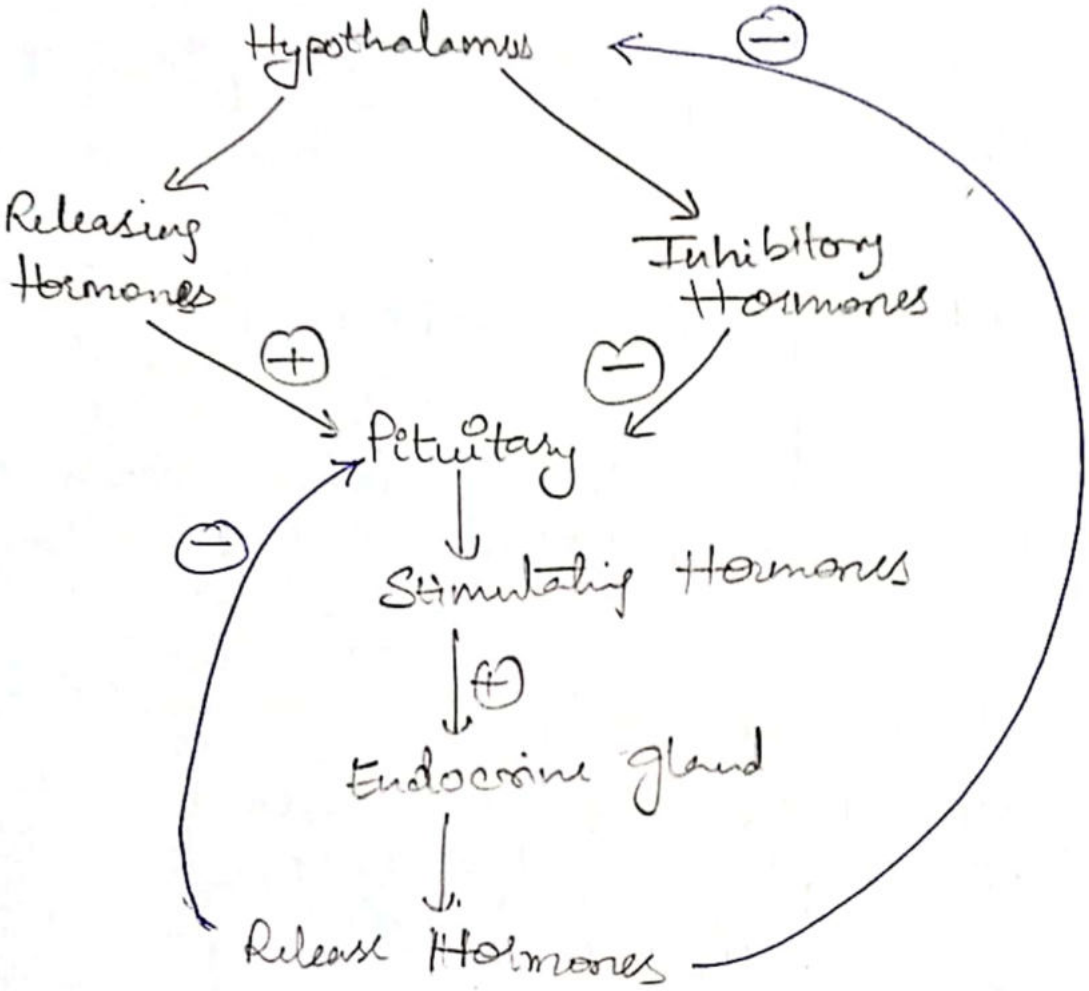
Endocrine glands (Marrow)



Pituitary Gland ⟹ Master Gland.

- Anterior
  - Acidophillic cells ⟹ GH, PrL. } Twin Hormones
  - Basophillic Cells ⟹ ACTH, TSH, FSH, LH.
- Posterior Pituitary → Produce → No Hormon
  - Stores
    - → ADH
    - → Oxytocin

POMC
(Pro-Opio-Melano-Cortin)

Endorphin — MSH. — ACTH.

Post. Pit → ADH → From Supra Optic N. of Hypothala.

→ Oxytocin → Para-Ventricular N. of Hypothalamus
(Partitution)

Growth Hormone → depends on Age → Max → Adolescence
→ Lower → Oldage

→ Max — during early stage Sleep
→ dec. during later stages of Sleep

Hypothalamus

(Syn. GHRH drug = Sermorelin for Pit. dwarfism) GHRH (+) → Ant. Pituitary ← (−) GHIH (somatostatin) [Analogue drug = Octreotide for Acromegaly]

Ant. Pituitary → GH (Hyperglycemic/Diabetogenic) → ↑ Blood Glu

Stimulus for inc. GH.

- Hypoglycemia
  - Fasting
  - Starvation
  - Exercise
- Ghrelin
- Stress
- NREM sleep.

Stimulus which dec GH

- Obesity
- REM sleep
- Somatostatin

GH actions

- Direct Action → GH itself act → Anti-insulin like action
  - Causes Hyperglycemia
  - Lipolysis
- Indirect Action → mediated by "Somatomedins" (Insulin like G.F) IGFs → Insulin like actions
  - Anti lipolysis

GH (+) → Liver → produces.

Direct & Indirect actions on Bone Growth

Pre-chondrocyte —(GH)→ Chondrocyte

For Fusthe Bone growth ⟹ Somatomedins (IGFs) are needed.

GH excess → Children → Gigantism
→ Adults → Acromegaly

GH dec → Children → Dwarfism
→ Adults → Simmonds Syndrom

If patient is dwarf but GH levels Normal
GH Receptor mutation
GH level normal
Somatomedins dec
} Laron's Dwarfism

Prolactin ⟹ Production of Milk

Stimulus which inc PROLACTIN

- Pregnancy
- Lactation
- Sleep
- Strenous Exercise
- Stress
- Sexual Intercourse

Stimulus which dec Prolactin sec

- PRIF (Dopamine)
- L-DOPA
- Bromocriptine

ACTH levels

- Highest → early morning (5 am)
- Lowest → evening (3 pm)

Thyroid Gland.
- Para follicular / C-cell → Calcitonin
- Follicular cells → T_3 T_4

Needs
- Diet Iodine (Reduced form Iodide (I^-))
- Tyrosine (Thyroglobulin = 115 tyros)

Synthesis of T_3 T_4

Na-I^- Symporter (NIS) ⟹ 2° Active transport

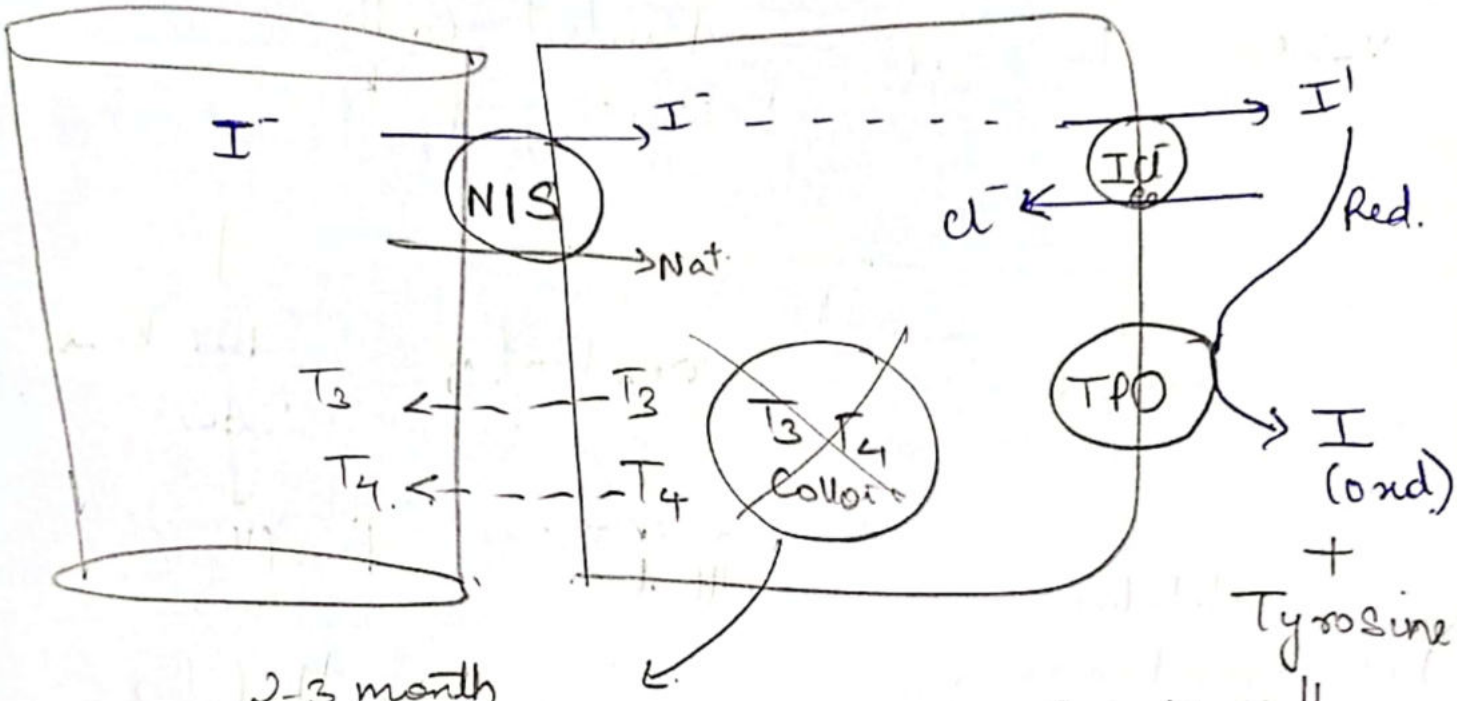
⟹ Present on B/L surface of
1. Thyroid Gland.
2. Parotid Gland
3. Placenta.
4. Mammary gland.

⟹ Excess uptake of I^- by NIS inhibit T_3 T_4 production
This is called "WOLF CHAIKOFF EFFECT".

I^--Cl^- Exchanger/Pendrin Channel Protein ⟹ Apical/luminal Surface
- Thyroid gland → Its mutation → Goiter
- Inner ear → Sensorineural deafness

"PENDRED SYNDROME"

vessel. Follicular cell lumen



MIT + MIT ⟹ DIT

MIT + DIT ⟹ T_3 (Active)

DIT + MIT ⟹ Reverse T_3 (Inactive)

DIT + DIT ⟹ T_4

Thyroid PerOxidase (TPO)

⇒ Apical / Luminal Surface

⇒ Membrane bounded Protein / Enzyme

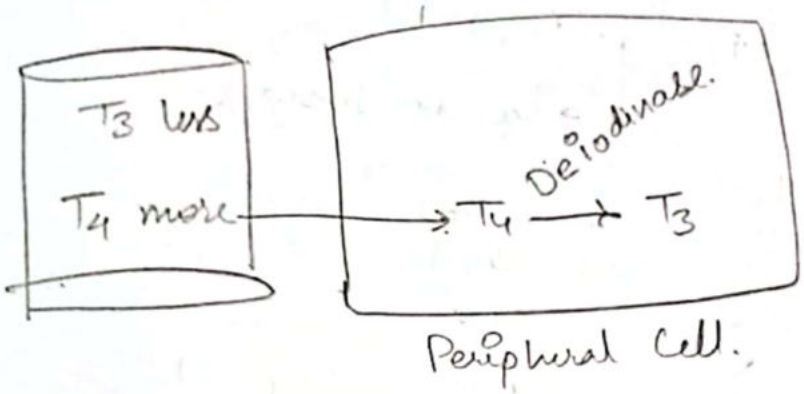
T_3 T_4 in blood vessels

1% → Free → Active

99% → Binded with Binding Protein

- 70% binding → Globulin (TBG - Thyroid hormone Binding Globulin)
- 20% binding → Albumin
- 10% binding → Pre-Albumin (or) Transthyretin
  - → Common B.P for
    - → T.H
    - → Vit-A

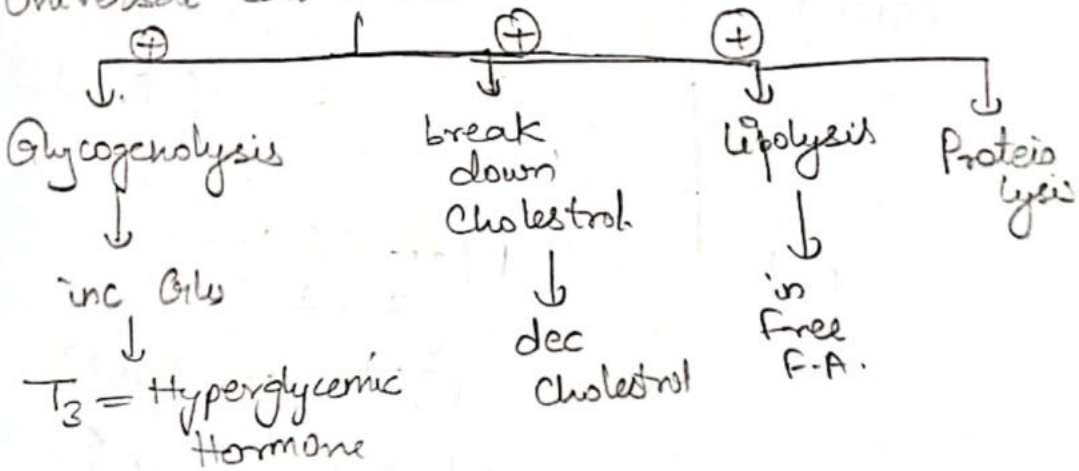
T_3 Vs T_4	
⇒ Active	Less Active
⇒ Rapid	Slow Onset
⇒ less $t_{1/2}$	Long $t_{1/2}$ (6-7 days)
⇒ less in blood	more in blood
⇒ Physiological actions.	⇒ T_4 - drug (✓) Pharmacological actions



Functions of T_3

1. Inc Metabolism ⟶ BMR
   ↓
   Inc O_2 consumption

2. Universal Catabolic hormone



3. T_3 ⟶ uncoupler of ETC
   ↓
   No ATP
   Heat (↑) Thermogic Action

Hypothyroidism ⟹ Cold Intolerant
Hyperthyroidism ⟹ Heat Intolerant

4. Development Role
   - Brain (Myelination) ⟹ ① Congenital Hypothy Mental Retard.
   - Bone ⟹ ② Stunted Growth

T_3 in Heart

T_3 (+) → ↑ NE → β-Rec → ↑ H.R.
→ ↑ Myocardial contract.

Thyroid Storm Treatment ⇒ β-blocker ⇒ P-propranolol

Pancreas ⇒ tail Region ⇒ Islets of langerhans

① α-cells ⇒ Glucagon → ↑ Blood Glu → hyperglycemia

② β-cells (55%) → Insulin → dec. Blood Glu
→ Amylin → Potentiates the action of insulin
→ C-peptide : Insulin
1 : 1.

∴ C-peptide assay is done

C-peptide = Endogenous Insulin Marker

③ δ-cells ⇒ Somatostatin
↳ Universal inhibitor

④ F-cells ⇒ Pancreatic Peptide (PP)

Discovered by Banting & Mcleod

- 1st protein to be completely sequenced ⟹ Sanger
- 1st prepared via RDNA tech ⟹ Insulin

Insulin + Zinc ⟹ Normally it's combined with Zn as Zn provide stability to Insulin structure.

Transcription factor for Insulin Synthesis ⟹ Hepatocyte Nuclear Factor (HNF)

↓

Mutation

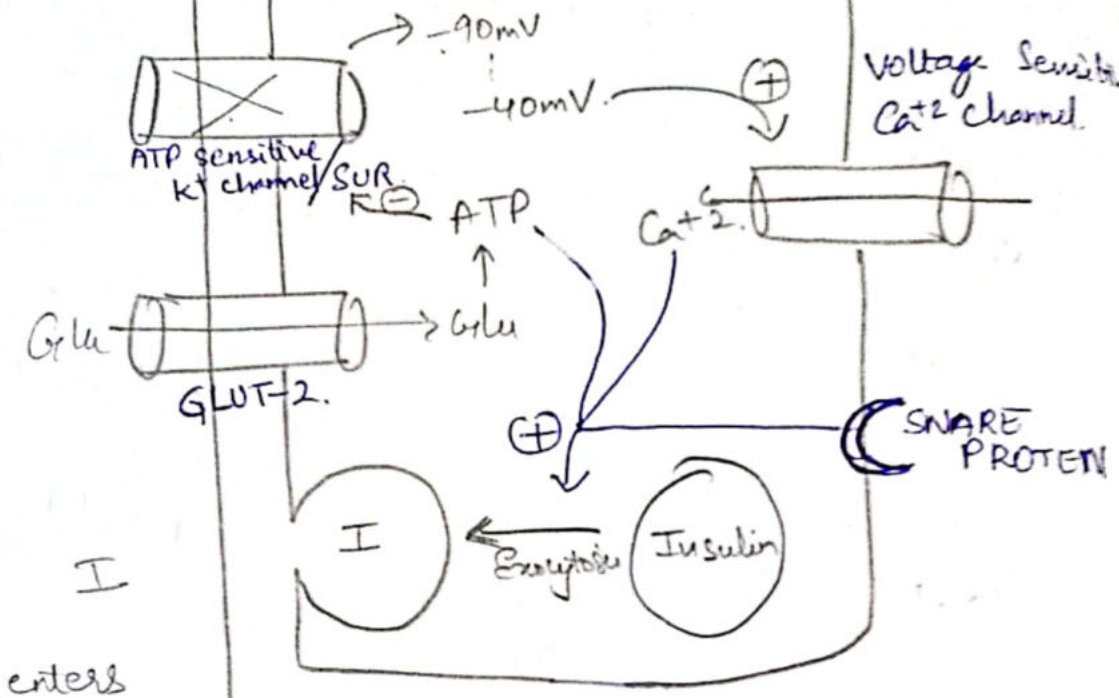
↙

MODY

Maturity Onset Diabetes - Young.

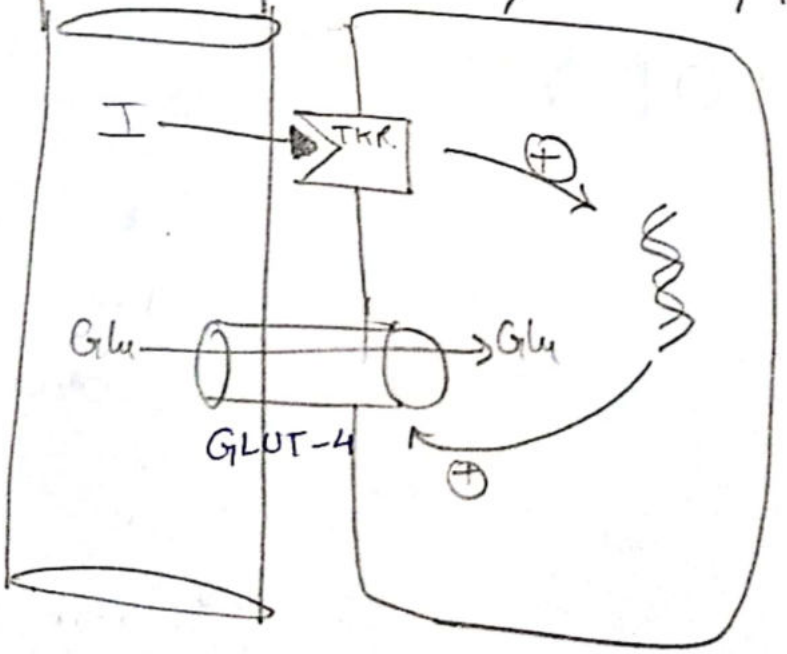
⟹ Blood Glucose < 30 mg/dl ⟹ Coma

β-cell of Pancreas



I enters Heart, Sk. Muscle, Adipose tissue

Heart Cell / Sk. Muscle / Adipocyte



Secretion of Insulin by β-cell.

RMP = −90mV

Inc Glu

⇓

Influx of Glu in β-cells

⇓

by Glu sensors (GLUT-2)

⇓

Inc Glycolysis TCA

⇓

Inc ATP

⇓

ATP sensitive K^+ channel / SUR closes

⇓

K^+ efflux dec

⇓

−90mV to −40mV

⇓

opens Voltage Sensitive Ca^{+2} Channels

⇓

Now ATP (✓) Ca^{+2} (✓) SNARE protein (✓) ⇒ Exocytosis of Insulin ⇒ Enters blood

Insulin also dec K conc.

∴ Hyperkalemia

Insulin – Dextrose given

↓

as Insulin also dec Blood Glu.

Glu uptake Inc in Heart, Muscle, ~~Adipose~~ tissue

⇑

GLUT-4 Inc.

⇑

DNA to produce GLUT-4

⇑ ⊕

Tyrosine kinase Receptor ($2\alpha, 2\beta$)

⇑

Reaches Heart, Muscle, Adipose tissue.

⇑

K+ Sensitive K+ channel / Sulphonyl Urea Receptor (SUR)

inc ATP ⟹ closes SUR ⟹ inc Insulin Release

Insulin Secretogogues ⟹ Sulphonyl ureas ⟹ closes SUR ⟹ inc Insulin Release

⇓

∴ Used in DM

⟹ ATP K^+ channels Openers ⟹ dec. Insulin Release

⇓

Eg:- Diazoxide

⟹ Insulin → $t_{1/2}$ → 4-6 min → long term response

↓

UNIVERSAL ANABOLIC.

Insulin

(+) → Glycogenesis, Lipogenesis, Glycolysis, Link Reaction

(−) → Glycogenolysis, Gluconeogenesis, Lipolysis

- Inc Glucose
- Inc Glucagon
- GI hormones which Inc Insulin ⟹ INCRETIN
  - Gastrin
  - Secretin
  - CCK.

⇓

Ex- GLP-1

degraded → Glucagon Like Peptide -1.

DPP-IV

Analoge (Exenatide) ← DM treatment

DPP-IV ⊖

DPP-IV Inhibitor — Gliptins → Sita-Gliptins

dec Insulin Secretion →
- Somatostatin
- Diazoxide
- Hypoglycemia.

Para-Sympathetic N.S ⟹ Inc. Insulin Sec.
(Ach, Vagal Stimuli)

Sympathetic →
- (mostly) α_2 action ⟹ dec Insulin Sec ⊕
- β_2 action ⟹ Inc Insulin Sec

Inc. Blood Glu ⇓ Hyperglycemic ⇓ Counter regulatory hormone

Blood Glu ⇓ Hypo-glycemic ⇓ INSULIN

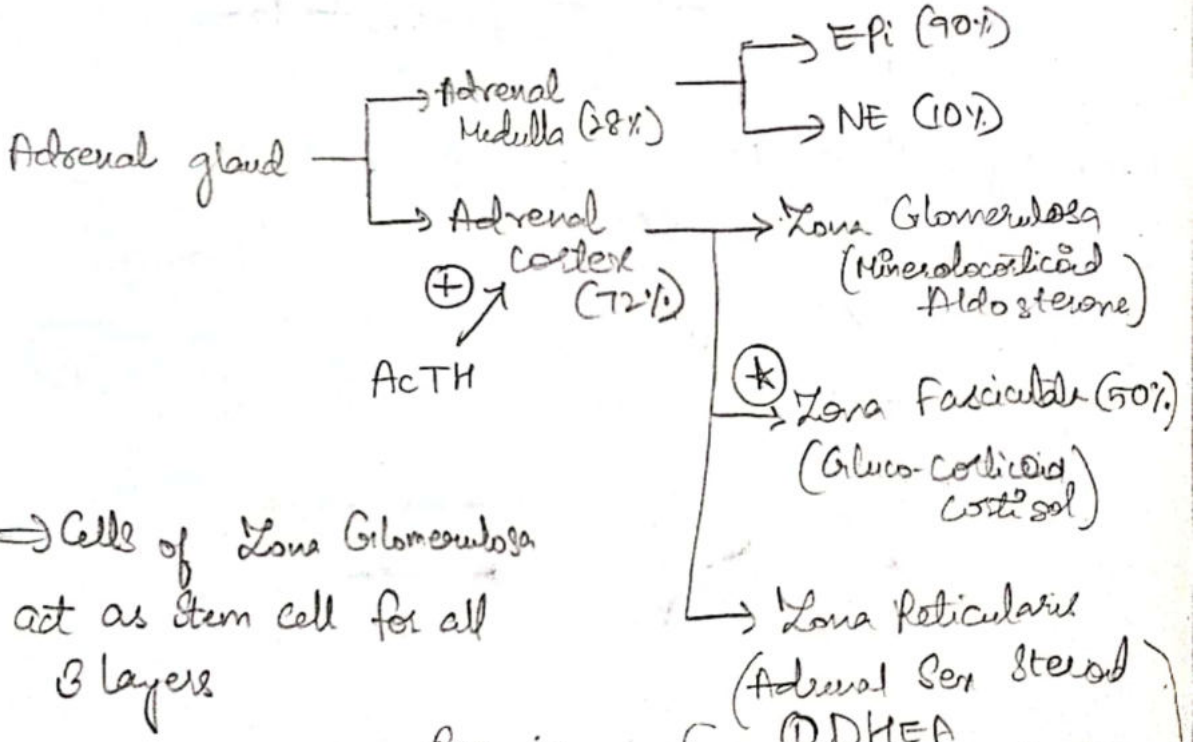
① GH ⟹ Response for Early morning hyperglycemia in DM ⇓ Dawn Phenomena

② T_3

③ Glucagon

④ Cortisol

⑤ Epinephrine



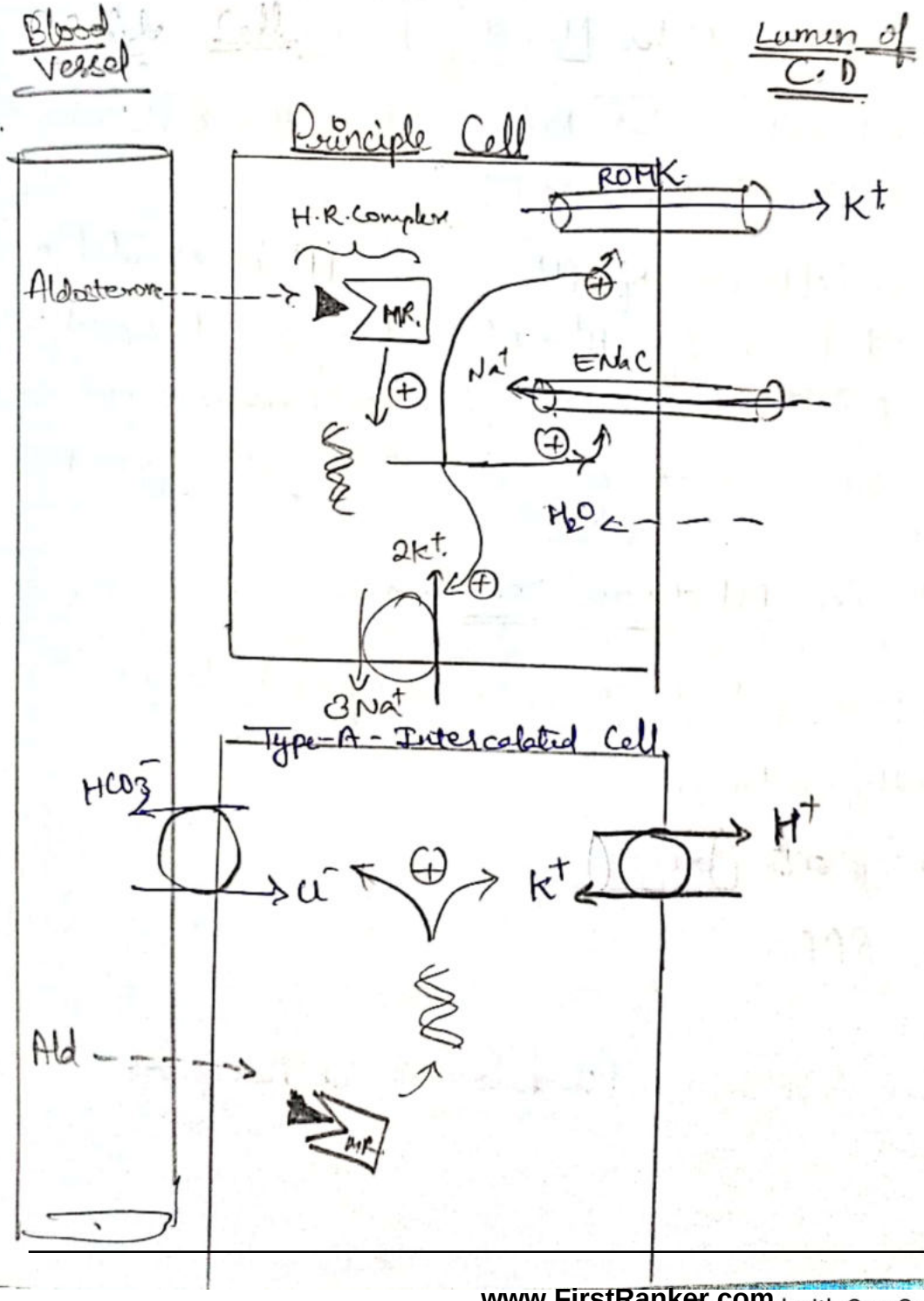
⟹ Cells of Zona Glomerulosa act as Stem cell for all 3 layers

Req. in both Males & Females
① For Libido
② Growth of Axillary & pubic hair

Na^+ & H_2O reabsorbed
K^+ & H^+ excreted

Acts on Collecting Duct Cells → Principle Cells (P-cell)
→ Intercalated cells (I-cell)

→ Life saving hormone ⟹ Aldosterone
↓
$t_{1/2}$ – 20 min



Channel (ENaC)

→ ENaC Blocker → Diuretics → Amiloride

→ ENaC overactive → $[Na^+]$ ↓ in Hypertension (↓) } Liddle's Syndrome.

⇒ ROMK (Renal Outer Medullary Potassium Channel)

⇒ Principle cell absorbs Na^+ ∴ intern H_2O & it also secrete K^+ by ROMK.

→ Under influence of Aldosterone H^+ is excreted in Type-A Intercalated cell in CD lumen by $H^+ - K^+$ exchanger at apical Surface At B.L. Surface $HCO_3^- - Cl^-$ exchanger move HCO_3^- to Blood & Cl^- in Intercalated cell Type-A.

What Inc. Aldosterone Secretion :-

→ Most potent Stimulus → Hyper Kalemia
→ Hyponatremia
→ Hypotension
→ RAAS

⇒ Liver don't have Mineralocorticoid Receptors

→ 90-95% Binded → CBG / Transcortin

$t_{1/2}$ → 90 Min

Cortisol Binding Globulin.

Cortical Secretion → Circadium Rythm → Max → Early morning (8am)
→ least → Evening / Sleep (3pm)

Actions of Cortisol

1. Protein Metabolism → dual Role
   - Muscle → Proteolysis → Catabolic → Alanine formed
   - Liver → Production of Plasma proteins → Anabolism
2. Carbohydrate metabolism → ↑ Glu by Gluconeogenesis
   Ala → Pyr → Glu
   ∴ ↑ Cortisol → ↑ Glu → Adrenal DM.
3. Lipid Metabolism → ↑ Lipolysis → ↑ Free F.A.
4. ↓ phospholipase A
   ↓ Prostaglandins
   ↓ Release of Histamine
   ↓ IL-II
   ∴ Cortisol is Anti Inflammatory
   ⇓
   LARGE DOSAGE REQ

At Bone → Inc Osteoclast Activity → Causes Bone Resorption

7. At Blood Cells → dec Eosinophils
dec Lymphocytes
Inc RBC
Inc Neutrophils

8. At GIT → Inc. Gastric acid secretion
∴ Inc Cortisol → Peptic ulcers

9. At Reproduction → dec GnRH → -ve regulator

Permissive Action of Cortisol → Presence Enhance → Catecholamine
↓
Lipolysis
Broncho dilator

Ca^{+2} → 50% → Bounded/Inactive → B.P ; Albumin
Ca^{+2} → 50% → Free/Active/Ionic
- → Muscle contraction
- → Exocytosis
- → Blood coagulation

⇒ H^+ & Ca^{+2} has common Binding Protein i.e. Albumin

∴ if pH dec ⇒ inc $[H^+]$ ⇒ dec binding of Ca^{+2} to Albumin
↓
Bind to Albumin

∴ Acidosis ⇒ inc Free Ca^{+2}
Alkalosis ⇒ dec Free Ca^{+2}
↓
Causing Hypocalcemic Tetany

3 Hormone 3 organ Model

① PTH } inc Blood Ca^{+2}
② Vit-D }
③ Calcitonin → dec Blood Ca^{+2}

① Bone (Ca^{+2} Bank)
② GIT
③ Kidney

Teriparatide

→ Source : Chief Cell of Para-thyroid Gland

→ PTH = 84 Aa ∴ Protein Hormone.

→ PTH binds to PTHR of Osteoblast of Bone

Osteoblast produces "Rank Ligand"

⊕

This Stimulates Osteoclast ∴ inc differentiation inc Activity

∴ Bone Resorption occurs by acid proteases

∴ For Osteoporosis patient

Rank ligand blocker = Denosumab is used which dec. Bone resorption

PTH at Bone.

PTH

↓

PTHR of Osteoblast

↓⊕

Rank ligand

↓⊕

Osteoclast

↓

Acid proteases

destroys Hydroxy apatite $Ca^{2+}PO_4^{-}$

⇓

∴ $[Ca^{+2}]$ inc

$[PO_4^{-}]$ inc

occurs at Kidney
inc $[Ca^{+2}]$
dec $[PO_4^-]$

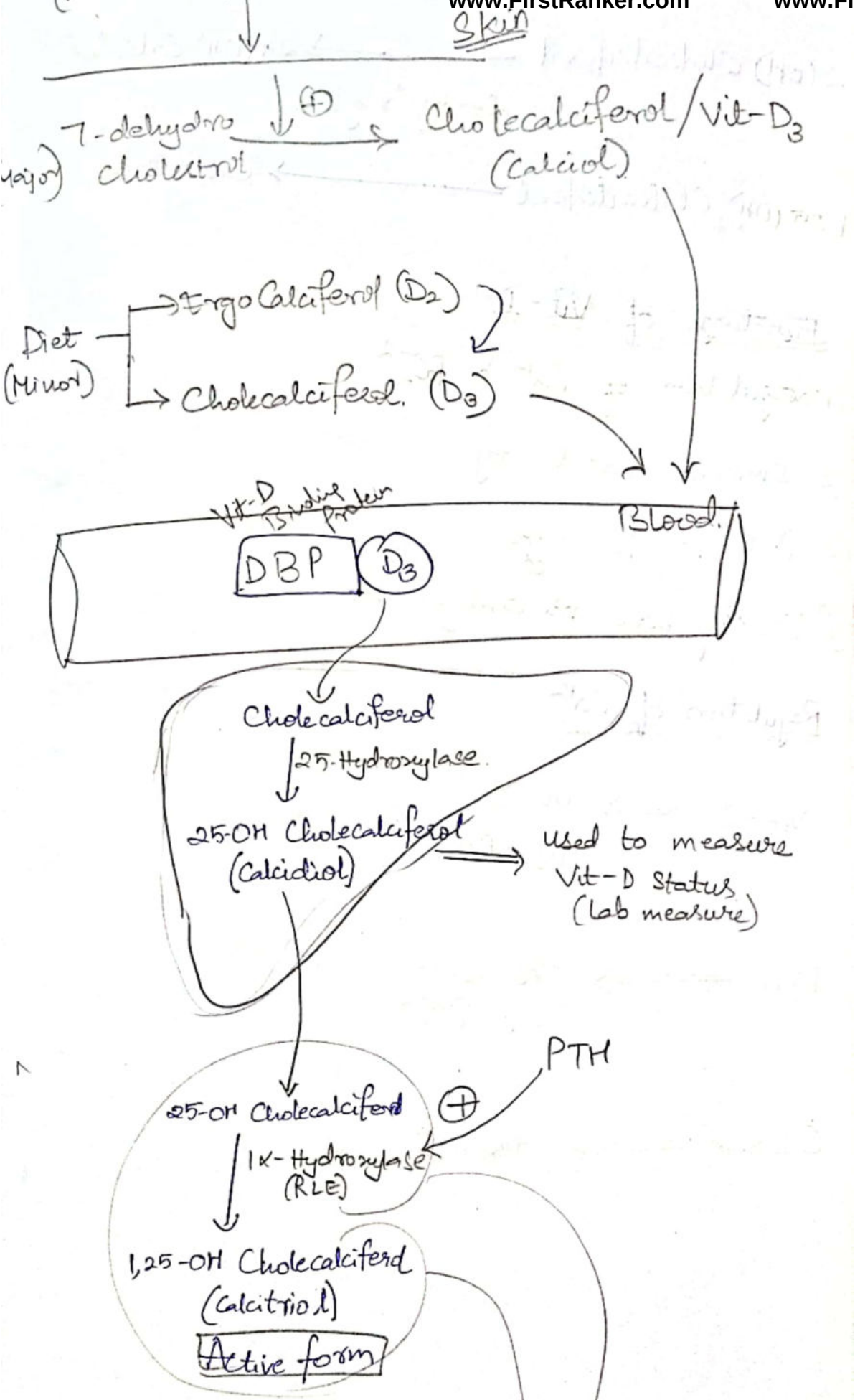
⇒ PTH ⇒ PO_4^- terminating Hormone.

⇒ Most Imp Phosphatonin of Humans = PTH

PTH at Kidney :- ① inc Ca^{+2} absorption ⟹ at DCT.

PTH
⊖
$Na^+ - PO_4^-$ co-transport at PCT
⇓
dec. Na^+ & PO_4^- Reabsorption at PCT
⇓
∴ PO_4^- is excreted

PTH at GIT :- PTH
⊕
inc Vit-D
↓
inc Ca^{+2} absorption



① Ca^{+2} absorption in duodenum is by Vit-D

Vit-D ⟹ Calbindin ⟹ inc $[Ca^{+2}]$ absorbtion

② At Bone :- exactly similar to PTH.

Vit-D
↓
Vit D Receptor on Osteoblast
↓
Rank Ligand
↓ (+)
Osteoclast
↓
Acid proteases
↓
Bone Resorption
↓
inc $[Ca^{+2}]$
inc $[PO_4^-]$

③ At kidney ⟹ Similar to PTH. ⟹ ↑
↳ inc Ca^+ Reabsorbtion at DCT

but Vit-D ⟹ inc PO_4^- Reabsorbtion

Overall Action ⟹ Vit-D → inc $[Ca^+]$ & $[PO_4^-]$

'C'-cells ⟹ Calcitonin ⟹ Salcatonin
of Thyroid glan ↳ Salmon fish

At bone ⟹ Receptor at Osteoclast

Calcitonin
↓⊖
Osteoclast
↓
dec Bone Resorption

At kidney ⟹ inc Ca^{+2} excretion

Medullary Cancer of Thyroid tumour ⟹ Para follicular cell ⟹ Ruc Calcitonin

∴ Calcitonin ⟹ tumour marker

Para-neoplastic Syndrome of lung Cancer ⟹ Hypercalcemia of Malignancy
⇓
due to PTH Related peptide
↳ Squamous cell
↳ Small cell