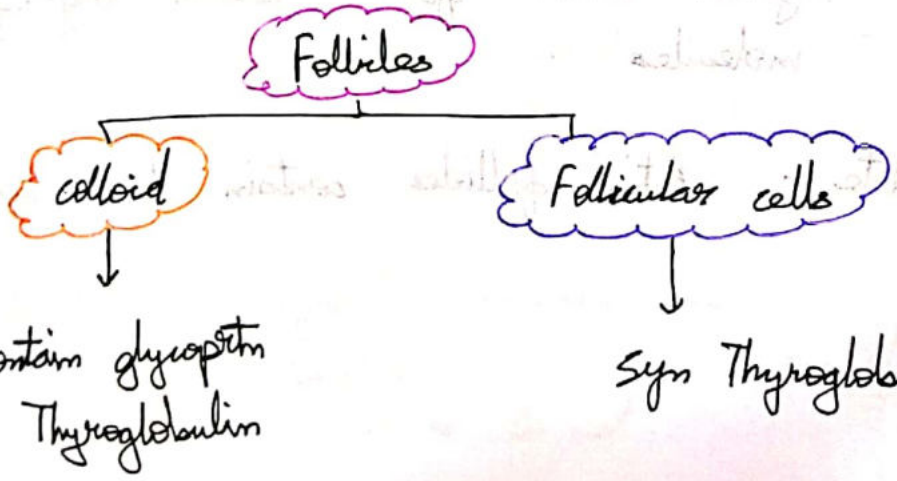
- Secretes 3 major hormones
  - Follicular cells → Thyroxine (T_4)
    → Tri iodothyronine (T_3)
    } ↑ Metabolic rate
  - Parafollicular cells or C cells → Calcitonin → calcium metabolism
- Thyroid gland is the only gland that stores its secretions extracellularly
- Fetal thyroid begins to function during fourteenth wk of gestation.
- Total hormones secreted by Thyroid gland
  → 93% → Thyroxine
  → 7% → T_3
- Almost all T_4 is converted to T_3 at the tissues but its conc in blood is more
- T_3 is 4-5 times more potent than T_4
- Thyroid gland contain large no of follicles (100-300μm in diameter)

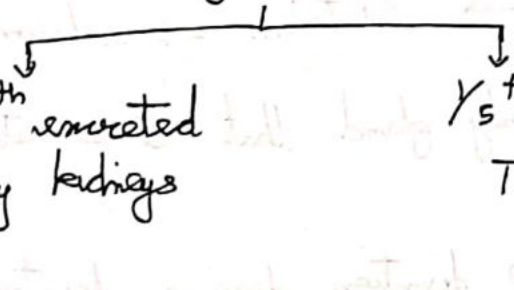


Thyroglobulin contains the thyroid hormones [iodinated tyrosine]

Blood flow is 5 times its wt.

- Normal syn of Thyroid hormones requires 50 mg of iodine in the form of dietary iodides per year. Or 1 mg per week.

- Fate of dietary iodides



=> Thyroglobulin :-

- Mol wt = 335,000
- glycoprtn.
- Syn by ER & golgi apparatus & secreted into the follicles
- Each molecules of TG contains 70 tyrosine aa residues
- Thyroid hrmns form within thyroglobulin molecules

Note :- Active follicles contain less colloid.

Synthesis of Thyroid hormones :-

① Iodide trapping :-

- Transport of iodide ions from blood into the follicular cells for syn of T_4 & T_3
- I^- ions are transported by $2Na^+/I^-$ symporter. It is an example of sec active transport
- The energy for the transport is provided by the conc gradient of Na^+ created Na^+/K^+ ATPase pump
- The capacity of this pump helps conc iodide 30x of blood normally & upto 250 times during maximal activity of gland.
- Rate of iodide trapping influenced by TSH
- I^- is transported into the follicle thru pendrin [Cl^-/I^- counter transporter].

② Oxidation of Iodide ion :-

- An essential step in formation of thyroid hormns I^- is oxidised to nascent Iodine (I°) or I_3^- which combines with Tyrosine to form iodinated tyrosine.
- Enzyme :- Thyroid peroxidase and associated H_2O_2 located in apical mem of cell or attached to it.

(3) Organification of Thyroglobulin :- print in thyroglobulin

- Binding of oxidised I to tyrosine, to form mono & di iodotyrosine.

- Tyrosine $\xrightarrow{+I_2^-}$ Monoiodotyrosine $\xrightarrow{+I_2^-}$ diiodotyrosine

- Enzyme :- Thyroid peroxidase
  time taken :- sec to minutes

(4) Coupling of Iodotyrosine residues :-

- MIT & DIT present within the thyroglobulin molecules are coupled to form thyroid hormones.

MIT + DIT $\xrightarrow{\text{Thyroid peroxidase}}$ 3, 5, 3' tri iodothyronine (T_3)

DIT + DIT $\xrightarrow{\text{Thyroid peroxidase}}$ 3, 5, 3', 5' tetra iodothyronine (T_4) or Thyroxine.

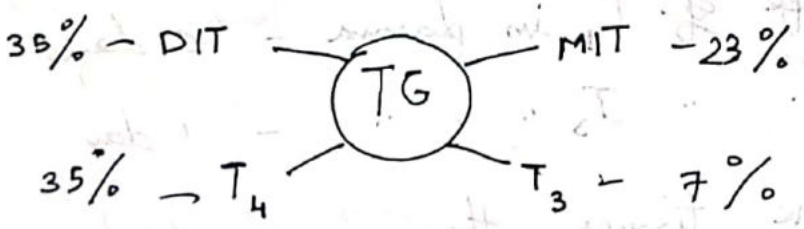
DIT + MIT ⟶ RT_3 - reverse T_3 ↓ No func significance

- The thyroid gland has an unusual ability to store large amts of hormones
- After the synthesis of Thyroid hormones each Thyroglobulin molecules contains 30 T_4 molecules and a few T_3 molecules.
- Sufficient amt of hormone is stored within the gland to meet the thyroid hormone

remain ~~of~~ body ~~after~~ the next 2 - 3 months.

(5) Rlz of T_3 & T_4 from thyroid gland :-

- Thyroid cells at their apical surface extend pseudopod extensions around small portions of colloid to form pinocytic vesicles that enter the thyroid cells.
- Lysosomes digest the thyroglobulin in the pinocytic vesicle & rlz T_3 & T_4 into the cell.
- T_3 & T_4 diffuse out into the blood capillaries and are carried to their target organs.
- About 3 quarters of the iodinated tyrosine in TG molecule never become thyroid hrmns.



- During TG digestion the I of MIT & DIT is cleaved & recycled by deiodinase enzyme
- daily rate of secretion :-
  T_4 - 80 µg/day
  T_3 - 4 µg/day

But at the level of tissues almost all T_4 is converted to T_3.

T_3 - hrmn used by the Tissues.

⇒ Transport of thyroid hormones :-

- About 99% of T_4 & T_3 immediately combine with plasma prtns syn by liver.
  They are as follows :-

  ① Thyroid binding globulin - 67% of T_4
  ② Thyroid binding pre albumin
  ③ Albumin - 53% of T_3.

- T_4 & T_3 are rlzd slowly to the tissues bcz of high affinity of plasma binding prtns. especially T_4
- Half life of T_4 in plasma - 6 days.
  " " " T_3 " " - 1 day
- In the tissues they again bind with the intracellular prtns and are stored in the target organs.
- Thyroid hormones have slow onset & prolonged duration of action as they are bound to plasma prtns for a long time.

T_3 acts more rapidly than T_4

⇒ Metabolism & excretion :-

- T_4 acts as prohormone as T_3 is 4-5 times more potent than T_4
- Intracellular thyroid hormone receptors → more affinity for T_3.
- There are 3 types of Deiodinase enzymes

  D_1, D_2 } Responsible for most of the conversion of $T_4 \rightarrow T_3$

  D_3 – skeletal muscle, CNS, liver
  ↳ inactivates T_3
  inactivates $T_4 \rightarrow RT_3$

- After inactivation they are conjugated with sulfates & glucuronides & excreted in bile
- However in intestine there may be partial reabsorption after deglucuronidation.

Physiological functions of Thyroid hormones :-

- Genomic effects :-
  - The most general effect of T_3 is to cause transcription of a large no of genes.
  - It binds to its intranuclear receptor which is present as a heterodimer along with retinoid x receptor.
  - The thyroid hormone receptors are either attached to DNA strands or in close proximity to them.
  - As a result many prtns are syn in the target cell which can be enzymes, structural prtns, func prtns like carriers, ion channels etc.

- Non genomic effects :-
  - Independent of genomic effects
  - They are :- (1) Regulation of ion channels
    (2) .. of oxidative phosphorylation
    (3) Activation of 2nd messgr systems like cAMP & prtn kinase signalling cascades.
  - Site :- cell mem, cytoplasm
    mitochon of heart, adipose tissue, pituitary

- This occurs by two ways

① Thyroid hormone ↑ the no & activity of mitochondria which in turn ↑ the rate of formation of ATP to energise cell func.

② T_3 ↑ Na/K^+ ATPase pump — energy is used and heat prod ↑

- Effect on Growth :-
  - effects are both general & specific
  - Hypothyroidism :- skeletal growth retarded
  - Hyperthyroidism :- skeletal growth greatly ↑ but the bones also mature earlier with early epiphyseal closure — eventual ht of adult may be shortened
  - Thyroid hormones necessary for growth & dev of brain during fetal life and few first yrs of post natal life.

- Metabolic effects :-

① Carb metabolism :-
- ↑ glucose uptake by cells
- ↑ glycolysis
- ↑ gluconeogenesis > glycogenolysis

www.FirstRanker.com

rate of absorption from GIT

(↑) insulin secretion [secondary effect]

(2) Fat metabolism :-

- (↑) lipolysis
- (↑) mobilisation of fatty acids
- (↑) FFA conc in plasma
- (↑) oxidation of FFA by cells
- (↓) cholesterol, phospholipids & triglycerides in plasma

Heme in prolonged hypothyroidism → (↑) cholesterol in plasma → atherosclerosis

(↓) cholesterol in plasma is by (↑) cholesterol secretion in bile and its loss in feces

(3) Protein metabolism :-

- T_4 in physiological dose is anabolic and (↑) prtn syn

- T_4 in pharmacological dose causes (↑) prtn catabolism due to high BMR

(4) H_2O & mineral metabolism :-

T_4 administeration

(1) In normal person — mild diuresis with loss of K^+

② In myxoedematous person — marked diuresis with excretion of Na^+

③ In hyperthyroidism — mild diuresis with K^+ & Ca^{2+} excretion in urine.

⑤ Thyroid hormone ↑ requirement of Vitamins as they ↑ enzyme syn.

Vitamins are part of or act as coenzymes of various enzymes.

T_4 also needed for conversion of β carotene to Vit A. Hence in hypothyroidism it causes carotenimia. [sclera not yellow]

⑥ Thyroid hormone ↑ BMR

Hyperthyroidism :- BMR ↑ upto 60-100% above normal

Hypo :- BMR becomes 50% of normal [absence of T_3 & T_4]

⑦ Effect on body wt :-

↑ T_3 & T_4 — ↓ body wt

↓ T_3 - T_4 — ↑ body wt

↑ T_3 & T_4 also ↑ the appetite which may counterbalance the effect.

Effect of thyroid hormone on various systems :-

① CVS :-

- ↑ in metabolism of tissues ⟶ ↑ blood flow to the tissues
- ↑ SV ⟶ ↑ cardiac output
- ↑ heart rate
- ↑ heart strength with slight excess of hormone due to ↑ enzymatic activity

Excessive $T_4 > T_3$ ⟶ weakening of heart muscle due to ↑ protein catabolism.

- ↑ in systolic BP ↓ in diastolic BP due to ↑ Bld flow thru tissues

↑ pulse pressure.

② Respiratory Sys :-

↑ O_2 utilisation
↑ CO_2 production ⟶ ↑ Rate of respiration

③ GIT :-

- ↑ appetite > hunger
- ↑ rate of secretion of digestive juices
- ↑ GI motility
  - Hyper - diarrhea
  - Hypo - constipation.

- ↑ in muscle strength

But in hyper → ↓ in strength due to ↑ in prtn catabolism

- Fine muscle tremors → Hyperthyroidism.

(5) CNS :-

- ↑ rapidity of cerebration

hyper → nervousness & other psychoneurotic disorders

hypo → loss of intellectual func
memory loss
mental & physical lethargy

(6) Effect on sleep :-

- Hyperthyroidism :- person feels fatigue due to exhausting effects on CNS & Muscles but unable to sleep due to excitatory effects on synapses

- Hypo :- somnolence [sleep of 12-14 hrs]

(7) Endocrine system :-

- Thyroid hormones ↑ the need of the tissues for the hormones & hence ↑ normal secretion from other endocrine glands.

(8) Reproductive System :-

Hypo
- ♂ - loss of libido
- ♀ - Menorrhagia - Excessive menstrual bleeding
Polymenorrhea - frequent
Amenorrhea

♂ - Impotence
♀ - Oligomenorrhea
Amenorrhea.

=> Regulation of Thyroid hormone secretion :-

(1) TSH :- Thyrotropin

MW = 28000
glycoprotein < α - 89
β - 112

- ↑ secretion of thyroid hormones.
- Effects of TSH on thyroid gland :-
  1. ↑ proteolysis of thyroglobulin → releases hormones into blood
  2. ↑ activity of iodide pump → ↑ formation & iodination
  3. ↑ iodination of tyrosine
  4. ↑ size & secretory activity of thyroid cells
  5. ↑ no of cells
     cuboidal epithelium → columnar epithelium
- TSH ↑ all secretory activities of thyroid gland.
  Most ☆ early effect is to initiate proteolysis of thyroglobulin.
- Acts thru G_sPCR → cAMP system

H. Thyrotropin releasing hormone
3 amino acids → Paraventricular nucleus (PVN)

- Secreted by Hypothalamus → stimulates secretion of TSH from Ant Pituitary.

- Exposure to cold → best stimuli for rly of TRH
  ↓
  Rly of TSH from AP.

- Excitement & anxiety → inhibits the rly of TRH

The above two effects are not observed after the hypophysial stalk is cut.

- TRH binds to TRH receptors
  ↓
  Phospholipase C is activated
  ↓
  PIP_2 → IP_3 → Ca^{2+} influx
  PIP_2 → DAG

- ↓ leptin levels → inhibit TRH rely by PUN
  ↑
  Prolonged fasting
  ↓
  ↓ TSH → ↓ T_3 & T_4
  ↓
  ↓ BMR & conservation of energy when food supply is scarce.

Anti thyroid substances :-

I Thiocyanate ions :- ⊕ iodide trapping

- Thiocyanate, nitrate and perchlorate ions act as competitive inhibitors of iodide transport by $2Na^+/I^-$ symporter.
- Administration high thiocyanate ions
  ↓
  competitive inhibition of $2Na^+/I^-$ symporter
  ↓
  ⊕ iodide trapping
- Thiocyanate does not stop formation of thyroglobulin but merely prevents iodination of tyrosine by ⊕ rate of iodide trapping.
- ⊕ Thyroid hormones ⟶ stimulate AP to secrete more ⊕ TSH ⟶ size of thyroid gland ⊕ ⟶ goitre.

II Propylthiouracil :- blocks thyroid peroxidase enzyme
- ⊕ ~~iodination~~ oxidation of iodide ion
  ↓
  ⊕ iodination of tyrosine
  ↓
  ⊕ Hormone formation
- Does not effect thyroglobulin formation.

→ (↑↑) secretion of TSH

↓

overgrowth of gland

↓

goitre.

III High conc of inorganic iodides :- Wolff Chaikoff effect

- High conc of I^- in blood → (↓) activity of Thyroid gland
[intake of I^- > 2mg/day]

- (↓) Rate of iodide trapping → (↓) iodination of Tyr
- (↓) TPO activity
- ☆ Endocytosis of colloid by follicular cells is paralysed → Release of Thyroid hormones is shut down.

- (↓) in activity of Thyroid gland

↓

(↓) in size > (↑↑) in blood flow to the gland.

Beg of this high conc of I^- are administered before thyroidectomy to (↓) the amount of surgery and especially to (↓) the amnt of bleeding

- Adaptation to high iodide intake normally occurs by reducing expression of $2Na^+/I^-$ symporter [NIS] which causes intra thyroid iodide level to fall

Some point

- TPO activity then returns to normal and thyroid hormone synthesis resumes within days to weeks

NOTE :- Thyroid hormones also (↑) β adrenergic receptors and enhances catecholamine responsiveness

Catecholamines in turn (↑) lipolysis and (↑) ~~Thermogenin in brown fat~~ (↑) deiodinase type 2 enzyme (D_2)

D_2 converts $T_4 \longrightarrow T_3$

T_3 (↑) Thermogenin ⟶ (↑) prod of heat

↓

prevents energy trapping in ATP

(↑) heat prod.

=> Hyperthyroidism :-

- Thyroid gland (↑) 2-3 times its normal size bcoz of tremendous hyperplasia & infolding of follicular lining

- Causes :-

(1) Graves disease :-

- Autoimmune dyz
- Thyroid stimulating immunoglobulins (TSI) are produced

→ prolonged stimulation of TG upto 12 hrs instead of 1 hour by TSH

→ suppress TSH rly by AP
Hence TSH conc less or almost zero

② Thyroid adenoma :-
- Large amnts of $T_4 > T_3$ rlyd by a tumour of TG
- Adenoma ↓ the secretory activities of the remaining parts of TG as it ↓ the secretion of TSH by AP.

③ Exophthalmos :- Most common feature of hyperthyroidism
- Protrusion of the eye balls
- Epithelium of eye → dry and irritated leading to ulceration of cornea.
- Cause :- edematous swelling of retro orbital tissues & degenerative changes in extra ocular mscls.

Immunoglobins against eye mb found in plasma.

④ Diagnostic tests :-
1. conc of free T_4 in blood
2. BMR ↑ +30 to +60
3. conc of TSH in plasma
4. conc of TSI ↑ High in thyrotoxicosis
   ↓ Low in adenoma.

Treatment :-

① Surgical removal of Thyroid gland :-

Patient is prepared for thyroidectomy by giving propylthiouracil for several weeks until BMR becomes normal

Then high conc of iodides are given to reduce the size and blood supply of Thyroid.

② Thyroid adenoma by radioactive iodine.

5 mCi of radio I is given

80-90% of injected I absorbed by hyperplastic thyroid gland.

=> Hypothyroidism :- ↓ secretion of $T_4 > T_3$

① Hashimoto's dzz :-

- Autoimmune dzz
- But here autoimmunity (antibodies) destroys the gland.
- There is auto immune thyroiditis — thyroid inflammation
  → progressive deterioration of the gland and finally fibrosis
  → ↓ hormone secretion

② Endemic Colloid goitre :-

- Caused by I deficiency in food stuffs
- Goitre → enlarged thyroid gland.

who live in areas where the soil is deficient in I^- [eg swiss alps, Andes] develop large thyroid glands — endemic goitre

- Lack of I^- ⟶ No prod of T_3 & T_4

↓

No inhibition of Ant Pituitary

↓

Excessive secretion of TSH

↓

(↑) prod of thyroglobulin colloid but there is no iodine for hormone prod

↓

Follicles (↑) in size ⟵ Thyroid gland may (↑) to 10-20 x normal size.

(3) Idiopathic colloid goitre :-

- There is no deficiency of I^- but hormone prod is reduced.

- Can be caused by thyroiditis / enzyme defects

(↓) T_3 & T_4 → (↑) TSH → Thyroid becomes nodular as TSH (↑) size of non inflamed portions of gland

enzyme defects → (↓) iodide trapping, (↓) TPO, (↓) deiodinase

④ Goitrogens :-

- They have propyl thiouracil type activity → Reduce T_3 & T_4
- TSH stimulated goitre takes place.
- Present in vegetables of Brassicaceae family like cabbages, turnips.

⑤ Myxoedema :-

- Develops in person who have almost total lack of thyroid hormone function.
- Bagginess under the eyes, swelling of the face Non pitting edema.
- Hyaluronic acid & chondroitin sulfate bond prtn present in ECF → tissue gel excessive

Non pitting edema → Bcoz of gel nature of excess fluid

⑥ Atherosclerosis in Hypo :-

↑ serum cholesterol

↓ in cholesterol excretion in bile → Atherosclerosis → CAD, deafness, Peripheral Vascular dzz

Diagnosis

① $T_4 > T_3$ conc ↓ in plasma

② BMR ↓ to -30 to -50

③ Administration of TRH → great ↑ in TSH secretion.

- Treatment :-

oral ingestion of one or more tablets of T_4

- clinical features of Hypo & Hyper :-

	Hyper	Hypo
General features	Fatigue	=
	↑ BMR	↓ BMR
	weight gain	weight loss
	High state of excitability	Extreme sluggishness
Temperature	intolerance to heat	intolerance to cold
CVS	↑ HR > CO	↓ HR > CO
GIT	mild to severe diarrhea	constipation
Skeletal sys	muscle weakness	m/s sluggishness
CNS	fine tremors Nervousness Psychic disorders	mental sluggishness
Sleep	fatigue but cannot sleep	Somnolence.

Menstruation

Oligomenorrhea

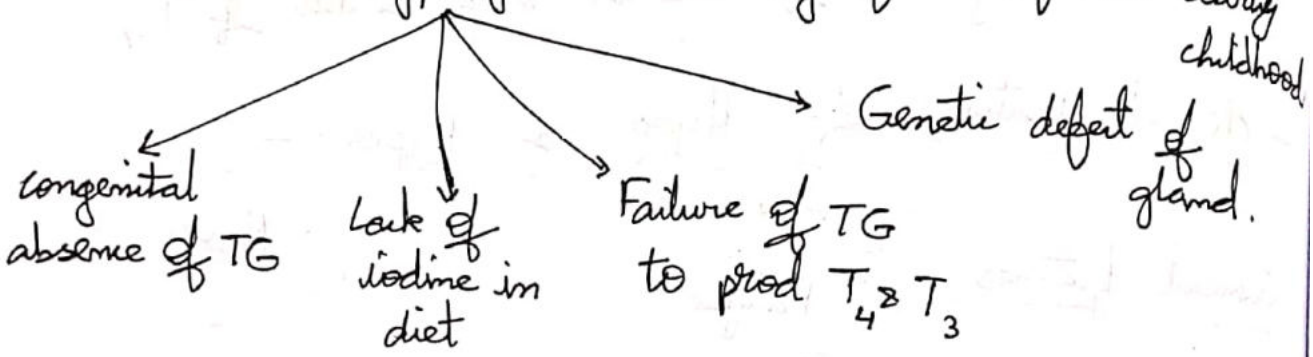
Menorrhagea
Polymenorrhea

Sexual func

♂ – loss of libido
♀ – (↓) libido

=> Cretinism :-

– extreme hypothyroidism during fetal life or early childhood



– Failure of body growth → mental retardation

Can be corrected any time by giving T_4 or I^-

Can be corrected only if treated within a few weeks after birth.

If not there is permanent mental retardation

caused due to retardation of grth, branching & myelination of neurons in CNS during critical period of dev of mental powers.

– A child with lack of TG appears normal at birth as it was supplied with Thyroid hormone from mother in utero.

- Retardation of skeletal growth > than that of soft tissues
  Bcoz of this disproportionate rate → soft tissues become v. large → obese, stocky & short appearance
- Tongue → v. large → obstructs swallowing & breathing
  ↓
  sometimes chokes the child. → guttural breathing

Glucose Homeostasis :-

Tissues in Pancreas

- Pancreatic acini
  - digestive juices
- Islets of Langerhans
  - 1-2 million in number
  - each 0.3 mm in diameter
  - organised around small capillaries into which they pour hormones
    - PP — 5% — Pancreatic polypeptide
    - α — 25% — glucagon
    - β — 60% — Insulin, Amylin
    - δ — 10% — Somatostatin

- The cells in islets of langerhans are closely inter-related allowing efficient cell to cell communication and control of some hormones by other hormones
  eg:- Somatostatin inhibits secretion of both insulin and glucagon.

- Insulin
- Discovered by banting & best
- Crucial for glu, prtn & fat metabolism
- Small prtn => MW :- 5808
- Structure :- Two amino acid chains A & B attached thru disulfide linkages
- Insulin synthesis :-

Steps :-

(1) Preproinsulin is syn by ribosomes (MW = 11,500)

(2) Preproinsulin cleaved by E.R to form pro-insulin (MW = 9000) having A, B and C chains.
Not physiologically active

(3) Pro insulin cleaved by golgi apparatus
C peptide is removed.

(4) Both insulin & C peptide are packaged into secretory vesicles and are rlzd thru exocytosis when needed.

5-10% of total secretory end prod is pro insulin

peptide activates two enzyme systems

Na^+/K^+ ATPase endothelial NO synthase

- Insulin circulates in blood in free form
- Half life = 6 min. Heme cleared from blood in 10 - 15 minutes
- Degraded by enzyme insulinase → Liver mainly, Muscle, Adipose tissue } Partly

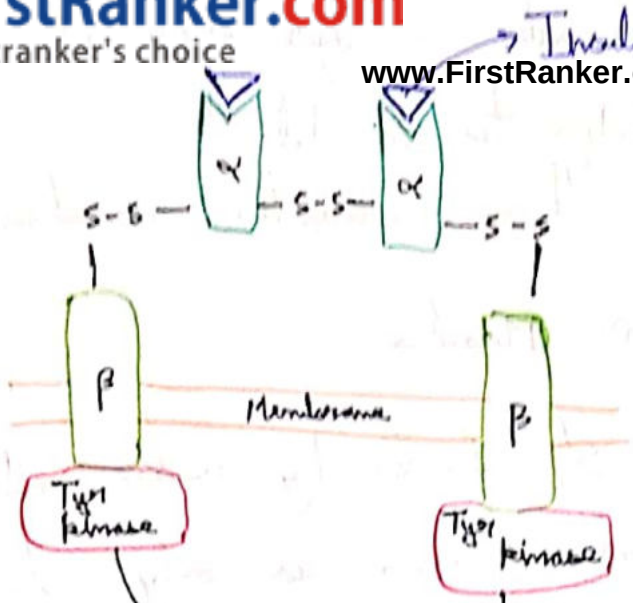
⇒ Functions of Insulin :-

- Hypoglycemic hormone
- promotes rapid uptake and utilisation of glucose
- Acts thru Enzyme linked Hormone receptor.

- Insulin receptor
  - Enzyme linked receptor MW = 3,00,000
  - Consists of 4 subunits → 2α, 2β attached by disulfide linkages

α - outside cell mem

β - protrude thru mem into cytoplasm



① Insulin binds to α subunit

② Autophosphorylation of β subunit

③ Activation of associated Tyrosine kinase

Phosphorylation of Enzymes including IRS (Insulin receptor substrate)

Change in activity of enzymes

Effects of insulin on Target cells

Within sec rapid increase in uptake of glu by most of the body's tissues especially skeletal m/s & adipose tissue

↓

mobilisation & translocation of glu transporters to cell membrane - GLUT4

↑ transport of K^+ amino acids & phosphates into the cell

Changes activity of enzymes

Much slower effect.

Syn of new prtns over a prolonged period by transcription of specific DNA sequences.

- insulin - formation of new pt.
Helps to remodel
cell's metabolic machinery.

- Effect of insulin on Muscles :-

① Causes ↑ uptake of glucose by muscle cells :-

- The resting muscle mem is only slightly permeable to glu as main source of energy during most of time is fat for muscles

- Glu is utilised by muscles in 2 cond :-

a) during moderate or heavy exercise
- does not require much insulin
- m/s contraction can causes translocation of glu transporters to cell mem

b) After a rich carb meal
- Blood glu conc ↑ after a meal which causes rel of insulin
- Insulin ↑ uptake of glu by muscles utilisation

- Amount of muscle glycogen :-
  - ↑ glycogenesis in muscles
  - excess glu is stored as glycogen upto a limit of 2-3% conc.

③ Causes ↑ protein synthesis and storage :-
By :-
  a) ↑ amino acid uptake
  [valine, leucine, isoleucine, tyr, phenyl alanine]
  b) ↑ transcription & translation
  c) ↓ prtn catabolism

④ ↑ the transport of K^+ into cell :-
By ↑ activity of Na^+/K^+ ATPase.

- Effect on Liver :-

① Promotes uptake, storage & utilisation of glucose :-
  - Most of glu absorbed after a meal stored as glycogen in liver
  - ↑ glycogenesis by activating glycogen synthase
    ↓ glycogenolysis by inhibiting Liver phosphorylase
  - ↓ gluconeogenesis .. .. enzymes promoting it

① uptake of glucose by activating glucokinase.

– Liver Acts as "Blood glucose Buffer"

After meal → Bld glu ↑ → Insulin is secreted

Above effects happen → glu stored as glycogen

Between meals → Blood glu conc ↓ → Insulin secretion ↓

↓ Reversal of above effects

↑ gluconeogenesis

↓ glycogenesis

↑ glycogenolysis [phosphorylase activated]

glucose phosphatase activated → rlz of glu.

glu rlzd from Liver → Maintain normal blood glu

Thus when blood glu
- V. High → Liver removes glu from blood & stores as glycogen
- Low between meals → Liver releases glu

60% of glu in meal is stored & rlzd from Liver in this way.

stored as liver fat :-

glu ⟶ fatty acids ⟶ incorporated into triglyceride

↓

Stored in Adipose tissue. ⟵ Transported thru VLDL

(3) (↑) prtn syn > storage

— Effects on Adipose tissue :-

(1) (↑) utilisation of glu > (↓) utilisation of fats as a source of energy ⟶ Acts as fat sparer.

(2) (↑) uptake of glu by adipose cells

(3) (↓) activity of hormone sensitive lipase :-
This inhibits / (↓) hydrolysis of triglycerides

(4) (↑) formation of αglycerol phosphate from glu
This provides glycerol for triglyceride syn in ~~liver~~.

↓

storage form of fat in adipose tissue

(5) (↑) triglyceride formation in liver

(6) (↑) K^+ influx.

(7) (↑) FFA syn.

Effects of insulin deficiency on Fats & fat metabolism

(1) Causes (↑) breakdown of triglycerides stored & rly of fatty acids.

By activating hormone sensitive lipase

↓

free fatty acids in blood (↑) greatly.

(2) (↑) in plasma cholesterol and phospholipids during insulin deficiency.

Promotes atherosclerosis in DM.

(3) Excess utilisation of FFA ⟶ ketosis :-

↑↑ β oxidation of FA

↓

↑↑ acetyl CoA

↓

(↑) Production of ketone bodies

β hydroxybutyric acid — Acetoacetic acid — Acetone

↓

ketosis

↓

Metabolic acidosis

Protein breakdown: ↑ blood aa
↑ prtn cat.
↓ prtn syn
→ Protein wasting → Serious effect of severe DM.

- Effects of Insulin on growth:-

Insulin & GH act synergistically to promote growth.

↑ aa uptake & prtn syn.

⇒ Mechanism of Insulin secretion :-

Glucose enters β cells
↓
Glycolysis and oxidative phosphorylation
↓
ATP is produced
↓
ATP binds to ATP sensitive K^+ channels which leads to their closure.
↓
Depolarisation of β cells
↓
Opening of Voltage gated Ca^{2+} channels
↓
Ca^{2+} influx
↓
Secretory vesicles bind to cell mem & rly insulin By exocytosis.

Sulfonylurea drugs also bind to ATP sensitive K+ channels & they have same effect (↑) insulin sr.

⇒ Control of insulin secretion :-

(*) Blood glucose concentration. – Most potent

(↑) insulin secretion

1. (↑) Blood glu conc
2. (↑) FFA in blood
3. (↑) aa in blood
4. GIT hormones [GLP1 > GIP]
5. GH, glucagon, glucocorticoid
6. Parasym stimulation acetylcho
7. β adrenergic stimulation
8. Insulin resistance, obesity
9. Sulfonylurea drugs

(↓) insulin secretion

- (↓) Blood glu
- α adrenergic stimulation
- Leptin
- fasting
- Somatostatin

– (↑) Blood glu stimulates insulin secretion :-

- Fasting bld glu level → 80 - 90 mg/100 ml of blood
  At this glu level insulin secretion is minimal at 25 ng/min/kg of body wt → v. less physio effects
- When Bld glu is (↑) several fold and is maintained at that level there is (↑) secretion of insulin in 2 Phases.

① Fast phase :-

- Rapid ↑ in insulin conc but is short lived
- due to rls of insulin from preformed vesicles of β cells. ie. labile pool of insulin
- Insulin lvl falls but remains above basal level.

② Slow phase :-

- slow and prolonged rls of insulin
- rls from stable pool of insulin
  new insulin is syn and rlsd into blood
- insulin peak reached is more than that of fast phase.

GI hormones :-

Gastrin, Secretin, CCK

GLP-1, GIP (

↳ Most potent — are also called incretins

↓

Cause an ↑ in insulin secretion

↳ Anticipatory response in preparation of ↑ blood glucose & aa

Also ↓ glucagon secretion

⇒ Role of insulin in switching B/W carbs & lipid metabolism

- When blood glu high → ↑ insulin
  ↓
  ↑ utilisation of glu & sparing of fats
- When blood glu low → ↓ insulin
  ↓
  ↑ utilisation of fats & glu is conserved.
- Hence insulin decides which nutrient acts as a source of energy from moment to moment.
- Other hormones involved in this switching mech are :- GH
  cortisol
  glucagon
  Epinephrine

- Rhd from α cells
- MW = 3485 29 amino acid chain
- Hyperglycemic hormone
- Functions are opp to that of insulin
- Effects on glucose metabolism

① ↑ glycogenolysis in liver

② ↑ gluconeogenesis in liver

- These are the most impt effects of glucagon
- Only a few micrograms of glucagon can cause bld glu to double or even ↑ more within a few min.

— Other effects :-

① ↑ lipolysis - breakdown of triglycerides in adipose tissue

② ↑ rly of FA from Adipose tissue & its utilisation.

③ ↓ synth of triglycerides in liver

Other effects :-

(1) Enhances heart strength
(2) ↑ blood flow to kidneys
(3) Enhances bile secretion
(4) ~~↑~~ ↓ gastric acid secretion

⇒ Control of glucagon secretion

(1) Blood glu conc :-
Low blood glu stimulates glucagon secretion [Hypoglycemia]

(2) ↑ aa ~~⇒~~ in blood stimulates glucagon rly
- glucagon ↑ aa uptake & ↑ gluconeogenesis

(3) Exhaustive exercise → ↑ glucagon
glucagon does not let blood glu to fall to hypoglycemic levels.

⇒ Somatostatin

- By δ cells
- 14 aa
- Half life = 3 min.
- Factors stimulating somatostatin rly :-
  ↑ Blood glu, aa, FFA
  ↑ conc of GIT hormones rshd from upper GI

Effects of somatostatin :-

(1) Inhibits secretion of both glucagon & insulin

(2) (↓) motility of stomach, duodenum & gall bladder

(3) (↓) both secretion & absorption in GIT.

(4) It (↓) the utilisation of absorbed nutrients by tissues preventing rapid exhaustion of the food & ∴ making it available over a longer period.

⇒ Blood glucose regulation :-

- Normal person – bld glu conc is narrowly regulated
- Fasting level ie before meal = 80 - 90 mg/100ml of blood

After a meal this bld glu level rises to 120 - 140 mg/100 ml within an hour so.

↓

-ve feedback mech are activated

[most important → ~~insulin~~ insulin feedback sys]

↓

Bld glu conc brought back to control level within 2 hrs after last absorption of carbs

- During starvation – opposite occurs

Liver rlys glucose.

- Regulation of Ca^{2+} is impt as it is the only nutrient that can be used as a source of energy by Brain, Retina & germinal epithelium of gonads.

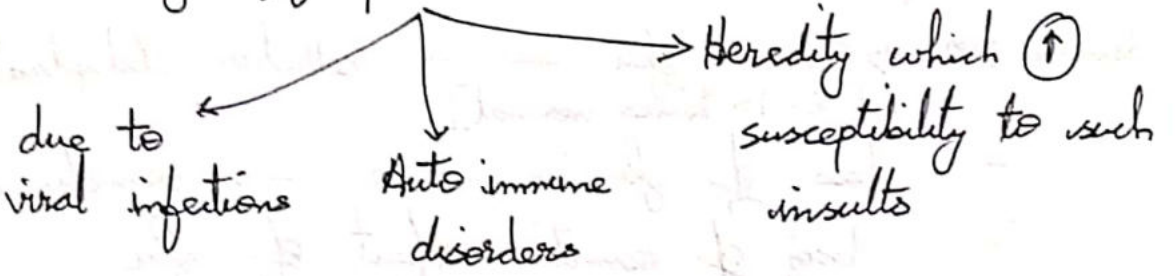
=> Diabetes Mellitus :-

- It is syndrome characterised by abnormal carb, fat & ~~lipid~~ protein metabolism.
- Caused due to insulin deficiency.
- It is of two types

Type I	Type II
- Insulin dependent	Non insulin dependent
- due to ↓ prod of secretion of insulin	due to insulin resistance
- Age of onset < 20 yrs	Age of onset ~~B/w~~ > 30 yrs usually B/w 50-60 yrs of age
- Juvenile diabetes	Adult onset diabetes
- Relatively rare 5-10% of total DM patients have type I	More common 90-95% of total DM patients.
- Low plasma insulin	High plasma insulin
- High glucagon can be suppressed	High glucagon ~~cannot be suppressed~~.

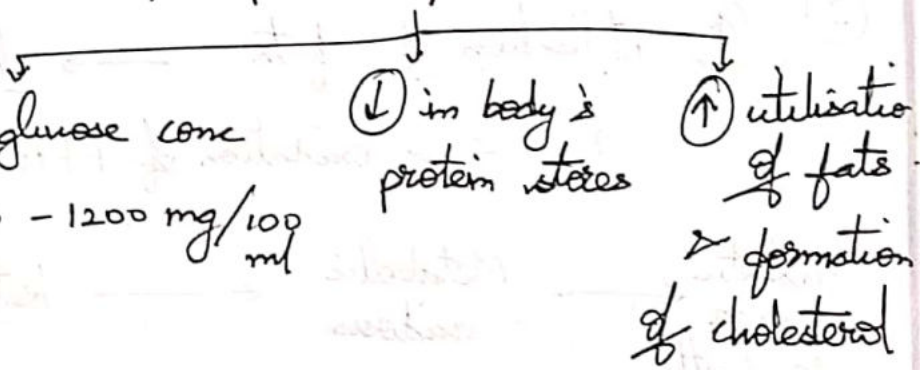
Type I diabetes :-

- ↓ secretion of insulin caused due to destruction or damage of β cells



- Age of onset — 14 yrs – 20 yrs
  Can occur in adulthood or any time during lifetime due to destruction of β cells.

- Type I DM begins abruptly within few days to weeks with 3 principal sequelae



- Clinical features :-

① Increase blood glucose causes loss of glucose in urine

- Blood glu levels exceed the blood threshold for the appearance of glu in urine which is about 180 mg/100 ml of blood
- More glu is filtered into renal tubules than can be reabsorbed → loss of glu in urine.

↑ Blood glucose causes dehydration :-

- glu can exert a large amnt of osmotic pressure in ECF

Severe DM → Excess glu ⟶ cellular dehydration
[8-10 times normal]

- loss of glu in urine → osmotic diuresis
bcz of osmotic effect of glu

Less water is reabsorbed → Large amount of urine is formed & excreted

→ Polyuria
→ ECF dehydration → ICF dehydration
→ ↑ thirst.

(3) ↑ utilisation of fats → ketosis :-

- ↑ use & oxidation of FFA → ↑ prod of ketone bodies

ketosis → Metabolic acidosis → diabetic coma & death

if not treated immediately.

Excess use of fats in liver → ↑ plasma cholesterol

Atherosclerosis → Hypertension

In diabetic coma → kussmaul breathing.

→ Tissue damage :-

- ① Blood glu ⟶ affects blood vessels in multiple tissues

↓

↓ Blood supply to tissues

↓

↑ risk for MI, stroke, ESRD, retinopathy blindness, ischemia & gangrene of limbs

- Peripheral neuropathy & autonomic N.S dysfunction.

(5) ↓ Body's protein stores

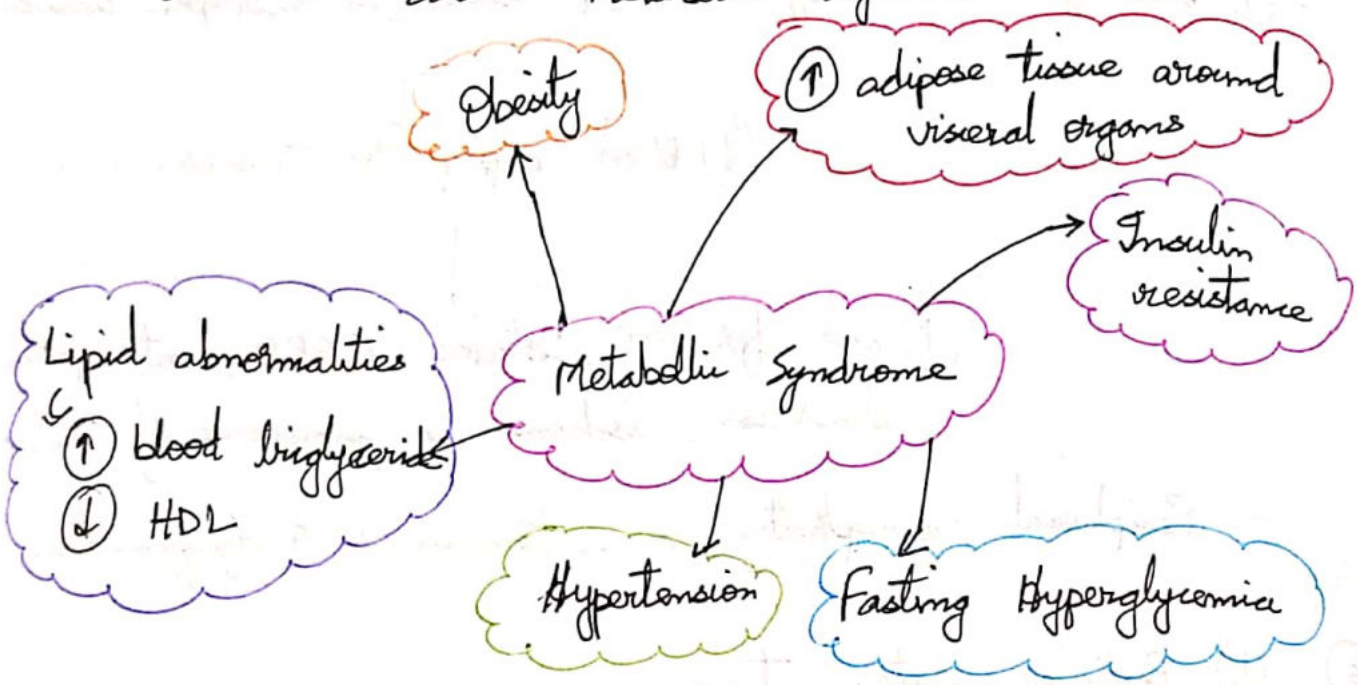
Severe untreated DM ⟶ Rapid wt loss & asthenia [lack of energy]

↓

Polyphagia [eating large amount of food]

- Type 2 Diabetes mellitus
  - Age of onset ⟶ >30 yrs usually B/w 50-60 but in recent times ppl younger than 20 yrs have type 2 DM due to ↑ prevalance of DM.
  - Obesity, insulin resistance & metabolic syndrome precede Type 2 DM.
  - In contrast to type 1 there hyperinsulinemia a compensatory response to insulin resistance

Insulin resistance is a part of cascade of disorders called Metabolic syndrome.



- Causes of insulin resistance
  1. Obesity
  2. Cushing's syndrome
  3. Acromegaly / gigantism
  4. PCOD, pregnancy / gestational diabetes
  5. Lipodystrophy [↑ accumulation of lipids in liver]
  6. Auto antibodies against insulin receptor
  7. Mutations of insulin receptor
  8. Mutations that cause genetic Obesity (Melanocortin receptor]
  9. Mutation of Peroxisome proliferator activated receptor
  10. Haemochromatosis (Tissue Fe accumulation]

↑ Type 2 develops due to prolonged insulin resistance

- Early stages of dzs → moderate hyperglycemia after a carb meal.

- Due to prolonged hyperglycemia & insulin resistance β cells become ~~ss~~ exhausted

Hence in later stages → (↓) insulin secretion from β cells [Not sufficient quantity]

↓

Sever hyperglycemia after a meal.

⇒ Treatment of type 1 DM :-

- By Administeration of insulin.

- Insulin → Regular acting → effects last for 3-8 hrs
  → longer acting → effects last for 10-48 hrs
  [insulin precipitated with Zn or prtn derivatives]

- Each patient is provided with individualised pattern of treatment with combination of longer acting & regular insulin

- Earlier Animal insulin was used which caused allergic & immune response in patients

- Nowadays human insulin prod by Recomb DNA tech is used.

Treatment of type 2 DM :-

① Lifestyle changes, ↑ insulin secretion & sensitivity :-

- Lifestyle modifications → Exercise
  → Calorie restriction
  → weight reduction
  ↳ helpful in early stages.

- Administering drugs :-
  - ↑ insulin secretion → sulfonyl urea drugs
  - ↑ " sensitivity → thiazolidinediones
  - ↓ liver gluconeogenesis → Metformin

- In late stages even insulin administration is required.

- ↑ insulin secretion by ↑ GLP-1, GIP
  → drugs that mimic incretins
  → drugs that inhibit dipeptidyl peptidase 4 [DPP-4]
  ↓
  This enzyme inactivates GLP-1 and GIP.

To reduce fat mass & achieve improved control of Blood glucose.

(3) Inhibition of SGLT-2 in renal tubules :-

SGLT-2 inhibitors eg :- dilfogiflozin

↓

(↓) Reabsorption of glu.

↓

(↑) loss in urine & (↓) conc of glu in blood.

Also causes osmotic diuresis → may help to treat hypertension

But risky for patients who are already taking other diuretics & anti hypertensives.

⇒ Physiological Basis of diagnosis of DM :-

(1) Urinary glucose :-

Normal person → No glu in urine

Diabetic " → small to large amnt of glu depending on severity of DM

(2) Blood glucose :-

- Normal fasting = 80 - 90 mg/100 ml

upper limit = 110 mg/100 ml

diabetes = >110 mg/100 ml

After meal normal = 120 - 140 mg/100 ml

diabetic = excessive

- Insulin conc
  - Type 1 – low
  - Type 2 – High

(3) Glycated Hb

Prolonged hyperglycemia → glucose binds to Hb permanently forming glycated Hb.

(4) GTT :-

oral dose of glucose 75g given
Assess glu metab. rate.

- Normal GTT :-

  fasting = <126 mg/dL

  after 2 hrs of glu dose = <140 mg/dL

- Diabetic GTT

  fasting = >126 mg/dL

  2 hrs post prandial = >200 mg/dL
  & other post prandial value

- Impaired GTT

  fasting PP values > upper normal limits but < diabetic values.

Severe type DM → ↑ ketone bodies → fruity breath [Equity]

=> Hyperinsulinemia :- Insulin shock.

- Happens when excess of insulin is administered to diabetic patients

- Effects :-

1. Hypoglycemia - 50-70 mg/100 ml
2. CNS becomes sensitised & excitable
3. Hallucinations / extreme nervousness
4. ↑ tremors & ↑ sweating
5. If glu levels fall to 20-50 mg/100 ml
   desire seizures & loss of consciousness
6. If glu level falls further → hypoglycemic coma

=> Histology of Adrenal cortex :-

Zones of Adrenal Cortex

Outer
Zona glomerulosa (15%)

- Small columnar acidophilic cells
- cells arranged in ovoid clusters
- Mineralocorticoid
  ↓
  Effect electrolytes of ECF
  principle mineralocorticoid — Aldosterone
- Secretion controlled by ECF conc of Angiotensin II > K^+

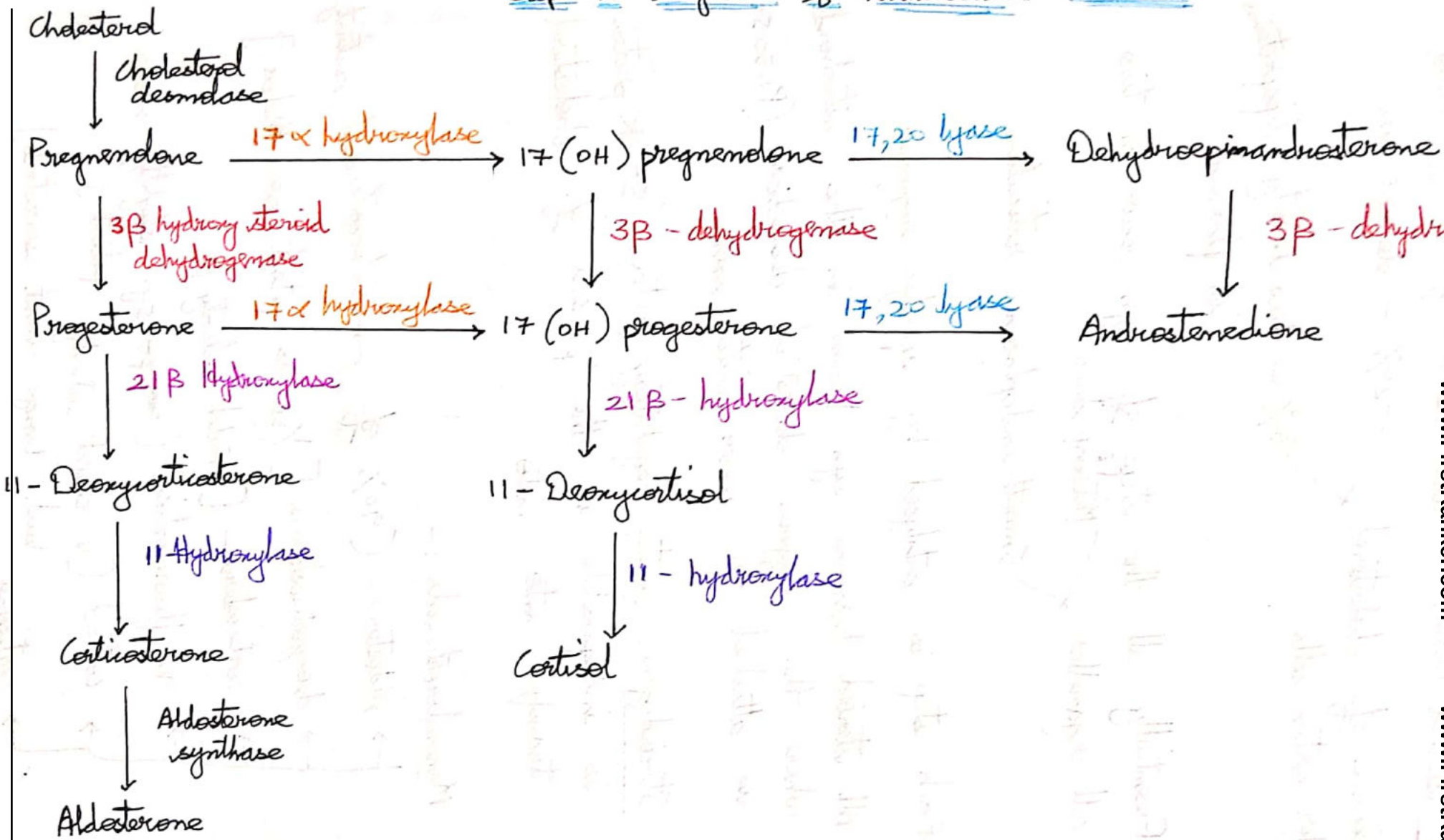
Middle
Zona fasciculata (80%)

- Large polyhedral light pink cells.
- Arranged in straight columns
- Glucocorticoid
  ↓
  (↑) Blood glucose
  Principle glucocorticoid
  ↓
  Cortisol
- Secretion controlled by hypothalamo-pituitary axis ie ACTH

Inner
Zona reticularis (5%)

- Small cells arranged as anastomotic cords
- Sex steroids
  ↓
  Adrenal androgens
  DHEA
  androstenedione

Steps in Biosynthesis of Adrenocortical hormones



Synthesis of Adrenocortical Hormones :-

- All steroid hormones are derived from cholesterol.
- Source of cholesterol for cortex cells
  - 20% – de novo syn
  - 80% – low density lipoproteins in plasma.
- Essentially all the steps of syn occur in two cell organelles
  - Mitochondria
  - Smooth endoplasmic reticulum
- Each step is catalysed by specific enzymes.
- All steroid hormone syn begins in the mitochondria where the enzyme cholesterol desmolase ($P_{450\,scc}$) is attached to inner mito mem.
- Steroidogenic acute regulatory protein (StAR protein) is indespinsable in the process of cholesterol transfer into mito.
- Mineralocorticoids :-
  - Aldosterone (90% of mineralocorticoid activity)
  - deoxycorticosterone [1/30 as potent as Aldos.]
  - corticosterone [mild activity]
  - 9α fluorocortisol [as po syn slightly more potent]
  - cortisol [v. slight activity but large amnt secreted]
  - cortisone

- cortisol [95% of gluco. activity]
- corticosterone [4-5% " " "]
- cortisone [synthetic as potent as cortisol]
- prednisone [" 4x " " " "]
- Methyl prednisone [" 5x " " " "]
- dexamethasone [" 30x " " " "]

	Plasma conc	mg/day
cortisol	12 mcg/100 ml	15
aldosterone	0.006 mcg/100 ml	0.15

- Mineralocorticoid activity of aldosterone is 3000 times that of cortisol. but conc of cortisol 2000 times more

=> Transport & excretion of Adrenocortical hormones :-

- 90-95% of cortisol transported bound to plasma prtns
  - Transcortin [mainly]
  - Albumin [lesser extent]
- Prtn bound hormone acts as a reservoir
- Degraded in liver by conjugation with glucuronic acid mainly & partly to sulfates
- These conjugated hrmns are excreted in bile [25%] and in urine.

- Mineralocorticoid deficiency causes severe NaCl wasting and hyperkalemia.
- Absence of Adrenocortical hormones → death within 3 days to 2 weeks.

Absence of Aldosterone

↓

↑ K^+ plasma conc

↓ Na^+ & Cl^- plasma conc due to rapid loss in urine

↓

ECF volume ↓

Bld vol ↓

↓

Cardiac output ↓

↓

Circulatory Shock. → death if not treated

Hence Mineralocort. → Acute life saving hormones.

Functions of Aldosterone :-

(I) Actions on Kidneys

(1) (↑) Reabsorption of Na^+ & (↑) Secretion of K^+

- This occurs mainly by principal cells of collecting tubules and to lesser extent in DCT & CD.

↓

Na^+ is conserved in ECF

(↑) excretion of K^+

- Lack of Aldosterone ⟶ loss of 10-20 g of Na^+ in urine per day ie loss of 1/10th to 1/5th of total body Na.

- Aldosterone escape :-

Excess of aldosterone causes (↑) in ECF volume (↑) BP but plasma Na^+ conc unaffected.

(↑) Aldosterone ⟶ (↑) Reab of Na^+

↓

Osmotic absorption of Equivalent amount of H_2O.

↓

Hence not much change in Na^+ conc.

Aldosterone mediated ↑ in ECF for 1-2 days

↓

↑ BP → Hypertension

↓

Kidneys

Pressure natriuresis → ↑ excretion of Na^+

Pressure diuresis → ↑ excretion of H_2O

Rate of gain of Na^+ & H_2O by the body is zero

↓

Balance B/w intake & output

↓

Aldosterone escape :- despite excess aldo. excretion of Na^+ & H_2O returns to normal.

However Hypertension persists as long as aldo. remain excess.

Excess Aldosterone → ↑ secretion of K^+ into tubules

- Excess Aldosterone → ↓ plasma K^+ conc

↑ secretion of K^+ into renal tubules

↑ K^+ influx into cells.

Hypokalemia [↓ from 4.5 mEq/L to 2 mEq/L]

↓

Severe m/s weakness

- ↓↓ Aldosterone → ↑ plasma K^+ conc

If plasma K^+ conc 60 – 100% above normal

↓

cardiac toxicity ← Weakness of Hrt
Arrythmias

Even higher K^+ conc → Heart failure.

2) Excess Aldosterone → ↑ tubular secretion of H^+ → Alkalosis.

Na^+ is exchanged for H^+ in intercalated cells of collecting tubules

II Action on Sweat glands :- conserve body salt in hot cond.

↑ Reabsorp of Na^+ & Cl^- in ducts

↑ Secretion of K^+ in ducts.

III Action on Salivary glands

Same as sweat glands

IV GIT :-

↑ Absorption of Na^+ especially in colon.

↓ loss of Na^+ in stools.

Note :- Severe Aldosterone deficiency → ↓ Na^+ Reab, ↑ Na^+ excretion → ↓ Plasma conc of Na^+ → ↓ ECF volume → ↓ Bld vol → ↓ CO & BP → (+) ↑ ADH rly → Vasoconstriction, Reabsorption of H_2O → further ↓ plasma Na^+ → ↑ thirst

Mechanism of Aldosterone Action :-

- Aldosterone is lipid soluble and can easily diffuse into the cell thru the cell membrane.
- Receptor of Aldosterone → Cytoplasmic.
- Steps :-

Aldosterone diffuses into the cell

↓

Binds to highly specific cytoplasmic mineralo-corticoid receptor (MR)

↓

Aldosterone - receptor complex or product of this complex diffuses into the nucleus and induces one or more DNA sequences

↓

mRNA is syn → diffuses out of nucleus & gets translated

↓

New proteins are synthesised

(1) New enzymes → Na^+/K^+ ATPase in the Basolateral mem

(2) Membrane transport prtns → Epithelial sodium channels & K^+ channels in luminal mem

About 30 min req before new RNA appears in the cells

About 45 min is req before the rate of sodium transport begins to ↑ the effect reaches max after several hours.

Note :- cortisol can also bind to MR receptors but most of cortisol is converted to cortisone by 11β-HSD2, which does not bind to MR receptor.

=> Non genomic effects :-

- Steroid hrmns bind to mem receptors that are coupled to 2nd mssg systems like

  (1) cAMP in vascular smooth cells > epithelial cells of collecting tubules

  (2) IP_3/DAG system

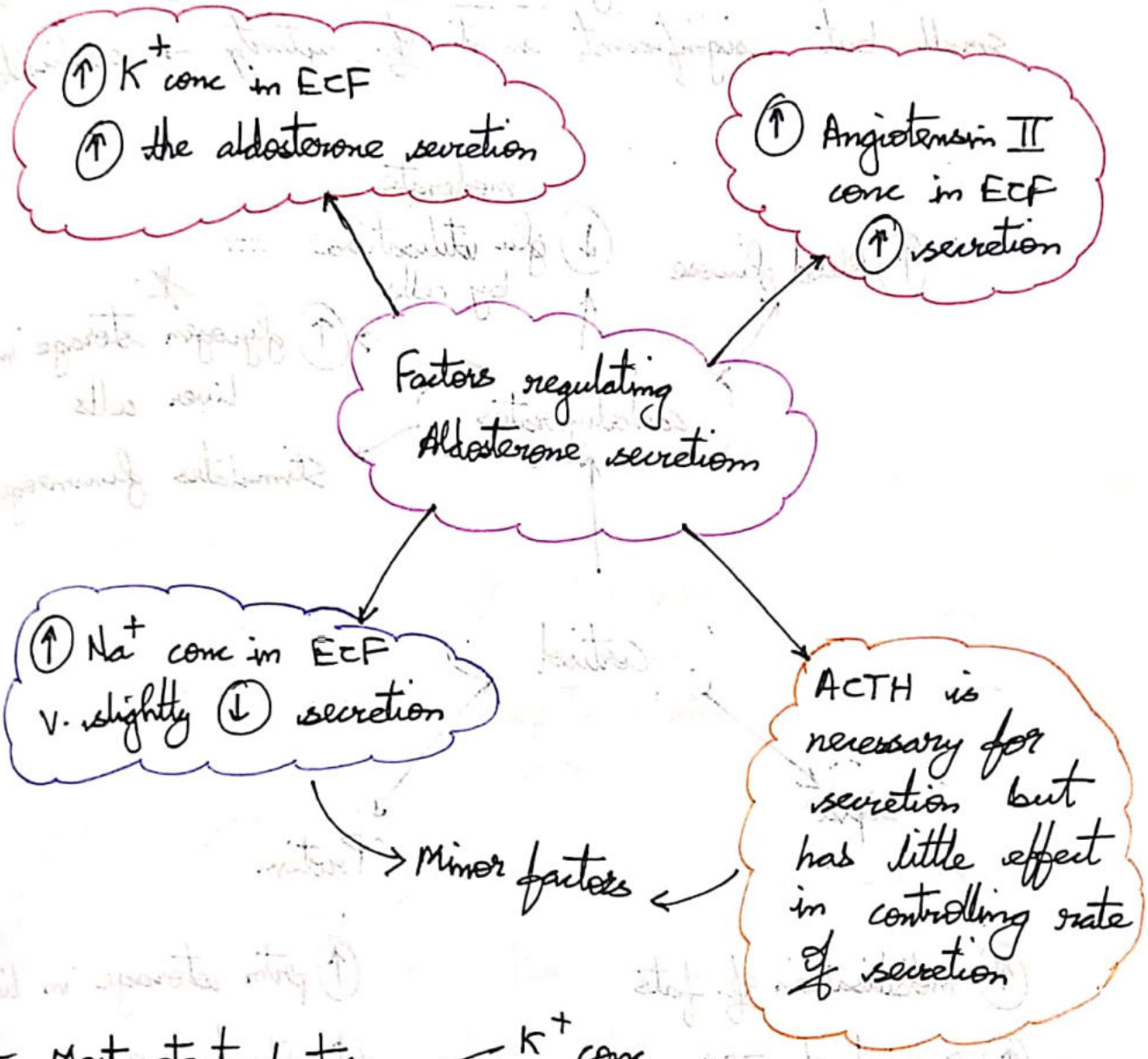
- Physio significance not well understood.

=> Transport of Aldosterone :-

- Aldosterone in circulation
  - Bound form – 60% [i.e bound to plasma prtns]
  - free form – 40%

Aldosterone has a relatively short half life of about 20 min.

regulation of Aldosterone secretion :-



- Most potent factors < K^+ conc
  Renin Angiotensin system.

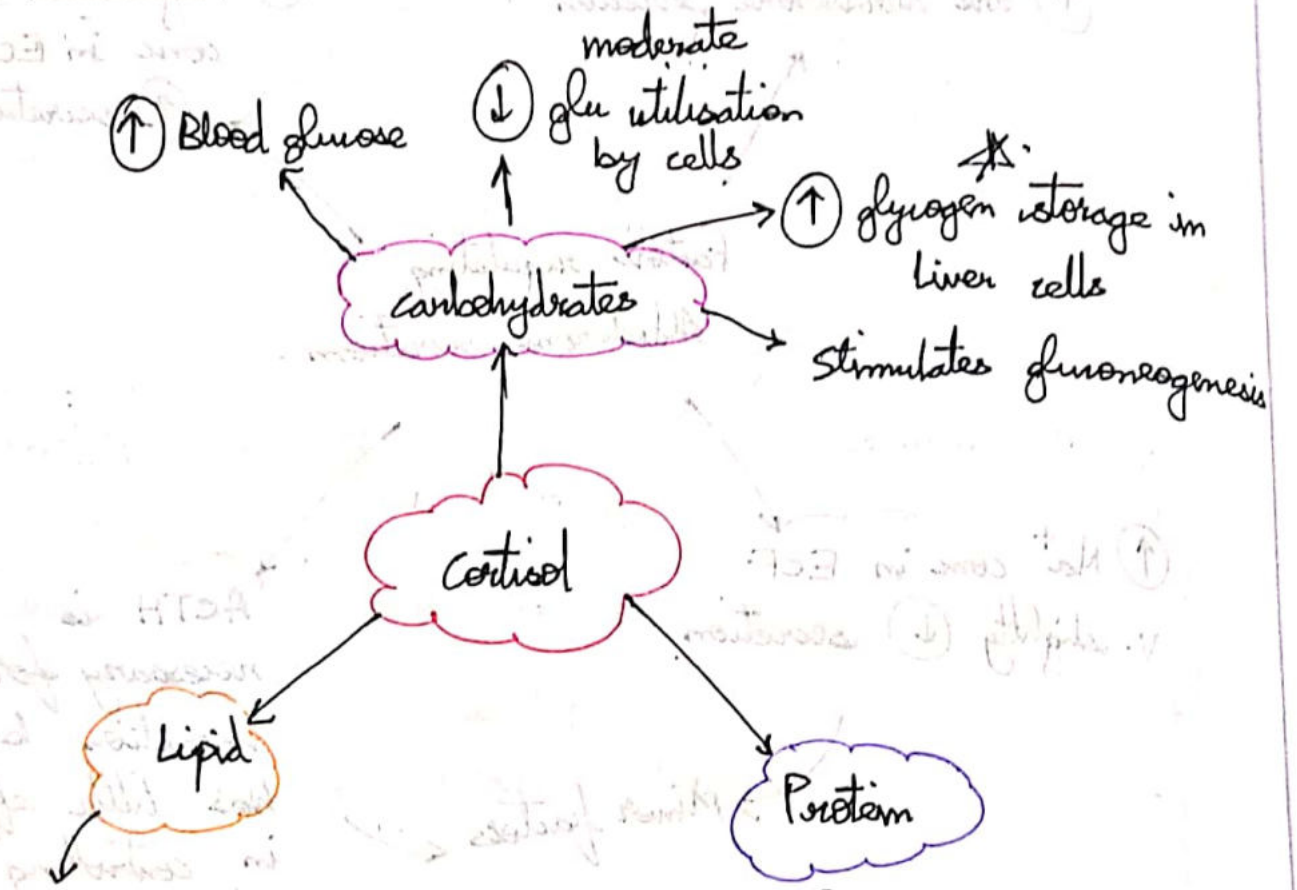
- Angiotensin - II secretion impt for aldosterone secretion during sodium depletion & ↓ ECF volume.

ACE inhibitor ⊖ formation of AT - II

↓

↓ rly of aldosterone.

- 95% of gluco. activity → cortisol [hydroxy corticosterone]
small but significant amt of activity → corticosterone



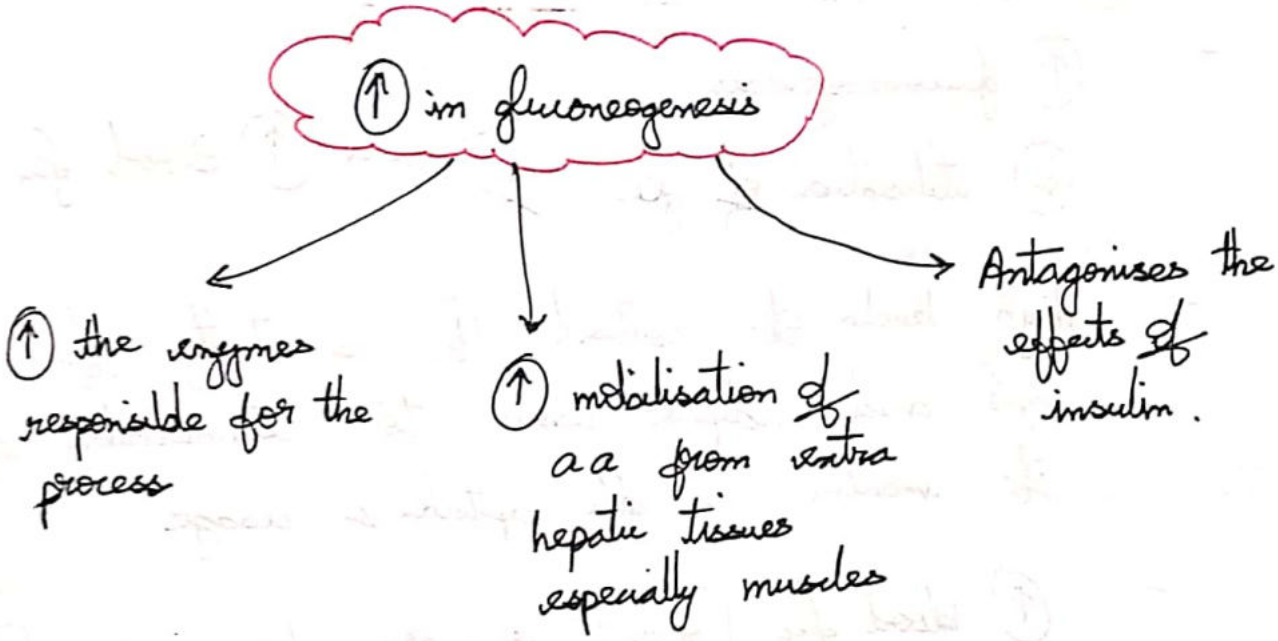
↑ mobilisation of fats
↑ β oxid of FFA

↑ prtn storage in liver
↑ Blood a.a
↑ prtn catabolism in all cells except liver cells
↓ prtn storage except in liver.

Effects on carbohydrate Metabolism :-

(1) Stimulates gluconeogenesis [amino acids → glu] :-

- Most impt metabolic effect
- Rate of gluconeogenesis ↑s by 6 to 10 times



- Net effect of cortisol → ↑ glu prod by liver
- ↑ glycogen storage in liver accompanied by ↑ gluconeogenesis potentiates the effects of the glycolytic hormns eg :- epinephrine, glucagon.

(2) ↓ glucose utilisation by cells :-

- Moderate ↓ especially by muscles > adipose tissue
- ↓s the translocation of GLUT-4 glu transporter from cytoplasm to cell membrane.
  ∴ causes insulin resistance

cortisol also ↑ the expression or phosphorylation of other signaling cascades that influence glu utilisation directly or indirectly.

(3) ↑ Blood glucose & Adrenal diabetes

- ↑ gluconeogenesis
  ↓ utilisation of glu → ↑ Blood glu.
- High levels of cortisol ↓ sensitivity of skl m/s and adipose tissue to stimulatory effects of insulin on glu uptake & usage
- ↑ blood glu [> 50% or more above normal] due to ↑ cortisol → Adrenal diabetes
  ↑ blood glu → ↑ insulin secretion but not sufficient enough in this condition.

— Effects on GIT:-
- Exerts trophic action effect on GI mucosa
- ↑ appetite [excess cortisol : wt gain]
-

① Reduces cellular prtn :-

- By ↑ prtn catabolism & ↓ prtn synthesis.
- P.stn stores of all cells ↓ except for liver cells.

Liver → opp effect → P.stn ↑.

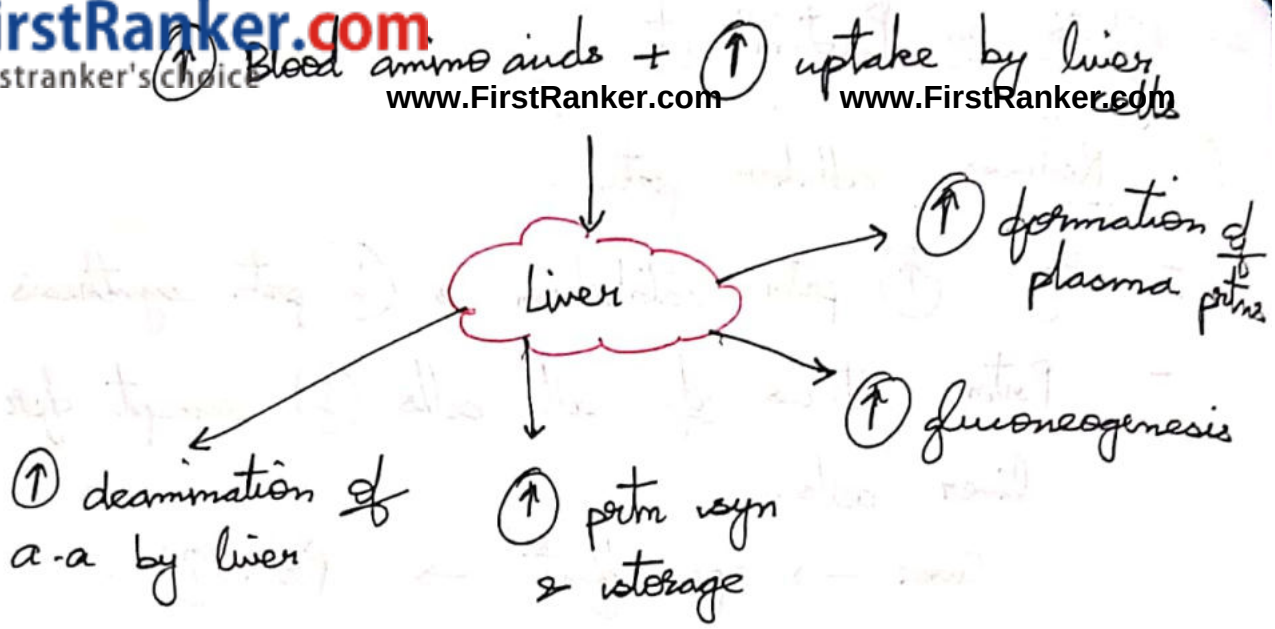
- excess of cortisol → M/s becomes weak
  → ↓ prtn in lymphoid tissue → Suppress immune system

② ↑ Liver prtn syn & storage :-

- By enhancing a.a. uptake by liver
- ↑ the enzymes for prtn syn in liver
- Plasma prtns syn by liver are also ↑.

③ ↑ Blood amino acid conc, ↓ a.a transport into extra hepatic cells. and ↑ transport into Liver cells :-

- cortisol ↓ a.a transport into skeletal m/s & then extra hepatic cells.
- cortisol mobilises a.a from non hepatic tissues especially skel. m/s.



— Effect on fat metabolism

1. ↑ mobilisation of FA
2. ↑ β oxidation of fatty acids
3. fatty acids are utilised as a source of energy
4. Excess cortisol causes obesity :-
   - Deposition of fat in chest and head regions leading to a buffalo like torso and moon shaped face.

— Effect on water & electrolyte balance :-

1. Mild Mineralocorticoid activity :-
   - ↑ Na^+ reabsorption
   - ↓ Na^+ excretion
   - ↑ K^+ secretion

   } Kidney [Renal tubules.]

as ADH antagonist :-
↑ GFR by ↑ CO & act on kidney
↓ secretion & inhibits action of ADH

- ↑ GFR ⟶ ↑ diuresis.
- Absence of cortisol :- Action of ADH potentiated
  water load is not disposed off ⟶ water intoxication
  ↓
  Brain cells absorb water ⟶ Convulsions, unconsciousness
  ↓
  death.

- Effect on Bone met :-
  1. Resorption of bone matrix :-
     ↓
     ↑ a.a. in blood
  2. Calcium resorption.
  3. ↓ Absorption of Ca^{2+} in GIT
  4. ↓ Reabsop of Ca^{2+} in Renal tubule

- Effects as a stress hormone :-
  Any physical / neurogenic stress
  ↓
  ↑ rly of ACTH
  ↓
  ↑ secretion of cortisol. → Activates SNS
  ↓ → Enhances the action of Epi & Norepi
  ↓
  ↑ a.a in blood
  ↓
  ↑ F.FA in blood
  Syn of life saving prtns ⟵ ⟶ Syn of glu.
  ↓
  use for energy

Different types of stress that ↑ cortisol secretion

Trauma

I4 DeSeRT

→ Intense heat or cold

Injection of Epi or Sympathetomimetic drug

Injection of necrotising sub beneath skin

Infection

→ Debilitating dz

→ Surgery

→ Restraining the animal

— Anti inflammatory effects :- High lvls of cortisol

→ ① Block inflammation process

② Reverse many effects of inflammation.

- GC has two basic Anti inflammatory effects

I blocks early stages of inflammation

II Rapid resolution of inflammation & ↑ rapidity of healing.

- It exerts these effects by :-

① Stabilising lysosomal membranes

② ↓ the mobility of WBC's & ↓ phagocytosis

③ ↓ permeability of capillaries

↳ prevents leakage of plasma into damaged tissue

especially T lymphocytes

(5) Reduces rly of interleukin 1 from white blood cells.

- Other effects :-

(1) Blocks inflammatory response to allergic reactions

(2) Effects on Blood cells.

I (↑) RBC's :-

(↑) prodn of erythropoietin

excess - polycythemia

II WBC's :- (↓) BEL

(↓) Basophils, eosinophils, lymphocytes.

→ acts as immunosuppressant.

excess :- atrophy of lymphoid tissues

(3) Immunosuppressant :-

Used to prvnt rejection of transplanted heart, kidney etc.

(4) Effects on CNS :-

(↑) neural excitability.

(5) Effect on connective tissue :-

(↓) proliferation of fibroblasts

↓

(↓) connective tissue

Mechanism of Action :- Similar to Aldosterone

- Binds to intra cyto receptor
- Hormone receptor complex induces spc. genes called glucocorticoid response elements

↓

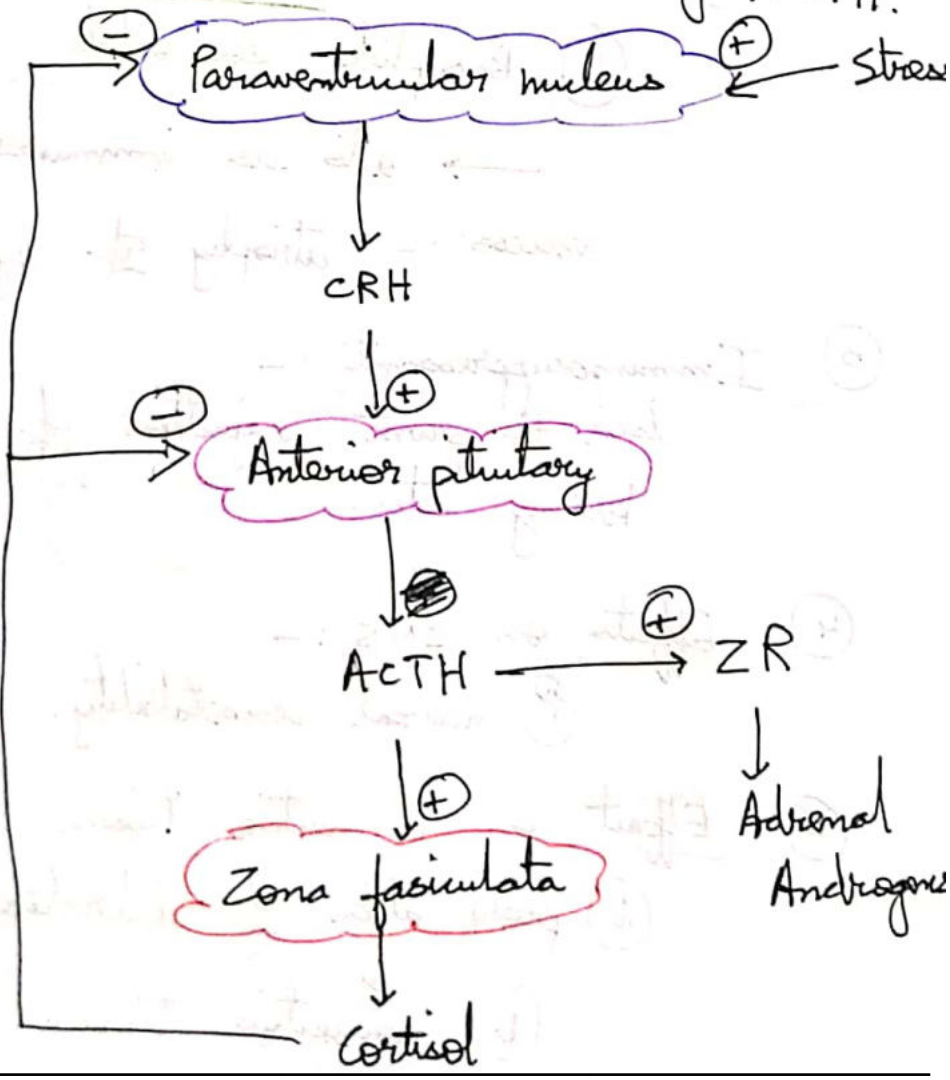
Formation of New prtns.

↓

Metabolic effects

- Req 45 - 60 min for prtn syn → several hours for full effects.

— Regulation of cortisol :- Controlled by ACTH.



ACTH

↓

Binds to receptor on cortical cells of ZF

↓

Activates Adenylyl cyclase

↓

↑ cAMP

↓

Activates enzymes for cortisol syn.

- Long term stimulation by ACTH – hypertrophy of ZF & ZR.
- Stress stimuli most potent for cortisol rly
  ↳ can even break thru –ve feedback circuit and cause prolonged cortisol secretion in times of chronic stress.
- Circadian rhythm of GC secretion :–
  The secretory rates of CRF, ACTH and cortisol are high in the early morning and low in the late evening.
  ↳ Bcoz of 24 hr cyclic alteration in the signals from the hypothalamus that cause cortisol secretion.

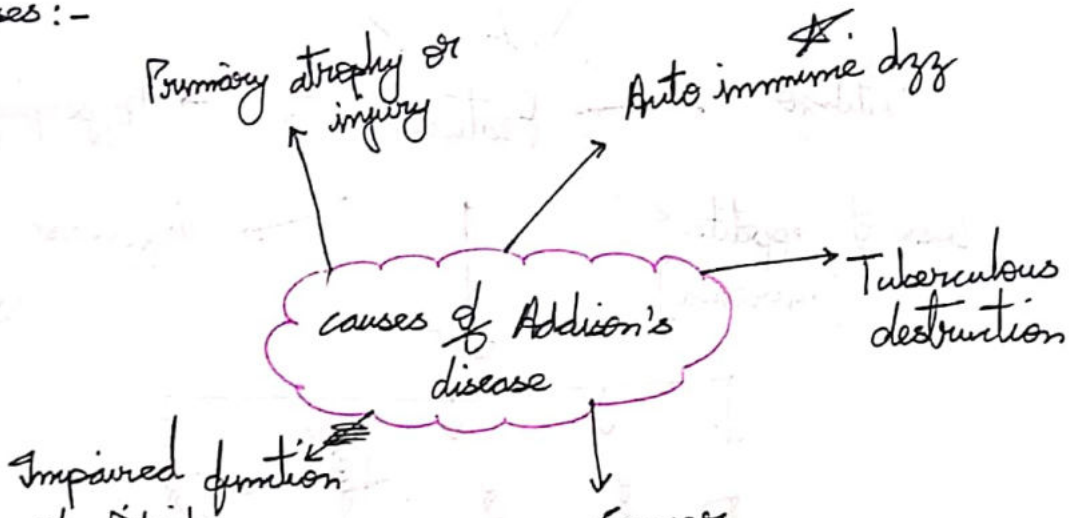
The precursor / prepro hormone of ACTH pro-opio-melanocortin (POMC) also acts as a precursor for several other peptide hormone like MSH, β-endorphin & β-lipotropin.

- It is a large prtn processed by prohormone convertase enzymes PC1 and PC2.
- Tissue spfc expression of these 2 enzymes results in diff peptides prod in various tissues
- When secretory rates of ACTH is V.V. high
  ↳ other POMC derived hormone also (↑).

⇒ Adrenal Androgens :-

- Several male sex hrmns (Androgens) especially DHEA and female sex hrmns estrogen & progesterone (some minute quantity) are secreted
  - Exert weak effects
    Mild effects in female – dev of pubic & axillary hair
  - Plays role in early dev of ♂ sex organs

- Addison's disease :- Also called Primary Adrenal insuff.
- Hypoadrenalism :- inability of the adrenal cortices to prod sufficient adrenocortical hormones.
- Causes :-



↓ low ACTH

↓

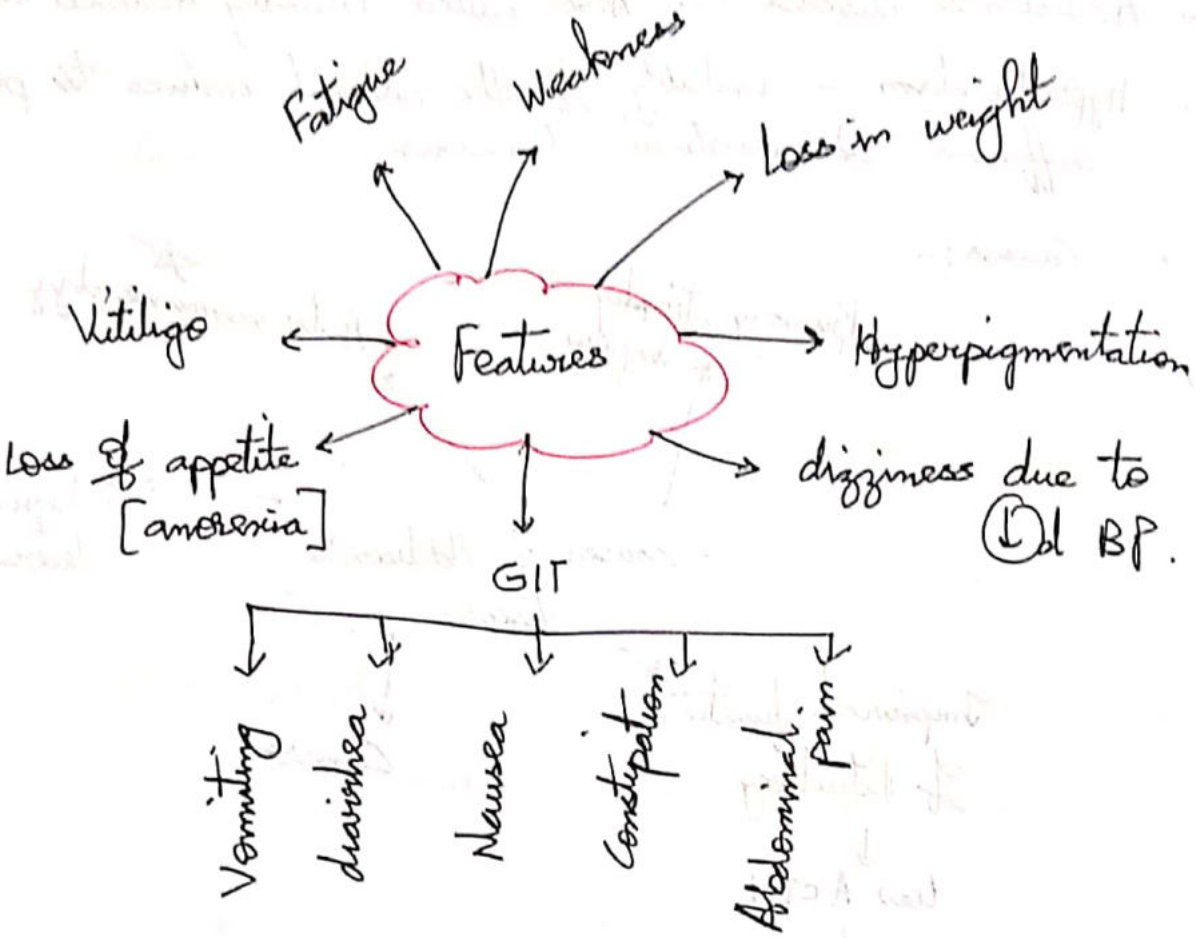
① Adrenocortical hormones – secondary adrenal insufficiency.

secondary insufficiency is much more common than Addison's dzz.

Lack of ACTH stimulation → Atrophy of Adrenal cortex.

- ACTH
  - low → Secondary insuff.
  - High → Primary insuff.

Features of Addison's dzz :-



- Mineralocorticoid deficiency :-

Hyperkalemia + ↑ excretion of Na^+, Cl^- & H_2O + Acidosis

↓ ECF vol

↓ Plasma vol → ↓ CO

↑ RBC conc.

↓ BP

↓

circulatory shock.

the total absence of Aldosterone death can occur within 4 days to 2 weeks.

- Glucocorticoid deficiency :-
  - Inability to maintain normal bld glu conc B/W meals
  - Inability to resist stress.
  - Lack of mobilisation of proteins and fats
  - Lack of GC makes the person with Addison's highly susceptible to effects of stress. Even a mild respiratory infection can cause death.

- Melanin pigmentation of mucous mem & skin :-
  - ↑ Melanin deposited in blotches especially thin skin areas such as nipples & lips.
  - ↓↓ cortisol → ↑ AP → ACTH ↑↑
    - ↳ Has 1/30 as much melanocyte stimulating effect as MSH

Also secretion of MSH which is one of the POMC derived hormones is also ↑ when secretory rates of ACTH is ↑.

- Treatment :-

Patient with total destruction of Adrenal glands → Untreated dies due to shock

→ can live if small quantities of Mineralocort > glucocort. are given daily.

Note :- Addisonian crisis :-

- In a person with addison's dzz GC output does not (↑) during stress.
- Even tho the person may require excessive amnt of GC during stresses like trauma, surgery etc.
- This critical need for extra GC and the associated severe debility in times of stress is called an Addisonian crisis.

(2) Cushing's syndrome :-

- Hypersecretion of Cortisol [mainly] and Adrenal androgens.

- causes
  - → Adenoma of AP ⟹ (↑↑) ACTH
  - → Abnormal func of Hypothalamus ⟹ (↑) CRH
  - → ectopic secretion of ACTH by a tumour
  - → Adenoma of Adrenal cortex.

Tumour of pituitary → excess ACTH secretion

↓

Plasma conc of ACTH High

" " " cortisol is also high

Overprod of cortisol by adrenal cortex → 20-25% of cases.

↳ ACTH is low in plasma.
due to feedback inhibition.

- can also occur when GC's are administered for a long time for therapeutic uses
eg:- in patients with rheumatic arthritis.

- Features

I ↑ Blood glucose conc.
sometimes to as high as 200 mg/dL

II Protein metabolic effects:-

1. ↓ Proteins in all body tissues except for liver.
Liver syn plasma prtns — unaffected
2. ↓ prtn in m/s → weakness
3. ↓ prtn in lymphoid tissue → immune system is suppressed
4. ↓ prtn in bone → osteoporosis
5. ↓ in connective tissue prtn [collagen] in subcutaneous tissue → easy tearing of the subcut. tissue → purplish striae

III Fat metabolism — Buffalo torso
Moon face.
- extra deposition of fat in upper abdominal & thoracic regions
- edematous appearance of face.

III Androgens:-
- Acne
- Hirsutism [↑ facial hair]

IV Hypertension.

- Treatment:-

(1) If caused by adenoma of adrenal glands
→ Removal of tumour

(2) ↓ing the secretion of ACTH

(3) ACTH secreting tumours — Surgical removal
Irradiation therapy

(4) drugs that ⊖ steroidogenesis
- Metyrapone
- Ketoconazole
- Amino glutethimide.

(5) drugs ⊖ ACTH secretion
- Serotonin antagonists
- GABA transaminase inhibitors

(6) Partial or complete bilateral adrenalectomy.

(3) Primary Aldosteronism [Conn's syndrome].

- Hypersecretion of Aldosterone
- Causes — Small tumours of ZG
  Hyperplastic adrenal cortices which secrete Aldosterone rather than cortisol
- Features :-
  1. Hypokalemia
  2. Mild Alkalosis
  3. Slight ↑ in ECF vol
  4. Plasma Na^+ conc inc by 4 to 6 mEq/L
  5. Occasional periods of m/s paralysis caused by Hypokalemia.
- Diagnosis :-
  1. Renin conc in plasma due to -ve feedback mech.
- Treatment :-
  - Surgical removal of tumour
  - Antagonists of mineralocort receptor
    eg :- spironolactone
    eplerenone.

4) Adrenogenital syndrome :- (Ty) androgens

♀ [female]

- Beard
- deep voice
- masculine distribution of hair on body & pubis
- growth of clitoris to resemble a penis
- ↑↑ Muscle mass due to more deposition of prtn
- Baldness if trait is prsnt

♂ [prepubertal male]

- Rapid dev of ♂ sex organs
- Rapid dev of secondary sexual characteristics

It is difficult to diagnose in adult male.

In this syndrome → excretion of 17-keto steroids [which is derived from androgens] is 10-15 times the normal.

Helps to diagnose.