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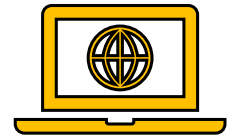
Pharmacology Concepts
By Rajesh Choudhary

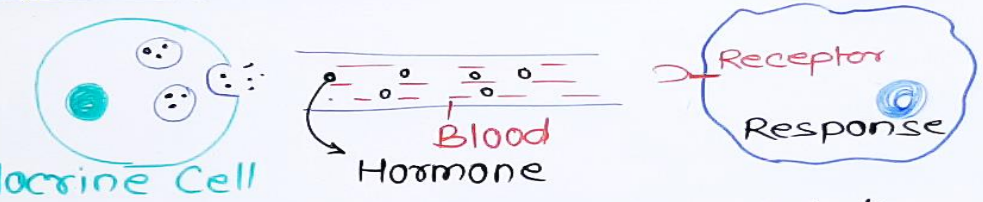
Endocrine Pharmacology Part 1



Pharmacology 2 | U2

ENDOCRINE PHARMACOLOGY (HORMONES AND RE[illegible] [illegible]RUGS)

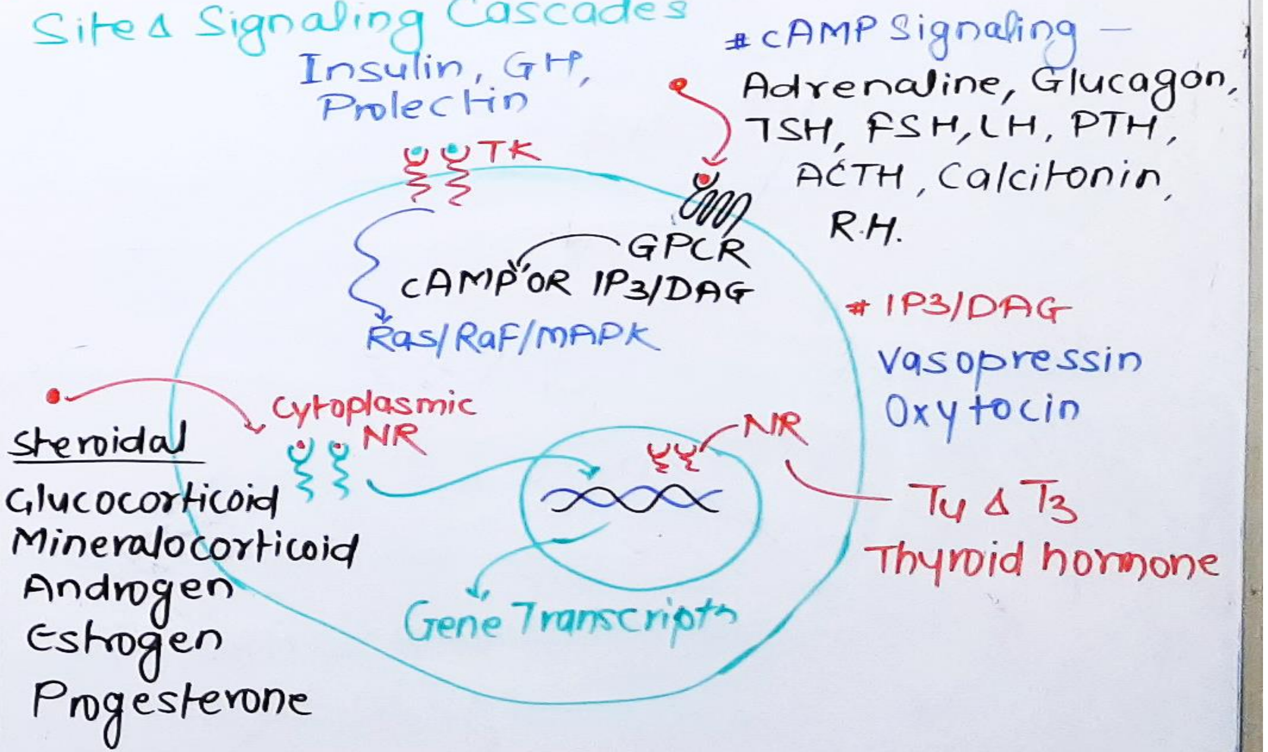
HORMONE (Greek - "Hormaein" - Stir up)



Role → Growth, Development, Metabolism, Reproduction, Aging, etc & maintain "Homeostasis"

1. Pituitary Hormones
   - A. Anterior :- GH, Prl, ACTH, TSH, FSH & LH
   - B. Posterior - Oxytocin & Vasopressin
2. Thyroid Hormones - Triiodothyronine (T_3), Thyroxine (T_4), Calcitonin
3. Parathyroid → Parathormone (PTH)
4. Pancrease → Insulin, Glucagon
5. Adrenals →
   - Cortex - Glucocorticoids (Hydrocortisone)
     - Mineralocorticoids (Aldosterone)
     - Sex Steroids (dihydroepiandrosterone)
   - Medulla - Adrenaline, Noradrenaline
6. Gonades - Androgens (Testosterone)
   - Estrogen (Estradiol)
   - Progestin (Progesterone)
7. CNS (Hypothalamus) - Releasing/Inhibitory Hormone
8. Placenta - Prolectin, Progesterone, etc

Site & Signaling Cascades

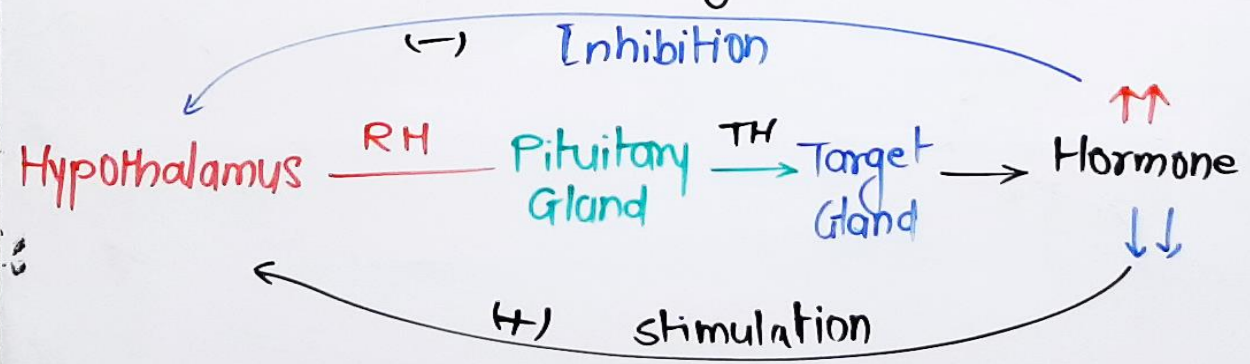


Anterior Pituitary Hormone & Related Drugs

Anterior Pituitary (Adenohypophysis), the master endocrine gland, which regulates other E. hormone.
Controlled by Hypothalamus through Releasing & inhibitory hormone (Master of master Gland)
APH → Peptides → Cell Surface Receptor (GPCR)

I Acidophil Cells
↳ Somatotropes - Growth hormone
↳ Lactotropes - Prolactin

II Basophil Cells
↳ Thyrotropes → Thyroid Stimulating Hormone (TSH)
↳ Corticotropes → Adrenocorticotropic hormone (ACTH)
↳ Lipotropes → Melanocyte stimulating hormone
↳ Gonedotropes → Follicle Stimulating Hormone (FSH)
→ Luteinizing hormone (LH)



Drugs Altering the Secretion of AP Hormone

A) Inhibition of GH Release
Sometostatin, Octreotide, Lanreotid

B) Inhibition of Prolactin Release
Bromocriptine (D_2 Agonist)
Cabergoline (Newer D_2 Agonist)
Apomorphine

C) Enhance Prolactin Release
Chlorpromazine, Reserpine

D) Alter Gonadotropin (Gn) Release
A. Superactive GnRH Agonist
Nafarelin, Goserelin, Triptorelin

B. GnRH Antagonist
Ganirelix, Cetrorelix

GROWTH HORMONE

191 Amino acid; Single peptide chain; MW 22000
Most abundant hormone synthesised by A. Pituitary

PHYSIOLOGICAL ACTION

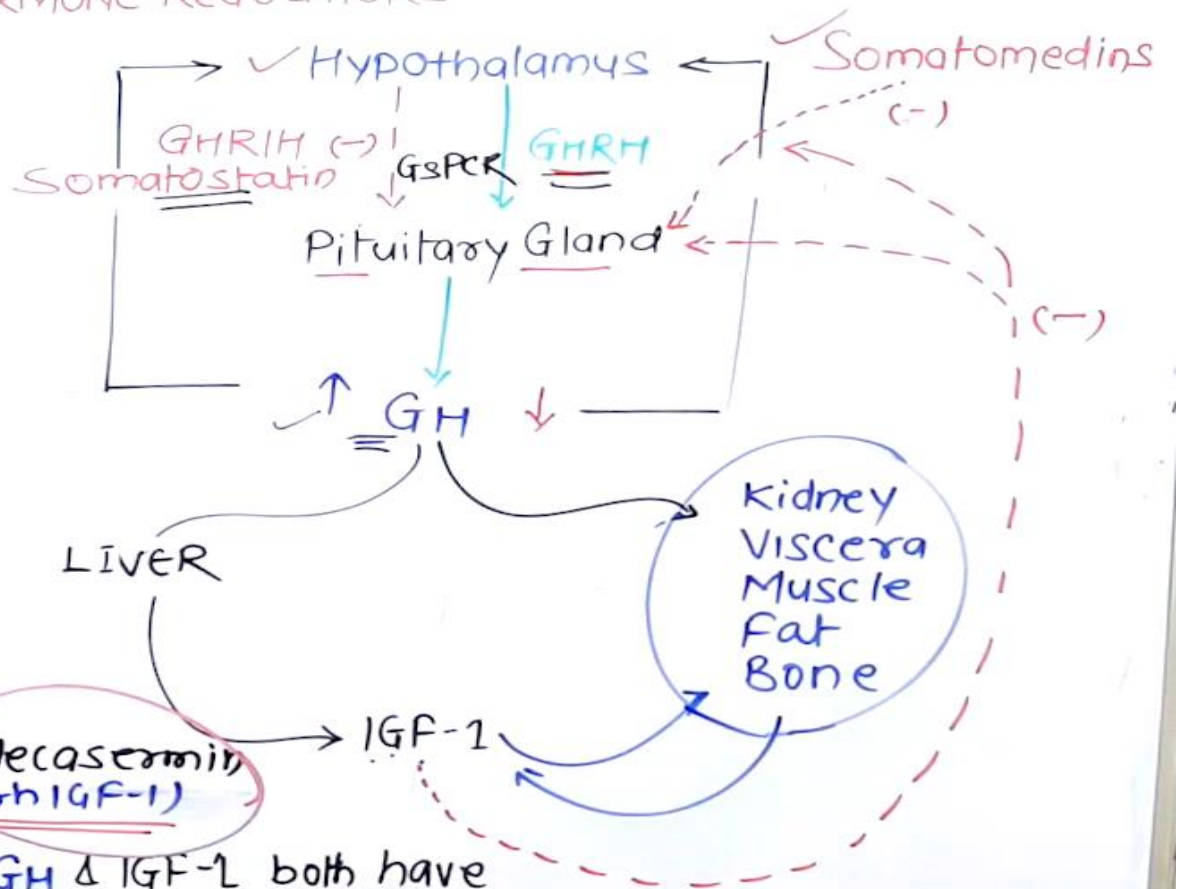
MOA :- GH ⟶ Enz Linked R ⟶ JAK-STAT Pathway

Growth & Developent, mainly Bone & SK. muscle
In childhood & adolescence, GH required for normal growth, but in adult GH maintains the mass of bone & muscle
Growth of Brain & Eye independent from GH
GH (+) ⟶ N_2 & Ca^{2+} retaintion ⟶ + N_2 balance
↓ (+)
Protein Synthesis ⟵ (+) Amino Acid uptake
GH also regulates metabolism in many organs
→ Liver, Intestine, & Pancreas, stimulates ↑protein Synthesis, Lipolysis in fats, ↑ blood Glucose through gluconeogenesis & glycogenolysis in Liver

USES – 1) Pituitary Dwarfism in childhood
2) Turner Syndrome (Girl with only X chromosome)
3) Chronic Renal insufficiency in Children
4) GH deficiency in adult
5) AIDS Related wasting

"Somatropin" (rh GH)

HORMONE REGULATORS –



GH & IGF-1 both have opposite effect

IGF ⇒ Lipogenesis & Glucose uptake by muscle

ADR – 1) Low Immunogenic - Allergy
2) Pain at injection site 3) Lipodystrophy
4) Glucose intolerance, 5) Hypothyroidism

GROWTH HORMONE INHIBITORS

↳ Somatostatin, Octreotide, Lanreotide

"SOMATOSTATIN" → 14 Amino Acid Peptides,

↳ Inhibits the Secretion of → GH, Prl, & TSH (APH),
Insulin & Glucagon (Pancreatic) and all GI Secretion (Gastrin & HCl)

Biological Action –

GI → Steatorrhoea, Diarrhoea, Hypochlorhydria

Blood Vessels – Constrict of splanchnic, Renal & Hepatic blood vessels

↓ GI mucosal Blood Flow → Useful to controll GI esophageal, ulcer bleeding

Use – # Adjuvant-value in Diabetic ketoacidosis
Acromegaly
Surgical removal of pituitary adenomas

* Its antisecretory action is beneficial in pancreatic, bilary, or intestinal Fistulae

Also Reduce the pencreatic surgery complications

"OCTREOTIDE" :– Synthetic Octapeptide

40 time more potent than somatostatin to reduce the secretion of GH

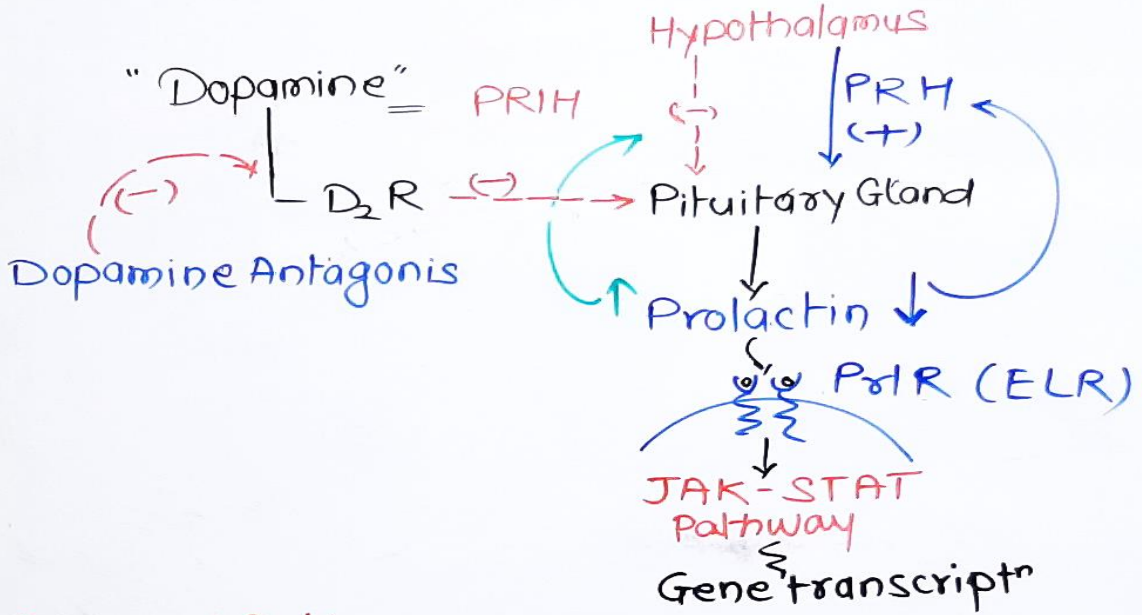
Weak inhibitor of Insulin secretion

Use :– Preferred for Acromegaly and Secretory diarrhoea associated with carcinoid, AIDS, Cancer Chemotherapy, or Diabetes.

ADR – # Abdominal Pain,
Nausea # Steatorrhoea
Gall stones
Hyperglycemia infrequent

PROLACTIN

↳ 199 Amino acid, Single chain peptide, MW 23000



Biological Action :-

It is a primary stimulus, together with Estrogen, progesterone, corticosteroids, insulin, thyroxin causes growth & development of Breast during pregnancy

Important for Milk production during Lactation (stimulates lactation)

It promotes proliferation of ductal as well as acinar cell in the breast & induce synthesis of milk protein & lactose

Prolactin supresses hypothalamo-pituitary gonadal axis by ↓ GnRH.

"Lactational Amenorrhoea" - Inhibiting ovulatn and fertility

Also affect immune response (T-Lymphocyte)

Patho-Physiological Involvement

Hyperprolactinaemia – Galactorrhoea-Amenorrhoea-infertility syndrome in woman, in male loss of Libido & ↓ Fertility

It is caused by Prl secreting tumors, prolong use of Antidopaminergic (Haloperidol, chlorpromazine, reserpine, etc), hypothalamic disorder, and Hypothyroidism

* No clinical uses

PROLACTIN INHIBITORS

↳ Bromocriptine, Cabergoline
↳ D_2 Agonist (+)

Dopamine (+) → D_2R → ↓ Prolactin Release

"BROMOCRIPTINE"

↳ Synthetic Ergot derivative → 2-bromo-α-ergo-criptin → Greater action D_2R
↳ At some site of brain → Partial Agonist/Antag. D_1R
↳ Also weak α_1-adrenergic Receptor Blocker.

Action → 1) ↓ Prl release → Antigalactopoietic#
2) Normally ↑ GH release, but ↓ GH release in pituitary tumor that causes Acromegaly#
3) has l-dopa like CNS action - Antiparkinson#
4) Stimulate D_2R (CTZ) - Vomiting*
5) *Hypotension - due to supression of central postural reflexes & α_1R blocking Activity
6) *Drease GI Motility

USE* - Hyperprolactinemia, Acromegaly, PD, Diabetes

ADR → Vomiting, Constipatn, Hypotension, confusion, psychosis, hallucinations

"CABERGOLINE" :- Newer D_2R-Agonist

↳ More potent, selective pituitary D_2R Agonist, & Longer acting ($t_{1/2}$ = 60h) than Bromocriptine
↳ twice a week
↳ 1st choice for - Hyperprolactinemia
↳ Blood Prl level fall within 2-4 weeks, & Woman can conceive within 1 year & Stopped when pregnancy occurs.
↳ Micro & Macro prolactimas show reoccurance during therapy, & neurological symptoms (Visual field defect) due to pressure on optic chiasma are relieved.
↳ Also useful in Acromegaly due to Pituitary adenoma (but less effective)
↳ dose - 0.25 mg (starts) twice weekly

GONADOTROPINS (Gns)

↳ Follicle Stimulating hormone (FSH)
↳ Luteinizing hormone (LH)

Both are Glycoproteins, 2-peptide chain
α chain = 92 AA, β-Chain, FSH-111 AA, LH-121 AA
Action → + Gametogenesis & Gonadal hormone

"FSH"

Female → (+) Follicle Growth & Estrogens
Male → (+) Spermatogenesis and has a trophic influence on Seminiferous tubules.
Absence of FSH → Ovarian & testicular Atrophy

"LH"

Female → induce preovulatory swelling of ripe graafian follicle & triggers ovaluation followed by luteinization of the rupture follicle and sustains the corpus luteum till to the next menstrual cycle.
Responsible for atresia of remaining follicle.
Influence of progesterone secretion
Male → (+) Testosterone secretion by interstitial cells

Regulation - Inhibin (Gonads) (−) Dopamine (−)

Hypoth. —GnRH, GqPCR→ PG → FSH & LH

FSH & LH —GsPCR (Target cell)→ Gonadal hormone Synthesis

USES :-

① In Amnorrhoea & Infertility
② To aid in-vitro Fertilization
③ In male hypogonadotropic hypogonadism

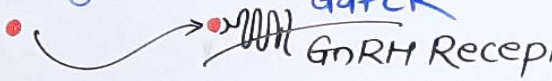
ADR- ① Ovarian hyperstimulation syndrome
(II) Polycystic ovary
(III) Ovarian bleeding
(IV) Multiple pregnancy
(V) Allergy, Edema, mood changes

SUPER ACTIVE / LONG ACTING GnRH AGONIST

Goserelin, Nafarelin, Leuprolide, Triptorelin

They are 10-15 times more potent than Natural GnRH

Longer Acting → 2-6 hours



Initialy, they trigger Gn Secretion, after 1-2 weeks they causes desensitizatn & down regulation of GnRH receptors, → ↓FSH & LH Secretion → ↓Gonadal Functn → ↓Gametogenesis & ↓G. Hormones

USES - By nasal sprey or injection (sc/im), once a month (Triptorelin & Goserelin)

↳ Precocious puberty, prostatic cancer, endometriosis, premenopausal breast cancer, polycystic ovarian disease.

↳ Also have contraceptive action For both M/F

ADR - Menopausal Symptom - Headache, Sweating, hot flashes, mood change, veginal dryness, Amnorrhoea, Loss of libido

GnRH ANTAGONIST

↳ Genirelix, Cetrorelix, Degarelix, Abarelix

↳ More extensively substituted act as GnRH Receptor Antagonist.

↳ They ↓ Gn Secretion without initial Stimulation

↳ Genirelix & Cetrorelix - Short acting (sc, daily)

↳ They are approved for inhibiting LH sugers during controlled ovarian stimulation in woman undergoing in-vitro fertilization.

Advantages over Long acting GnRH Agonist

↳ Quick suppression of Gn

↳ Lower risk of ovarian hyperstimulatn Syndrm.

↳ They achieve more complete supression of endogenous Gn Secretion.

THYROID HORMONE PHARMACOLOGY

HORMONES = Thyroxine (T_4), Triiodothyronine (T_3)

Mechanism = Nuclear Thyroid hormone receptors (TR)

Thyroid → T_4 (60-90 µg) & T_3 (10-20 µg)

T_4 —(Liver & kidney, Iodothyronin Deiodenase)→ T_3 → D_1, D_2, D_3 ISO form

* D_1 → T_3 (3,5,3-triiodoth—) + rT_3 (3,3,5-triidoth—
* D_2 → T_3 and D_3 → rT_3

PHARMACOLOGY & PHYSIOLOGICAL ACTION

1. **Growth & Development** ⇒ T_3 & T_4 are essential for normal growth & developement. Congenital deficiency leads to "Cretinism"

2. **Metabolism** :→ * **Lipids** → (+) Lipolysis by action of catecholamines & Lipolytic hormone → ↑ FFA & TG
   * Lipogenesis are also stimulated, ↑ Ch. metabolism
   * Hyperthyroidism → Hypercholesterolemia
   * **Proteins** ⇒ Mainly catabolism (Energy Sources)
   * Hyper → Weight loss & ↓ mucoprotein Syn.
   * **Carbohydrate** ⇒ ↑ BMR, + Glycogenolysis & Gluconeogenesis → "Hyperglycemia"

3. Calorigenesis → +BMR, Body temp.
4. **CVS** ⇒ Hyperdynemic state of circulatn due to demand
   (+) Cardiac Stimulatn → ↑ HR, ↑ CO, ↑ FC by upregulatn of β-receptor and (+) contractile action. ↑ Systolic BP
   Hyper- → Arrythmia, MI, CHF
5. **Nervous System** → Essential for normal function
6. **Skeletal Muscle** → In myxoedema → Flabby & Weak
   & in thyrotoxicosis → ↑ tone, tremor, myopathy
7. **GIT** ⇒ Diarrhoea (in Hyper)
8. **Kidney** - ↑ urinatn in myxoedema
9. (+) Haemopoesis
10. Reproduction - Impaired fertility in hypoth-cond"

Uses - # Cretinism (Thyroxine - 8-12 µg/day)

Myxoedema (Adult hypothyroidism)
Myxoedema Coma
Non-toxic Goiter
Thyroid nodule
Papillary carcinoma of thyroid

l-thyroxine - T_4
liothyronine - T_3

THYROID INHIBITORS

These are drugs used to lower the Functional capacity of hyperactive thyroid glands.

Thyrotoxicosis ⇒ Excessive secretn of thyroid hormone
↳ "Graves Disease" & "toxic nodular Goiter"
↳ Autoimmune dis. - IgG antibody → (+) TSH R

Thyroid Inhibitors -

Ⓐ Thyroid hormone Syn. Inhibitors - "Thioamides"
→ Propylthiourecil, Methimazole, Carbimazole

Ⓑ Inhibit Iodide Trapping - "Ionic Inhibitors"
→ Thiocynate ($-SCN$), Perchlorates ($-ClO_4$), Nitrates ($-NO_3$)

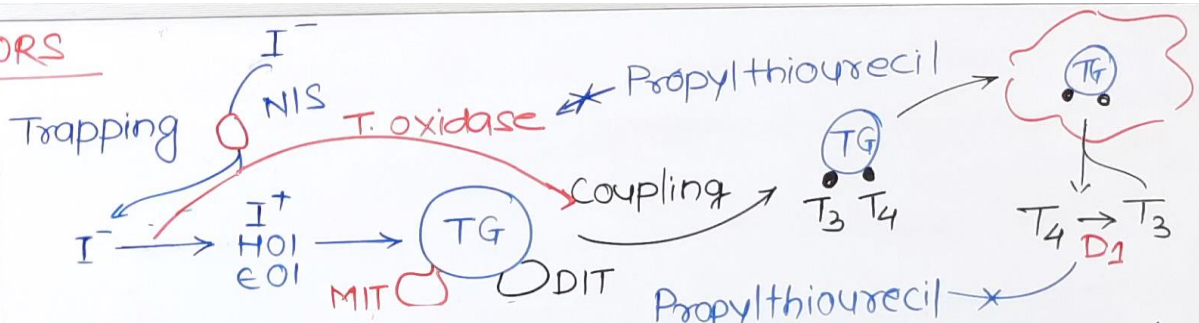
Ⓒ Inhibit hormone Release → Iodine, NaI, KI, Org. Iodide

Ⓓ Distroy Thyroid tissue → Radioactive I^{131}

THIOAMIDES (Anti Thyroid Drugs)

↳ In 1940s, thiourea derivetives produce Goiter & hypo-thyroidism in rats.
↳ open chain derivetives were found toxic, while methyl & propyl derivetive & thioimidazole derivetives like methimazole & Carbimazole were found to be safe

MOA = Propylthiourecil → ↓ T. peroxidase & Deiodination (D_1)
Carbimazole → ↓ T. peroxidase only



They bind to T. peroxidase & prevent oxdn of Iodide & idotyrosyl residue, thereby
(i) ↓ Iodinatn of tyrosine residue in TG
(ii) ↓ Coupling of idotyrosine residues to form T_3 & T_4

* At lower conc. of Thioamide = (ii) > (i)
* Higher dose → ↓↓ T_3/T_4 → ↑ TSH release → Goiter

P'Kinetics - orally absorbed quickly, metabolised by liver, widely distributed & cross placenta & enter to milk, excreted through urine

ADR = Hypothyroidiss, Goiter (overdose), Skin Rashes, GI intolarance, Joint pain, Liver damage, hair loss, etc

Uses ⇒ ↳ Thyrotoxicosis
⇒ As Definitive therapy
⇒ Preoperative
⇒ with I^{131}

THYROID INHIBITORS

RADIOACTIVE IODINE (I^{131})

↳ Normal isotop = I^{127}, Ractive isotops = I^{131}
↳ Physical half life of I^{131} - 8 days
↳ I^{131} emits γ-rays & β-particles (electrons)
↳ They show destructive effects on thyroid cells
⇒ I^{131} ⟶ Conc. at thyroid (Follicular Cell)

Emit β-particle (Radiation) within cells (0.5-2 mm) ⟶ Pyknosis ⟶ Nacrosis ⟶ Fibrosis ⟶ Partial distructn of thyroid tissues

↳ Administered as Sodium salt of I^{131} (orally)

Diagnostic Uses = 25-100 μ curie is given
= No distructive effect at this dose

Therapeutic Uses ⇒ Used in Hyperthyroidism due to "Grave's Disease" & Toxic nodular Goiter

dose = 3 to 5 m Curie, High dose is generally required for toxic nodular goiter than Grave's disease

Advantages -

→ Treatment is easy, simple, conveniently given on out-patient & inexpensive
→ No surgical risk, scare, injury to parathyroid
→ Permanent cure after controlling hyperthyroidism

Disadvantages -

→ Enhance the risk of Hypothyroidism
→ Long latent period of response
→ Contraindicated in pregnancy → Foetal thyroid may also destroyed
→ Not used in young patients (Hypothyroidism)
→ choice after 25y, if CHF, Angina, or other contraindicated to surgery

I^{131} may also used in "Metastatic Carcinoma of Thyroid" much higher dose are required & prior stimulation with TSH is recommended.

Hormones & Drugs Affecting Calcium Balance

2% of body wt (1-1.5 kg). 98% found in Bones

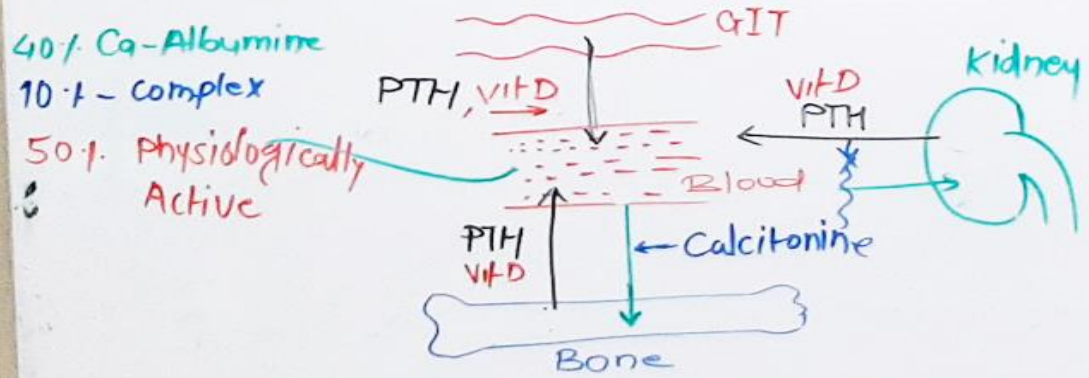
Physiological Role -

↳ Control Excitability of Nerves and Muscle.
↳ Regulate cell mem permiability & integrity
↳ Regulate muscular Contractn & Exocytosis of NTs and Exo/Endocrine release
↳ act as a intracellular messenger
↳ Also involve SA-node Automaticity and AV Conductn
↳ Essential for blood Coagulation
↳ Ca^{+2} serves structural function in Bones & teeth

Regulatn of Blood Ca^{+2} Level :- Normal - 9-11 mg/dL

Hormone :- ① Parathormone (PTH), ② Calcitonine,
* ③ Calcitriol (Active form of Vit D)

↳ They regulate "Intestinal Absorptn", "Exchange with Bone" and "Renal Excretion"



Absorptn & Excretn of Ca^{+2}

↳ Ca. is absorbed by facilitated diffusion from Intestine and also by Active transport Sys. under the influence of Vit-D
↳ Ca. abs ↓ by Complexing agent, Glucocorticoids.
↳ Ionised Ca^{2+} is filtered by G.F. but mostly reabsorbed.
↳ PTH & Vit D ↑ the renal reabsorption & Calcitonine ↓ the renal reabsorptn

About 300 mg Endogenous excreted daily, half in urine & half in Faeces
Daily diet 0.8-1.5g Ca^{+2} /→ 1/3rd only absorbed

Preparatn - $CaCO_3$, Ca. gluconate, Ca. citrate, Ca. lactate

ADR/Side Effect - Constipation, Excessive Gas, Bloating

Therapeutic Use -

Tetany - 10-20ml Ca. Gluconate (90-180 mg) IV, infusion rapid (10min) then slowly. Total - 0.5 to 0.9 g

Osteoporosis - Ca+VitD Supplements

Dietary Supplement -

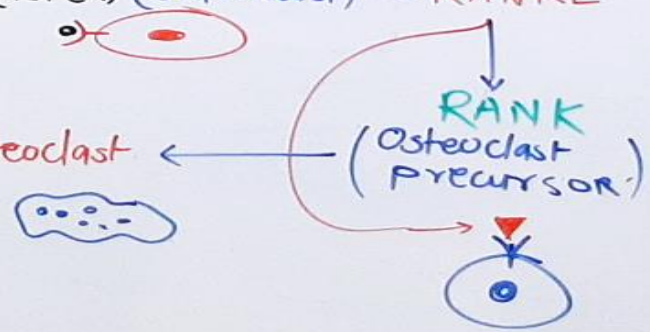
Child (1-10Y) - 0.8-1.2g
Young (11-24Y) - 1.2-1.5g
25-[illegible]Y - 1g

PARATHORMIONE

"Vassale & Generali" (1900) - Parathyroidectomy → Tetany
"Mc-Cullum & Voegtlin" (1909) - That is due to low plasma Ca^{+2}
In 1925 - PTH was isolated

PTH :- Single chain Polypeptide (84 Amino ā), MW: 9500
↳ It is synthesized as Prepro-PTH → PTH, & Stored in Vessicle. Secretn of PTH is regulated by plasma Ca^{+2} level through Ca-sensing Receptor (CaSR, GsPCR)
↳ Fall blood Ca^{+2} → (+) CaSR at Parathyroid Cell → ↑ PTH
↳ Chronic Hypocalcaemia leads to Parathyroid Hypertrophy & hyperplasia
↳ Changes in PO_4^{3-} also affect PTH secretn indirectly by altering plasma Ca^{+2} concentration
↳ Calcitriol (VitD) ↓ expression of PTH gene in parathyroid cell → ↓ PTH Productn

MOA :- PTH $\xrightarrow{(+)}$ PTH-R (GsPCR) (Osteoblast) → RANKL (Receptor for activat" of Nuclear Factor Kappa-B-ligand)



ACTION :- PTH ↑ the plasma Calcium level by -
1. Bone → PTH ↑ the reabsorptn of Ca^{2+} from bone
2. Kidney → PTH ↑ the Ca^{+2} reabsorption in DCT & ↓ Ca^{+2} Excretn. It also ↑ the PO_4^{3-} excretion
Hyperparathyroidism - ↑ Ca^{+2} excretn
Hypoparathyroidism - ↓ Ca^{+2} Excretn
In kidney, PTH also promotes 1-α-Hydroxylatn of 25OHD to Calcitriol (VitD)
3. Intestine - Indirectly ↑ Ca^{+2} Absorption

PTH → ↑ VitD (kidney) → ↑ Intestinal Absorptn

4. PTH → ↓ Ca^{2+} level in milk, Saliva & Ocular lens
Hypoparathyroidism → Cataract formatn

Hyperparathyroidism :- menifestations
↳ Hypercalceamia, Decalcificatn of bone, Muscle weakness, GI disturbance.
Treatment - Surgical removal of tumor & low Ca^{2+} diet
Hypoparathyroidism - Tetany, Convulsion, laryngospasm Cataract, Neurological disorder

Drugs that ↑ PTH Secretn -
Cinacalcet → + CaSR — PTH
Triparatid - Recombinant PTH, used in Sever Osteophoresis

ORAL ANTI DIABETIC DRUGS

Drugs used in treatment of Diabetes malitus

I) Enhance Insulin Secretion –

A) K_{ATP} channel Blocker

\# Sulfonyl urea = Tolbutamide, Glibenclamide, Glipizide, Glicazide, Glimepiride

\# Phenylalanine analouge = Repaglinide, Nateglinide

B) Dipeptidyl peptidase-4 (DPP-4) Inhibitors – Sitagliptin, Vildagliptin, Alogliptine

II) Overcome Insuline Resistance

A) Biguanide (AMP_K Activator) = Metformine

B) Thiazolidinedione ($PPAR_\gamma$-activator) – Pioglitazone

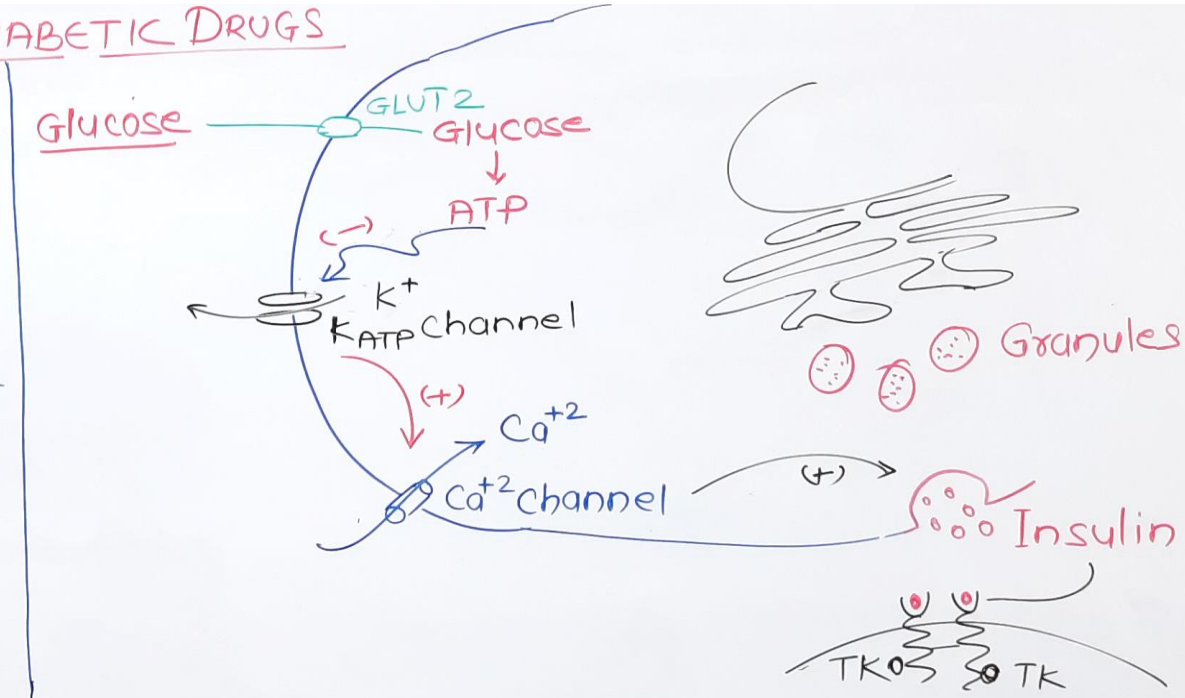
III) Retard Carbohydrate Absorption

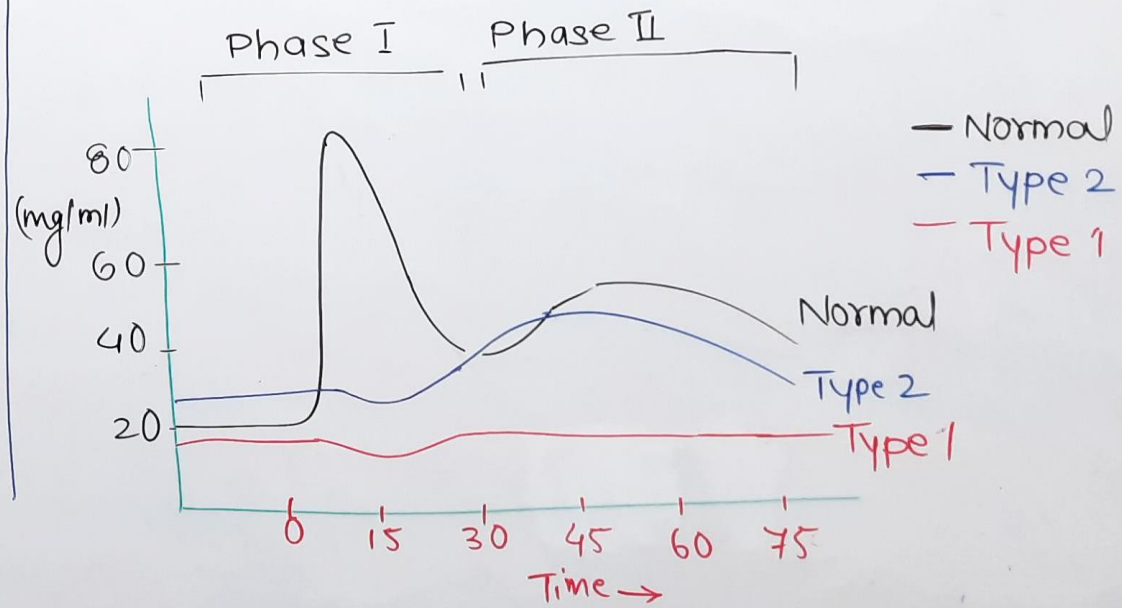
α-Glycosidase Inhibitor - Acarbose, Miglitol, Voglibase

IV) Others

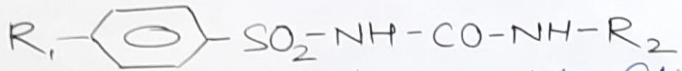
A) Sod-Glucose Cotransport 2 (SGLT-2) Inhibitor Dapagliflozin, Canagliflozin

B) D_2R Antagonist - Bromocriptin





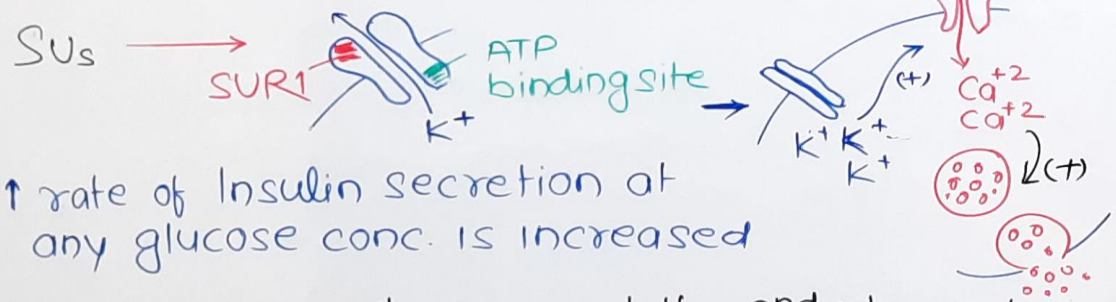
SULFONYLUREAS
ANTI-DIABETIC DRUGS



Tolbutamide, Glibenclamide, Gliclazide, Glimepiride

→ All the sulfonylureas significantly reduce the blood suger level in normal & type-2 diabetic patients, but not in type 1.

Mechanism of Action –



↳ ↑ rate of Insulin secretion at any glucose conc. is increased

↳ The SUs primarily augment the 2nd phase of insulin release with little effect on phase 1.

↳ They donot cause Hypoglycemia in pancreatectomized animals & in type 1 diabetic patients., indicating their indirect actn through pancrease.

↳ Additionaly, ↓ Glucagon secretion & Slow down the hepatic degradation of insulin.

Extrapencreatic Action –

Long term uses → Downregulatn of SUR1 → ↓ Insulin Seretion → ↑ Glucose tolerance

P'kinetics – Orally well absorbed, > 90% Protein binding.

low Vd (0.2–0.4 L/kg), Metabolized by Liver & produce active/inactive metabolite, that are excreted through urine.

* Dose adjustment required in Liver & Renal disease.

Drug Interactions –

↳ Displace from protein binding → Salicylate, Sulfadrugs phenylbutazone, etc

↳ Inhibit metabolism → Cimetidine, ketoconazole, etc

↳ Synergise/prolong action – Salicylates, sympatholytics, propranolol, lithium, Alcohol by inhibiting Gluconeogenesis.

↳ Drugs that ↓ actions – * Metabolic enz inducers,
* supress the Insulin release – Corticosteroides, thiazide, Furosemide, Oral contraceptives

ADR –

↳ Hypoglycemia

↳ weight gain, nausea, vomitting, Constipation

↳ Hypersensetive Reaction – Rashes, photosensetive, leucopenia, agranulocytosis,

DIPEPTIDYL PEPTIDASE-4 INHIBITOR

Drugs → Sitagliptin, Vidagliptine, Saxagliptine

"Sitagliptine"

↳ This is the first DPP4 Inhibitor developed in 2006
↳ Enhance the insulin secretion by selectively inhibit the DPP-4 enzyme & potentiate the GLP-1 & GIP action and ↓ Glucagon secretion
↳ Lower the blood suger level (meal time & fasting) in typ 2 diabetes
↳ Low risk of hypoglycemia as compared to SUs
↳ Lower the HbA1c - 0.2 to 1.2 %, similar as metformin
↳ Clinically used as adjuvant drugs in type-2 Diabetes

ADR :→ Nausea, Loose stool, headach, Rashes, allergic reactions (angioedema, dermitis)

THIAZOLIDINEDIONE (PPARγ AGONIST)

Rosiglitazone - Banned in India in 2010 due to serious risk of cardiovascular disease.

"Pioglitazone" → Banned in 2013 for carcinoma of urinary bladder, now lifted with warning label "not to used it as a 1st line drugs"

MOA → (+) PPARγ (located at Fats, muscles, etc) → ↑transcriptn of insulin responsive gene → Reverse Insulin resistance by ↑GLUT4 expre-ssion & translocation → Improve Glu. uptake

Action → # ↑insulin Sensitivity
↓ Hepatic Gluconeogenesis
Improve fatty acid metabolism & Lipogenesis
↓ HbA1c, # ↓ TG & ↑ HDL

ADR = Edema, weight gain, headach, mild anemia, CHF May occurs, Liver damage

Uses - In type II diabetes, ↓ blood Glucose & HbA1c 0.5 to 1.2 % without increasing insulin level
→ used as supplement with SUs/Metformin

ANTI DIABETIC DRUG

BIGUANIDE PHARMACOLOGY

1950s → Phenformin and Metformin
↳ Banned in 2003, -Lactic Acidosis

Metformin → It has no or little Hypoglycemic effects in nondiabetic patients unlike SUs. So it is "Euglycemic" it does not promot the β cell.
→ It improves lipid profile as well as in type 2 diabetes

MOA → It does not cause insulin release but acts in the presence of insulin.

→ (+) AMPk Δ regulates ↓
:→ ↓ hep. Gluconeogenesis → ↓ Glucose output
:→ Improve Glu. utelizatn, ↓ Insulin resistance
↳ ↑ Glycogen storage (muscle)
↳ ↓ Lipogenesis & ↑ FFA oxidation
:- Improve mitochondrial Respiration.

→ Also reduce intestinal absorption of glucose, hexose, amino ā & vit B_{12}

P'kinetic → absorbed orally, Excreted unchanged through urine (Cl ≈ GFR). ↑ risk of lactic acidosis in renal failure patient

ADR → Abdominal pain, Anorexia, bloating, metalic taste, - Lactic acidosis, vit B_{12} deficiency.

Contraindicatn → RF, Hypotension, HF, Respiratory & hepatic failure

Uses - Mainly in type 2 diabetes
↳ Antihyperglycemic, ↳ promoting weight loss
↳ Improve micro/macro vascular complicatn
↳ No accelaratn of β-cell failure
↳ ↓ HbA_{1c} 0.8 - 1.2 %

α-Glucosidase Inhibitors

↳ Acarbose, Miglitol, Voglibose

Carbohydrate —(α-Glucosidase)✕→ Digestion

↳ ↓ digestion, Absorptn of polysaccharide & Sucrose
↳ promote GLP-1
↳ ↓ HbA_{1c} - 0.4 to 0.8 %
↳ ↓ type 2 diabetes occurance after long time use in prediabetic patient
↳ ↓ Incidence of hypertension & cardiac disease