ENDOCRINOLOGY

INTRODUCTION

1) Mechanism of cellular action of hormones. (Brief answer)

- On target cell, hormone in combination with receptor acts by any of the following :-

i) By altering the cell permeability

ii) By activating intracellular enzyme (Secondary messenger system) — cell surface receptor

iii) Through effect on gene expression

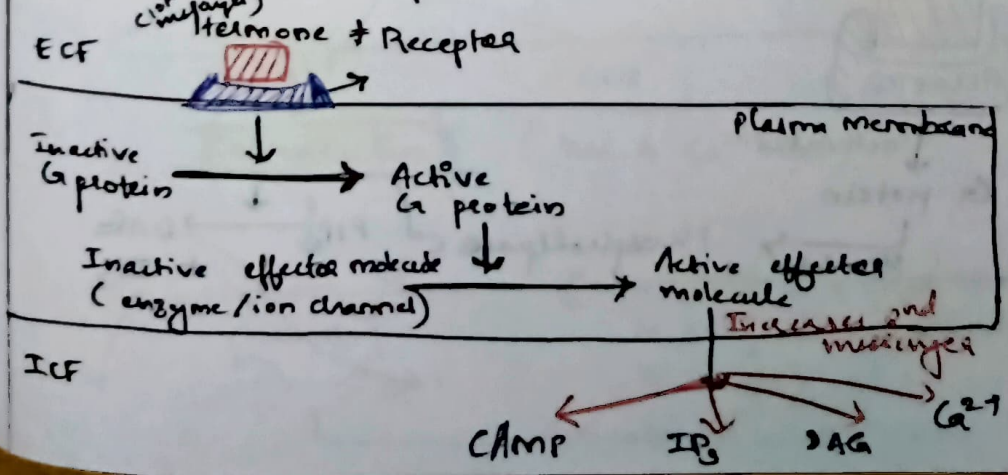
iv) Action through tyrosine kinase activation — intracellular receptors / cell surface

I) Change in membrane permeability

- Hormone bind with receptors present in cell membrane
- Causes conformational change
- Causes either closing / opening of ion channels (like Na^+, K^+)
- Eg:- Adrenaline, noradrenaline

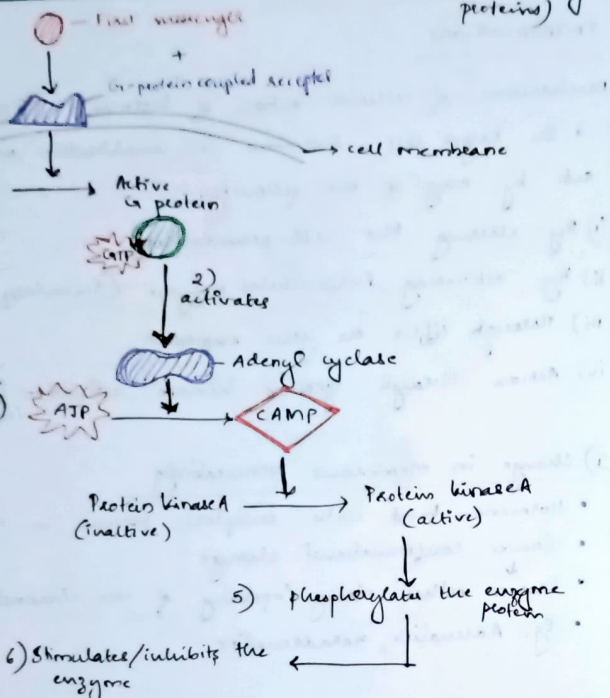
II) Secondary messenger system

- The hormone which acts on target cell acts as 1st messenger.
- Hormone + receptor ⟶ Hormone - receptor complex



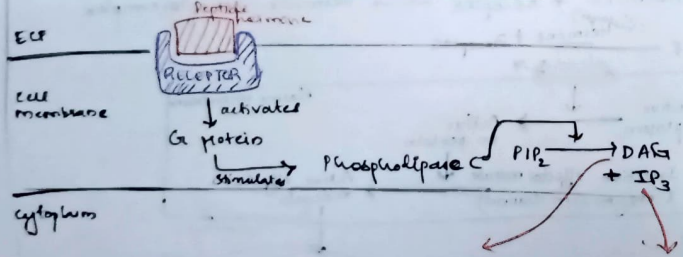
cAMP as second messenger

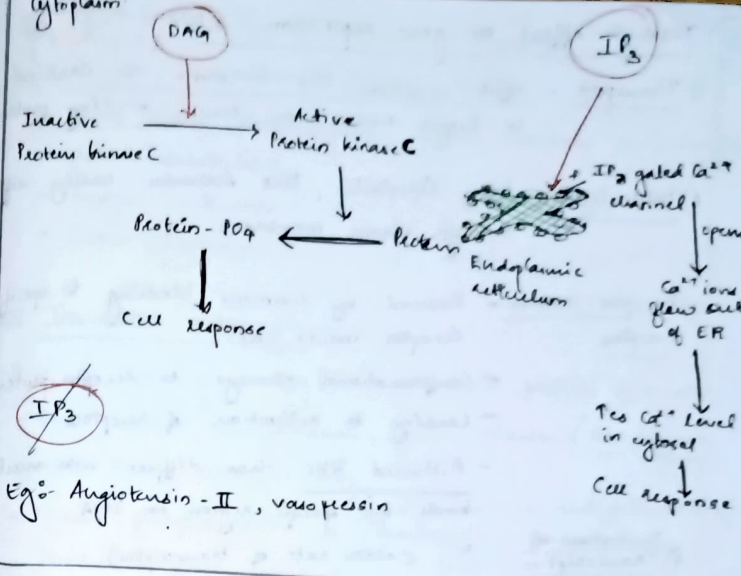
Gs protein (GTP binding proteins)



Eg:- Epinephrine, norepinephrine

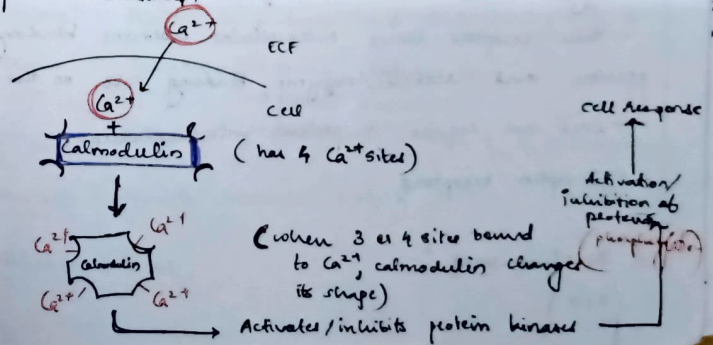
IP_3 and DAG as second messengers





Ca^{2+} - Calmodulin system

- Ca^{2+} acts as 2nd messenger along with another protein called calmodulin.
- Ca^{2+} entry into cells initiated by :-
  - changes in membrane potential that open Ca^{2+} channel
  - A hormone interacting with membrane receptors that open Ca^{2+} channels.
-



III) Through effect on gene expression (Draw diagram if required)

1) Transport – after secretion, the hormone is carried to target tissue on (Serum binding proteins)

2) Internalization – Being lipophilic, the hormone easily diffuse through plasma membrane

3) Receptor-Hormone Complex – Formed by hormone binding to specific receptor inside cell.
- Conformational change to receptor protein
- leading to activation of receptors
- Activated RHC, then diffuse into nucleus, binds on specific region on DNA

4) Initiation of Transcription ← (alters rate of transcription)

5) Translation – mRNA move out of nucleus and reaches ribosomes to promote translation
- Protein formed ⟶ cellular responses

IV) Action through tyrosine kinase activation (2 mechanisms)

• Enzyme-linked hormone receptors
- These receptors have extracellular hormone binding portion and catabolic/enzyme binding site on the inside.
- Does not require G-protein intermediaries.
Eg:- Leptin receptors

2 Mechanisms :-
(PTO)

(a) Due to binding of hormone to receptor,
- Receptor itself becomes tyrosine kinase
- this kinase phosphorylates tyrosine residues on intracellular protein substrates
↓
- Enzyme activation
↓
- Gene Expression

(b) JAK-STAT pathway

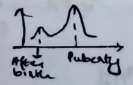
Due to hormone binding to extracellular portion of receptor,
↓
- Can attract intracytoplasmic tyrosine kinases (like Janus kinase)
- and then activates them
- Causes phosphorylation of (signal transducers and activators of transcription) ~~factor proteins~~ (STAT)
- Modulate gene expression

Eg:- Insulin, IGF, EGF, PDGF, ANF, GABA

V) PITUITARY GLAND

1) Growth hormone (Essay) / Somatotrophin

A) • Structure : Similar to prolactin and hCG
• Secretion : Pulsatile → episodic release
→ diurnal variations
→ peaks at stage 3 and 4 of NREM sleep



• Transport : Growth hormone binding protein (GHBP)
• Metabolism : liver

B) Mechanism of action

- Ot has a cell membrane receptor which has 2 subunits. On binding with GH, it becomes homodimer

Steps

1) GH binding
↓
2) Activation of JANUS tyrosine kinase (JAK 2)
↓
3) Phosphorylates signal transducers and activators of transcription (STAT)
↓
4) JAK-STAT pathway activated
↓
5) Cell responses (sometimes IP_3-DAG pathway)

C) PHYSIOLOGICAL ACTIONS ON GROWTH AND METABOLISM

I) Metabolic effects

i) On protein metabolism

- Anabolic effect - ↑es amino acid uptake into cells
- Stimulates transcription, translation
- Decreases catabolism of proteins and amino acids

ii) On fat metabolism

- ↑ level of circulating FFA : • Mobilises fat from adipose tissue
  • Hence, enhances conversion of FA → acetyl CoA
- Protein sparing effect : • FFA are utilised for energy
  • Thus, decreases breakdown of cell protein
- Ketogenic effect : • Excess GH, mobilises more FFA, so large amt of acetoacetic acid (ketone bodies) are formed and released into body fluids

iii) On carbohydrate metabolism

- GH is diabetogenic / hyperglycemic :- ⊖.
  - ↑es prodn of glucose by liver (gluconeogenesis, glycogenolysis)
  - ↑es insulin prodn and ↓es sensitivity to insulin (insulin resistance) and hence,
  - ↓es glucose uptake into adipose and skeletal muscle.

II) Actions on growth

i) Before closure of epiphysis

- GH ↑es length of bone
- Stimulates proliferation of chondrocytes and osteogenic cells.
- ↑es protein deposition by chondrocytes
- Stimulates osteoblastic activity, which converts cartilage into bone.

ii) After closure of epiphysis

- linear growth not promoted
- Bone thickening can occur through periosteal growth

D) SOMATOMEDINS

- Polypeptide growth factors secreted by liver and other tissues
- Effect of GH on growth, cartilage and protein metabolism depends on interaction b/w GH and somatomedins.
- Types → IGF-I / Somatomedin C
  IGF-II / Somatomedin A

IGF
↓
Insulin like growth factor
(as their effects are similar as of insulin on growth)

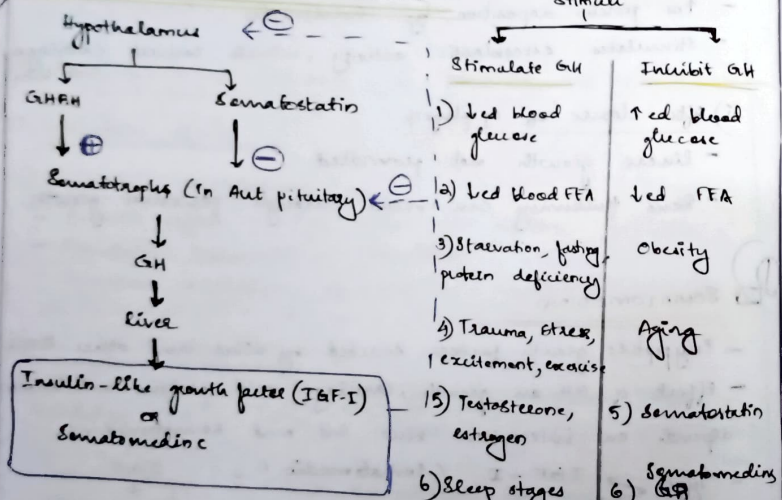
IGF - I

- Transport - bound to IGF binding protein
- Receptor - similar to insulin receptor
- Effects - helps skeletal and cartilage growth
- Regulation - independent of GH, required after birth (GH required before birth)

IGF - II (Multiplication Stimulating factor - MSA)

- Secretion independent of GH
- Adults (only in choroid plexus)
- Important for growth during foetal development

E) REGULATION OF GH SECRETION

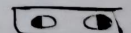


F) APPLIED

1) Gigantism

- **Causes** :- Hypersecretion of GH in young children before closure of epiphysis.
  - due to tumor of pituitary
- **Features**
  1) Abnormal height
  2) bitemporal hemianopia, headache - compression of optic chiasma by enlarged pituitary
  2) Bilateral gynecomastia, loss of libido / impotence
  4) large hands and feet
  5) Hyperglycemia caused by GH leads to excess insulin
  6) Over-activity of β cells of pancreas, leading to degeneration of these cells, def of insulin, DM.
- **Treatment** : Irradiation of tumor

2) Acromegaly

- **Causes** :- Hypersecretion of GH in adults after closure of epiphysis
  - Tumors → Extrapituitary (Hypernephroma) → GHRH secreting
  - Intrapituitary → GH secreting
- **Effects** :- Height not increased
  - But, bones become thicker and soft tissues continue to grow
  - ↑ prolactin (20-40% of patient)
- **Clinical features**
  1) Bitemporal hemianopia 
  2) Prognathism - protrusion of lower jaw due to elongation and widening of mandible
  3) Acromegalic facies - Overgrowth of malar, frontal and facial

bones combines with prognathism to produce coarse facial features called acromegalic facies.

4) Kyphosis - changes in vertebra causes a hunched back

5) Gynecomastia with/without lactation

6) Cardiomegaly, splenomegaly, renomegaly, hypertension

7) Enlarged hand and feet

8) Osteoarthritis

- Treatment : i) Surgical resection of tumor
  ii) Drugs : Somatostatin analogues
  GH receptor antagonists
  Dopamine agonists

3) Dwarfism

- Causes → Endocrinal
  → Genetic
  → Nutritional

i) Endocrinal causes

PITUITARY DWARF	HYPOTHYROID DWARF / Cretin
• Due to GH def since childhood	• Due thyroid hormone def
• Normal mental activity	• Mentally retarded
• Sexually mature	• Sexually immature
• Diff parts of body are proportionate	• Diff parts are disproportionate

ii) Genetic cause :

- Laron dwarfism (GH insensitivity syndrome)
  - Plasma GH is normal/elevated
  - GH receptors are unresponsive (due to mutation in gene for receptors)
  - Marked ↓ in plasma IGF-I.
- African pygmies
  - Normal plasma GH
  - Plasma conc. of GH binding protein ↓
  - Plasma IGF-I conc fails to ↑ at time of puberty

iii) Nutritional cause :

Marasmus and rickets

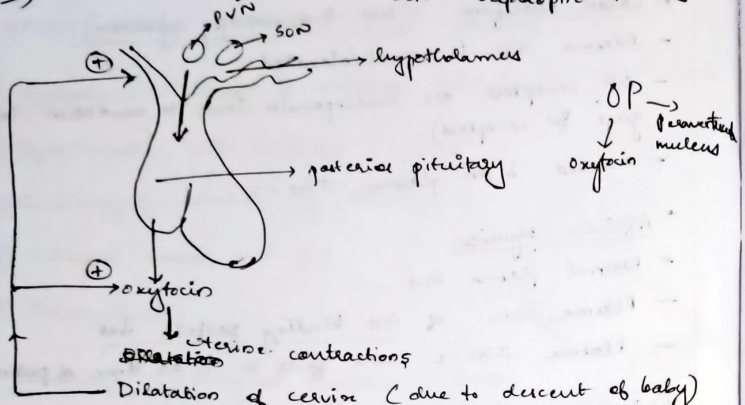
2) Neuroendocrine reflexes. (Brief answer)

I) Milk ejection reflex

Suckling of breast
↓
Stimulation of touch receptors of nipple
↓
Touch pathway
↓
Supraoptic and paraventricular nuclei of hypothalamus
↓
Oxytocin
↓
Myoepithelial cells of breast
↓
Milk ejection

PVN – paraventricular nucleus
SON – supraoptic nucleus

II) Parturition Reflex



- Throughout pregnancy, oxytocin inhibited by estrogen and progesterone.
- Towards term → estrogen, progesterone ↓es, oxytocin ↑
  → oxytocin receptors ↑ed

III) Melatonin secretion

Retinal receptors
↓ Retino-hypothalamic tract
Suprachiasmatic nucleus of hypothalamus
↓
Brainstem and spinal cord
↓
Superior cervical ganglion
↓
Symp noradrenergic fibres
↓
Pineal gland
↓
Melatonin

ADRENAL GLAND

I) CORTISOL (ESSAY)

The main glucocorticoid secreted by human adrenal cortex is cortisol.

I) Synthesis

Cholesterol
↓ Desmolase
Pregnenolone
↓ Dehydrogenase
Aldosterone ← Progesterone → Cortisone
↓ 17-α Hydroxylase
17-α-hydroxyprogesteron → 11-deoxycortisol → Cortisol
(21-β-hydroxylase; 11-β hydroxylase)
↓
Androstenedione
↓
→ Testosterone

II) Transport – Mostly bound to protein (95%)

- 90% Transcortin / Corticosteroid Binding Protein
- 7% Albumin
- Rest free form (active)

III) Regulation

II) ACTIONS → Physiological / Pharmacological

PHYSIOLOGICAL

A) Metabolic actions (BA)

- Effect on carbohydrate metabolism :-
  - ↑ blood glucose level → stimulates gluconeogenesis by activating enzymes and also by mobilising AA from extra hepatic tissues to liver
  - ↓ peripheral utilisation of glucose by ↓ oxdn of NADH to NAD
  - Anti insulin action - ↓ sensitivity of cells to insulin

- Effect on protein metabolism :-
  - ↓ of cellular proteins except liver :-
    - ↓ protein synthesis, ↑ breakdown decreases AA transport to extrahepatic tissues
    - Decrease formn of mRNA
  - ↑ liver and plasma proteins by
    1) AA transport into liver
    2) Stimulates enzymes (deaminases and transaminases)

- Effect on fat metabolism :-
  - Causes lipolysis by mobilising FA from adipose tissue → FFA for energy
  - ↑ Oxdn of FAcids → ketone bodies formn
  - ↑s food intake by stimulating HT

- Stimulates fat synthesis by stimulating lipoprotein lipase and 6-Phosphate dehydrogenase in some tissues more rapidly than mobilised → deposition occurs in chest, head and trunk

Buffalo hump, moon face appearance

- Effect on water and electrolyte balance :-

Promotes diuresis by :-

1) provides adequate GFR by ↑ing glomerular blood flow
2) Antagonists the action of ADH in renal tubule
3) Enhance ADH destruction in liver

→ ↑ retention of Na^+ and excretion of K^+ by kidneys

B) SYSTEMIC ACTIONS

1) MUSCLE

- Optimal amount is required for muscular efficiency
- ↑s cardiac and skeletal muscle performance
- Excess → cause decrease in muscle mass and strength
- deficiency → profound muscle weakness

2) BONE

- lowers plasma Ca^{2+} level by inhibiting osteoclast formn and activity
- Excess cortisol cause osteoporosis by decreasing bone mass and mineralisation

Applied

Mechanism
- 1) ↓ syn of Type I collagen
- 2) Inhibit syn of osteoblasts

3) ↓ed absorption of Ca^{2+} and PO_4^{-} from intestine, increased renal excretion.

4) Increases PTH secretion → bone resorption occurs

3) CVS and vasculature

- Maintain vascular reactivity by inhibiting Na^+/Ca^{2+} exchanger
- ↓ed responsiveness of arterioles to catecholamines → vasoconstrictor effects
- On heart → ↑es myocardial performance

Applied:- In adrenal insufficiency
↓
Vascular smooth muscle unresponsive to catecholamines
↓
impairs vascular compensation for hypovolemia
↓
Vascular collapse

4) CNS

- Influences electrical activity of brain, mood and behaviour

Applied
Adrenal Insufficiency
- Causes EEG slower than normal β rhythm
- personality changes like irritability, apprehension, inability to concentrate

Excess
- decrease threshold of electrical excitation of brain
↓
Stimulates excitability
↓
Convulsions
∴ Corticosteroids not given in epilepsy.

5) GIT

- ↑ HCl and pepsin secretion
- ↓es mucosal cell proliferation

6) Respiratory

- Maturation of fetal lung and surfactant

7) Connective tissue

- Inhibits collagen synthesis, so used in CT disorders
- Slows degrading effect of collagenase in joint tissues
- Reduces fibroblastic activity
↓
↓ skin thickness, thinning of capillary walls
↓
Become fragile → Intracutaneous haemorrhage (of cortisol in excess)
(purplish striae)

8) Blood cells and lymphatic organs

- ↓ circulating eosinophils by ↑ing sequestration
- ↓ circulating lymphocytes by
1) inhibiting mitotic activity of lymphocyte precursors
2) ↓ed secretion of cytokines IL-2 → ↓ proliferation of lymphocytes
3) Size of lymph nodes & thymus → decrease
4) Inhibition action of NF κB
- ↑ in basophils, neutrophils, monocytes, platelets
- ↑ no. of RBCs by stimulating erythropoiesis

C) PERMISSIVE ACTION (BA) on :-

- Small amount of glucocorticoids must be present for certain metabolic fns, though it is not producing actions by themselves
- Glucagon and catecholamines —produce→ Calorigenic effects
- Catecholamines → to exert lipolytic effect
  → produce pressor effect and bronchodilation

D) STRESS SITUATION

- Protects against stress by maintaining vascular reactivity, permissive action on catecholamines
- In stress, ACTH increase by the action of stimuli in HT

✱ PHARMACOLOGICAL

1) Anti-inflammatory action

- Can block early stages of inflammation even before it starts
- If inflammation has already started, it causes rapid resolution and healing.

Mechanism of preventing development of inflammation and resolution

- inhibit activation of transcription factor NF kB that stimulates production of inflammatory mediators
- inhibit (phospholipase A2) PLA 2 → decrease arachidonic acid – (precursor of mediators)
- stabilise lysosomal membrane – ↓ release of proteolytic enzymes
- ↓ capillary permeability, ↓ migration of WBCs into inflammed area

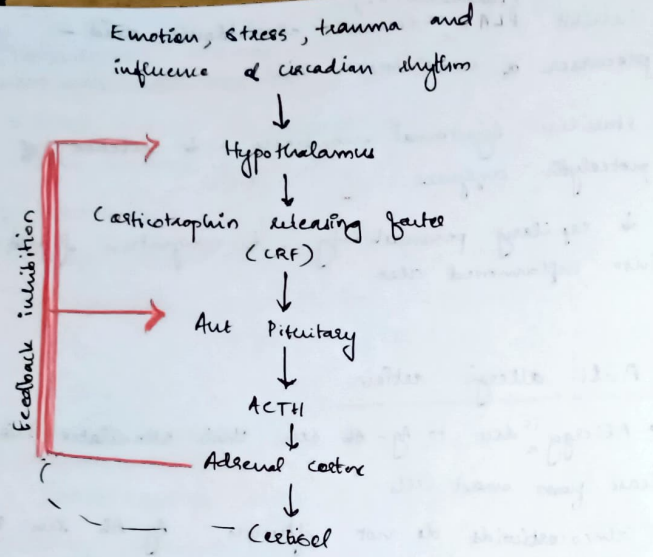
2) Anti-allergic action

- Allergy is due to Ag-Ab rxn that stimulates histamine release from mast cells.
- Glucocorticoids do not influence Ag-Ab rxn & effects of histamine once histamine released.
- MECHANISM :-

1) Prevents growth of mast cells
2) inhibit intracellular syn of histamine
3) inhibit release of histamine

IV) REGULATION OF CORTISOL SECRETION

- Adrenal cortex under control of hypothalamo-hypophyseal axis → hypothalamus - pit - adrenal axis
- The secretion of ACTH and consequently cortisol follows a circadian rhythm due to hypothalamic control.
- ACTH → min during night
  → max during early morning (6-8 am).



2) ALDOSTERONE

I) It is the chief mineralocorticoid and these are secreted from Zona glomerulosa.

II) FUNCTIONS

1) Effect on renal tubules
- Na^+ reabsorption from tubular fluid into tubular epicell
- K^+ excretion (active reabs of Na^+ in exchange for
- H^+ " H^+ and K^+)

2) Effect on ECF volume
- when Na^+ reabsorbed, water also reabsorbed
- cause ↑ in ECF volume

3) Effect on BP
- Due to ↑ ECF, BP ↑ed

ALDOSTERONE ESCAPE (Renal compensatory mech) (escape occurs only in kidney)

It is a phenomenon in which, despite persistent high levels of aldosterone, Na^+ retention does not continue indefinitely and edema does not worsen beyond a certain point.

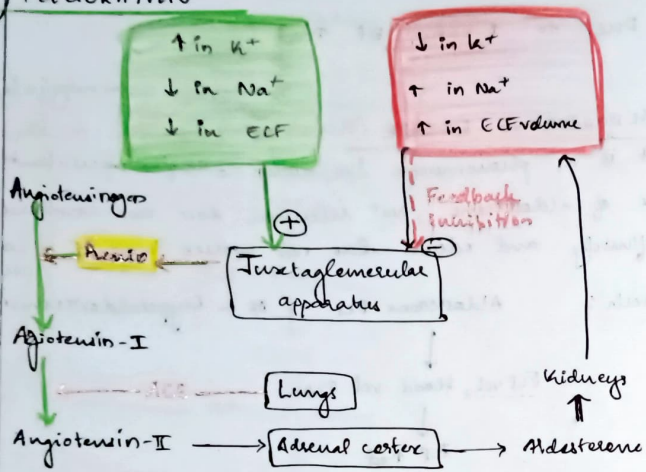
- Mech:- Aldosterone ↑es (As in hyperaldosteronism)
  ↓
  ECF vol, blood vol ↑es
  ↓
  BP ↑ed
  ↓
  ANP (from atrial muscles)
  ↓
  Excretion of excess Na^+ and water through urine (Pressure natriuresis and diuresis)
  ↓
  Content of Na^+ and water comes to normal

- Effects on other gland (other than kidney)

1) Salivary gland and sweat gland
- Na^+ reabsorption
- ∴ increased K^+ in saliva and sweat

2) Intestine
- Enhance Na^+ absorption from intestine esp. in colon and prevents loss of Na^+ through feces

III) REGULATION



IV)

- Stimulatory agents for aldosterone secretion are given in order of imp :-

1) ↑ in K^+ conc in ECF
2) ↑ ed activity of RAAS
3) ↓ in Na^+ conc (Hyponatremia)

V) Mechanism of Action

Aldosterone binds to cytoplasmic receptor → moves to Nucleus (complex)

↓

Here it alters transcription of mRNA

↓

Proteins with altered fn → ↑ the activity ENaCs (rapid effect)
→ ↑ syn of ENaCs. (slow effect)

- Aldosterone activates the gene for serum and glucocorticoid regulated kinase (sgk)

↓

↑es ENaC activity

- Aldo also ↑es activity of membrane Na^+-K^+ exchangers. This produces ↑ in intracellular Na^+.

VI) APPLIED

Adrenal cortex

Hyperactivity
- Cushing's (Gluco)
- Hyperaldosteronism
- Adrenogenital syn (Virilism)

Hypoactivity
- Addison's disease

CUSHING'S SYNDROME

Hypersecretion of glucocorticoids. ↑ in gluco is accompanied by ↑ed secretion of adrenal androgens.

CAUSES

- Adenomas of ant pit that secrete ACTH
- Abnormal fn of hypo that cause single level of CRH
- Ectopic secretion of ACTH
- Adenomas of adrenal cortex

NOTE - Cushing syndrome due to ant pit tumors are called Cushing's disease.

SIGNS AND SYMPTOMS

1) Disproportionate distribution of body fat produces :- (Due to)
   - Moon face - fat accumulation on face
   - Buffalo hump - fat " in upper back
   - Pot belly - fat " in upper abdomen

2) Purple striae - reddish purple stripes on abdomen, due to
   - Stretching of abdominal wall by ↑ed subcutaneous fat
   - def of collagen fibres due to protein depletion (causing thinning of skin)

3) Thinning of extremities

4) Muscle are poorly developed due to protein catabolism

5) Bone resorption and osteoporosis

6) Facial hair growth and acne (effect of androgens)

7) Wound heal poorly and minor injuries cause bruises and ecchymoses.

8) Blackening of skin due to pigmentation of skin by MSH like activity of ACTH

9) Mental abnormalities

10) Hypertension due to ↑ed retention of Na^+ and water

Treatment

1) Removal of tumor (adrenal)

2) Tumors in pit gland → removed by radiation

3) Serotonin antagonists and GABA transaminase inhibitors (inhibit ACTH secretion)

4) Bilateral adrenalectomy if ACTH sec cant be controlled

HYPERALDOSTERONISM

Depending upon causes, classified as :-

- 1° hyperaldosteronism (Conn's syndrome)
  - Renin secretion is depressed (due to feedback suppression)
  - Effects :- 1) hypokalemia → muscles are paralysed
    2) slight ↑ in ECF and blood volume
    3) hypertension
  - Causes : Adenoma of zona glomerulosa
    adrenal hyperplasia
    adrenal carcinoma
  - Treatment : Surgical removal of tumor

- 2° hyperaldosteronism
  - Occurs due to extrapyramidal causes
  - Causes : Cirrhosis
    heart failure
    nephrosis

Adrenogenital Syndrome (Virilism)

- Tumor of zona reticularis.
- Effects: Extensive masculinizing
  - In Females: develop of male sec sexual characters such as beard, deeper voice, muscular body enlargment of clitoris
  - In prepubertal: Same effects + rapid sex organ development males

Addis