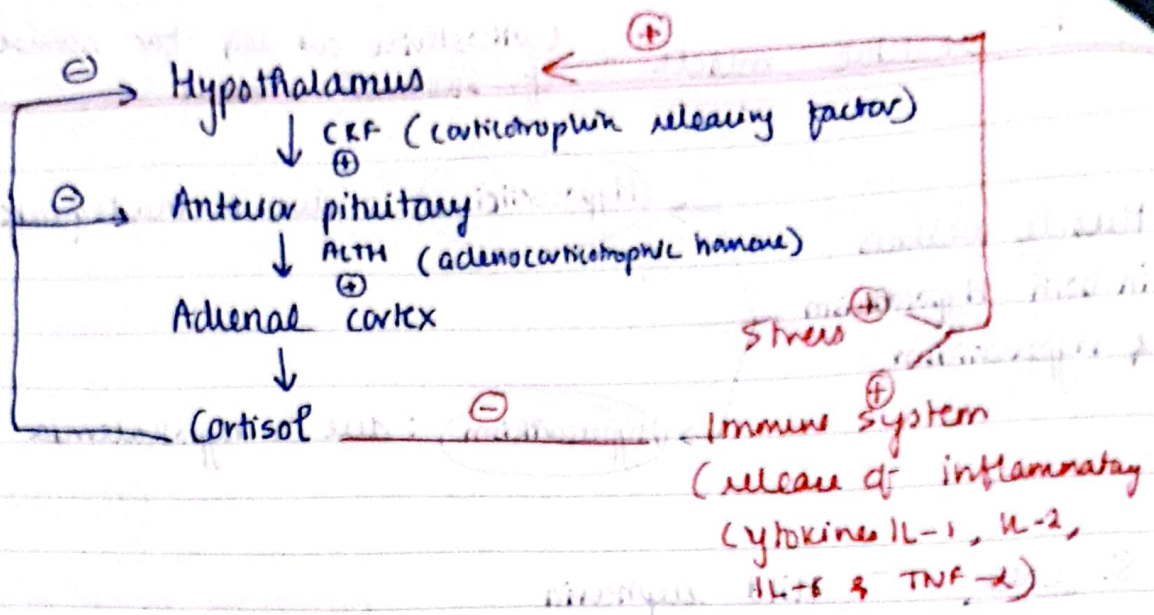
Clinical : - Immunosupressent → Organ transplant.
- Allergic reactions.

Mineralocorticoid actions

1. Enhances sodium resabtion in DCT
2. ↑ K^+ excretion
3. Water retention.

Clinical : HT & water retention.

HYPOTHALAMO - PITUITARY AXIS



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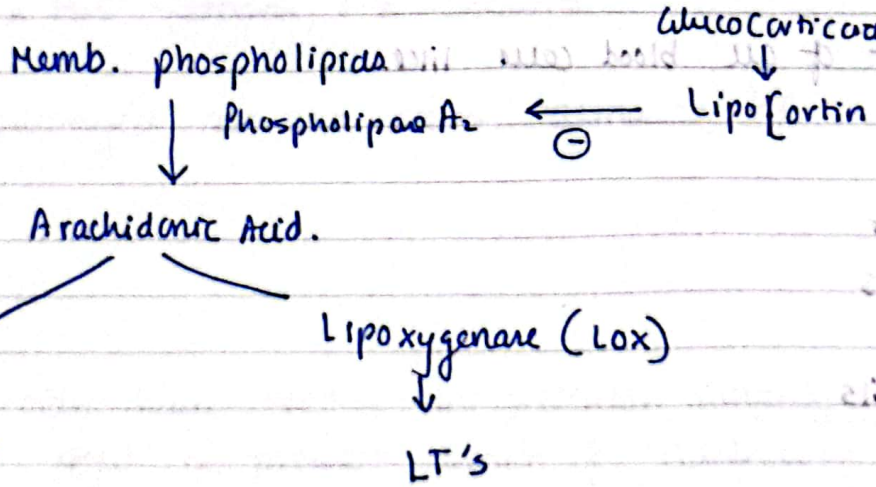

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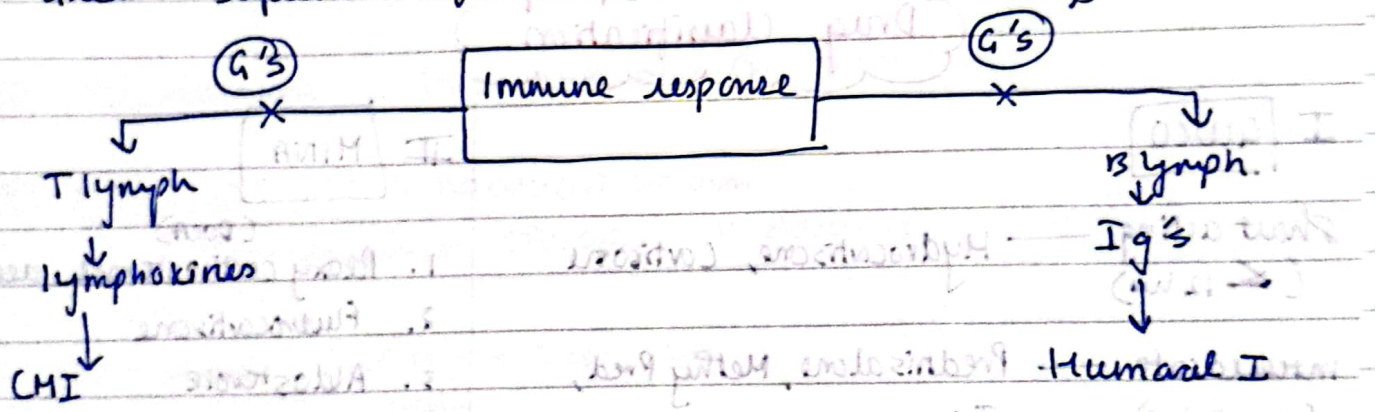

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M.O.A of corticosteroids

Steroids → cells → G receptor binds inside nucleus as form complex

↓

Dimerised

Transcription
DNA → mRNA.

↓

protein.

↓

Altered cell function.

Drug classification

I GLUCO

- Short acting. (≤ 12 hrs) — Hydrocortisone, Cortisone
- Intermediate (12 - 36 hrs) — Prednisalone, Methy Pred, Triamcinolone
- long acting (+36 hrs) — Paramethasone, Dexamethasone, Betamethasone.

II MINA

(DOCA)

1. Deoxy corticosterone acetat
2. Fludrocortisone
3. Aldosterone

PK:
- except DOCA all absorbed orally
- Met by CYP450
- Prone to DI
- excreted in urine after being met in liver by conjugation.

① Hydrocortisone – Rapid onset.
– (=) equal M & G activity
– ✓ I.V, tropically

② Cortisone : Prodrug of ①

③ Prednisolone – 4x potent.
– HPA suppression
– Selective 'G' activity

④ Methyl P – More selective & potent than ③
– ✓ transplantation ☆

⑤ Triamcinolone: – More potent than ③
– selective 'G' action

⑥ Dexa & Betamethasone – V. Potent, ✓ Highly selective
– Supp of HPA
– ✗ fluid retention / ✗ HT
☆ used in cubral edema & reduce intra cranial tension

⑦ Paramethasone – Intermediate b/w ③ & ⑥

⑧ DOCA : – only mineralocorticoid action ☆
– Replacement therapy in Addison's disease

⑨ Fludrocortisone ✓ Min & Gluco action
✓ orally.
✓ Addisons disease.

⑩ Aldosterone – MOST POTENT MINERALOC
– ✗ used because ↓ bioavailability.
Difficulty in dose regulations

Uses: Replacement therapy

① **Acute adrenal insufficiency**

- HydroCortisone / Dexamethasone + Saline / Glucose

② **Chronic adrenaline insufficiency (Addison's disease)**

- HydroC + DOCA

③ **Congenital Adrenal hyperplasia** (Adrenogenital syndrome)

- genetic deficiency of 21-hydroxylase.
- HydroC + FludroC daily.

Non-endocrinal uses:

- Skin
- Intestine
- Collagen.
- Autoimmune.
- Lung.
- Infection
- Eye

} diseases

- Cancers (ALL, Hodgkin's lymphoma)
- Rheumatoid arthritis.
- Osteoarthritis
- Gout

Adverse effects:

1. HPA suppression.
2. CNS: Behavioural disturbances, insomnia
3. Eye: Glaucoma, cataract.
4. GIT: peptic ulcer.
5. Cushing's habits: moon face buffalo hump
6. Met defects: Hyperglycemia.
7. Water retention, Na+ retension.
8. hypokalemia ⟶ muscle weakness ⟶ myopathy.
9. Osteoporosis.
10. Growth retardation (in Rex & betamethasone) Children

MCQ ✡

Contraindications

1. Peptic ulcer
2. DM.
3. HT
4. Preg
5. ~~Pregnancy~~ TB
6. Osteoporosis.
7. Epilepsy.
8. Renal failure
9. Psychosis.
10. Chronic ♥ failure.

general instructions in corticosteroid therapy:

- single & short dose × ampule
- long term dangerous.
- × abrupt withdrawal HPA suppression

To minimize HPA supp:

- ✓ short acting drug ✓ short period.
- alternate day dose.
- local preparation ✓

Steroid syn inhibitors / Antagonists ✡ MCQ.

1. Metyrapone (test. of cushing syn)
2. Aminoglutethimide (best cancer, Cushing syn due to tumors)
3. Trilostane (Cushing, primary hyperaldosteronism)
4. Ketaconazole
5. Mifepristone (anti progestin drug)
   Gluco receptor antagonist