THYROID

Thyroid gland produces. what all hormones?

T_3
T_4
] follicular cells

Calcitonic → para follicular cells

TSHX → pituitary gland.

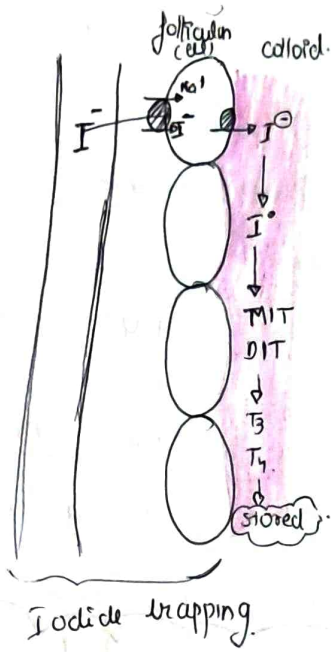
T_3	T_4
Short acting	long active.
more active	less active.
small amount	more amount

Synthesis.

① Iodide uptake (I^-)

- $Na^+ - I^-$ symporter transports Iodide from blood into thyroid follicular cells.

② Pendrin → moves Iodide from follicular cells into Colloid



Iodide trapping.

③ Oxidation & Organification

- In colloid, Thyroid peroxidase (TPO) carries out oxidation & Organification.

Iodide (I^-)
TPO | oxidation
I°

Iodine + Tyrosine in Thyroglobulin
organification

Mono Iodo Tyrosine (MIT)
Diiodo Tyrosine (DIT).

④ Coupling.

MIT + DIT = T_3
DIT + DIT = T_4
DIT + MIT = rT_3.

⑤ Storage inside Colloid.

Secretion

⑥ Thyroglobulin containing T_3 & T_4 is taken up into follicular cells.

↓

by lysosomal enzyme breaks down thyroglobulin & release T_3 & T_4 into cytoplasm.

↓

T_3 & T_4 is released into blood stream.

peripheral Conversion of $T_4 \rightarrow T_3$

- T_3 is active form
- but T_4 is in larger amount
- T_4 ⟶ T_3.

5'-deiodinase.

in liver ✓
kidney ✓
skeletal muscle. ✓

T_3 - 3, 5, 3' - Tri Iodo thyronine

T_4 - 3, 5, 3' 5' - Tetra Iodo thyronine

rT_3 - 3', 5', 3 - T_3

Disorders.

- Hypothyroidism
- Hyperthyroidism.

HYPO

If hypo → then we can give hormone.

ie, we can give → more active short acting.

T_3 – Liothyronine.

T_4 – L-thyroxine.

→ less active, long acting.

See, we need to manage hypothyroidism for whole day... so we need long acting. ie,

T_4 – L-thyroxine

It is the DOC for ANY case of Hypothyroidism.

So, do we use liothyronine at all?

Yes, It's short acting + very active.

used in → Emergencies.

ie,

Myxedema Coma

It can be used in this condition

But!

DOC is L-thyroxine itself.

It is the DOC in Any situation of hypothyroidism?

Even in Emergencies.

We gradually ↑ Dose in hypothyroidism drugs.

Symptoms of Hypothyroidism

- Cold Intolerance.
- weight gain.
- Sympathetic system activity ↓ (BP, HR ↓)

HYPER

- If hyper... we need to.

↓ formation

or

↓ action.

Symptoms

- wt loss.
- Heat Intolerance.
- Symp. stimulation {HR↑, BP↑, tremors}.

Drugs.

1. N-I symporter inhibitor
2. Thyroid peroxidase ⊖
3. Secretion into blood ⊖
4. Peripheral Conversion ⊖
5. thyroid destroying drugs: radioactive Iodine
6. Adjuvants – symptomatic relief.

NIS ⊖

- they ⊖ formation
- But we no used clinically as they are toxic.

1. perchlorate
2. pertechtenate
3. thiocyanate.

they are not used clinically But they are found in food like cabbage

- these foods can ↓ Hormone if taken too much. ∴ cause goitre
- so called → Goitrogens

② TP ⊖

- ⊖ formation of thyroid hormone.

- Thioamides
  - Carbimazole.
  - methimazole.
  - propyl thio uracil (PTU).

• potency more.	• potency low.
• long acting	• plasma T1/2 low ie, short acting
• no problem	• peripheral ↓ conversion
• more crossing.	• Placenta - low cross

- all three drugs can cross placenta
- leads to malformation
  1. Choanal atresia
  2. aplasia cutis.
- teratogenic.

- since PTU is ~~long~~ short acting and potency is also low.
- DOC is Carbimazole & methimazole.
- But placental crossing is low in PTU.
- So in 1st trimester we use PTU.

(Rest trimester use - PTU)

- But in others → C & M.

- 1st Trimester → PTU
- 2nd, 3rd Trimester → C M non-pregnant

NOTE OF CAUTION

- If we initially give Xg dose of antithyroid drug..
- we need to wait 3-4 weeks to analyse results as there will be already stored thyroid hormone and we are ⊖ formation of new.
- don't keep on increasing dose if we don't see results in 1/2 wks initially.
- Only after waiting 3-4 wks we should go further

③ Secretion ⊖

- Na Iodide
- potassium Iodide
- Lugol's Iodine.

- Here, they ⊖ secretion of both already stored and newly forming hormones
- ie, there is Immediate action. and we don't have to wait 3-4 weeks like for formation ⊖ drugs.

Secretion ⊖ are the fastest acting antithyroid drugs.

- But tolerance develops. ie, escape phenomenon occurs ie, ~~after~~ 4-5 days is only double. can't give it for months or so... as secretion ⊖ stops after tolerance development.

ie, they are used mainly pre-operatively for thyroid surgery

gland → small, firm, less vascular.
→ Surgery becomes easier.

(4) 5' deiodinase ⊖

Peripheral Conversion ⊖.

- PTU
- propranolol
- prednisolone.

(5) Thyroid Destroying Drug.

Radioactive Iodine.
I^{131}

I^{127} - Normal.

- Radioactive substances are non-specific.
- I^{131} is given orally.
- It is trapped from blood by (NIS) which is mainly only present in thyroid gland.
- So, whatever Iodine 131 we give, it will always reach only thyroid gland, so other organs doesn't take it up and gets destroyed.

- I^{131} is stored in thyroid in colloid which is at centre of thyroid follicles.

↓

so only they get destroyed & not other tissues.

- they emit β rays. that has low penetration power compared to x rays & γ rays. so that its effects only remains limited to thyroid gland.
- that is why we only use I^{131} and not other radioactive substance.

3 reasons

1. NIS is only in thyroid gland.
2. I^{131} is stored in centre
3. β rays - low penetration are produced.

- pregancy - all radiations are CI
- So I^{131} - CI in pregnancy.

$T_{1/2}$ of I^{131} → physical half life

↓

8 Days

is term used for radioactive substance.

not min, hrs.

Overdose : leads to hypothyroidism

Solution ?

- just stop drug.

ie, overdose are reversible

ie, after stopping drug, thyroid glands will produce hormone ✓

But

In I^{131}

it destroys gland. So it's hypothyroidism is ↓ IRREVERSIBLE ★

- In that case... we'll have to give L-thyroxine Life Long

So, it is CI in young patients

< 35 years

- we only give it to old patients.

⑥ Adjuvants.

(In hyper) for Controlling Sympathetic symptoms.

- β blocker → propranolol.
- CCB → verapamil, Diltiazem.

- we prefer β blockers

① the reason for Sympathetic Symptoms is β receptor

② they are also Peripheral Conversion ⊖.

Thyroid storm

- Severe hyperthyroidism thyrotoxicosis.
- Life threatening ↓ due to Excessive Sympathetic action
- person can die due to tachy cardia, ↑ BP etc..

So, DOC ↓ Life saving drug ↓ Propranolol

- Anti-thyroid Drug of choice in thyroid storm.

↓

PTU.

- DOC → propranolol
- anti thyroid DOC → PTU.

Pancreas

- Glucagon
- Insulin

Endocrine pancreas

islet of langerhans has 3 cell type.

α - glucagon → ↑ Sugar

β - Insulin → ↓ sugar.

δ - Somatostatin → ↓ Insulin & Glucagon

β cells secrete

→ Insulin

→ Amylin also.

Glucagon.

Used in

① Hypoglycemia.

How Glucagon ↑ Blood sugar?

glycogen (main mechanism) ↓ Glucose.

For glucagon to ↑ glucose, the main mechanism by ↓ break down of glycogen. ↓ But if someone has starved ie, not eaten food for say 1 week..... glycogen won't be present.

So in such cases... Glucagon is not effective.

Glucagon is not useful in

① starvation induced hypoglycemia

② Alcohol induced hypoglycemia. ↓ alcohol interferes with glycogenolysis also they are usually malnourished so glycogen ↓.

(2) DOC in

β blocker poisoning.

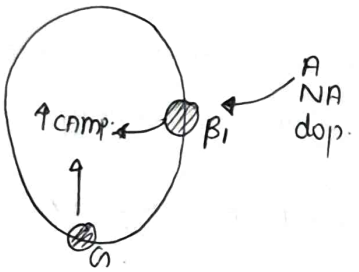
↓

Antidote / DOC

↓

glucagon

How?



β_1 receptor → GPCR.

↓

↑ cAMP.

↓

↑ Contractility. Conduction etc.

- β_1 receptors are acted on by NA, A, dop etc..
- In β blocker poisoning, there is excess β blocking action and A, NA, dop etc... can't act.
- Normally, when there is ↓ ♡ function, we give A, NA, dop.
- But here, we can't give.
- There is another mechanism by which cAMP↑

- glucagon receptors are present on ♡.
- glucagon acts on glucagon receptors to ↑ cAMP and thereby ↑ contraction, conduction, etc...
- Normally, why is glucagon's action not clinically significant?
- Cause β_1 agonist are always there and they produce 100% action... so 10% action of glucagon is not clinically detectable.
- But here, since β action is nil, this 10% becomes life saving.

DOC → β blocker poisoning

↓

Glucagon

β# poisoning.

(1) Glucagon DOC

(2) Atropine {parasym blocker}

(3) Calcium {direct stim}

(4) PDE ⊖ {⊖ cAMP metabolism}

Insulin.

(1) Type I DM: Insulin dependent

(2) Type II: Non-Insulin dependent

Type I DM

- pancreas are not producing Insulin at all
- so all patients of Type I DM are treated by

↓

Insulin — compulsory for treatment

Type II.

Non-Insulin dependent

- Even without Insulin we can treat
- Insulin → peptide so can't be given orally.
- So by chance, we'll have to take insulin injection
- so we don't prefer it.
- In cases we can treat without Insulin, we do so.

But in patients who has uncontrolled Type II is not Controlled with other pills..

- then we use Insulin.
- Insulin Non-dependent doesn't mean Insulin can't treat it...

It just means that even Without Insulin we can treat it.

(3) Pregnancy.

- Insulin don't cross placenta...
- If drugs crosses.. It will lead to hypoglycemia in fetus.
- Insulin is the safest antidiabetic drug in pregnancy.

(4) Diabetic Ketoacidosis

- very high glucose.

↓

DOC → Insulin. ☆

IV Insulin + IV fluid for dehydration

(5) Hyperkalemia - DOC

Drugs like Insulin & β_2 reuptor stimulants like Salbutamol

↑ Intracellular uptake of K+

- So Blood level ↓.

↓

Used in hyperkalemia Emergency.

So Side effect of Insulin

↓

Hypokalemia ☆

---

preparations

① Short acting → regular insulin

② Intern. acting → Neutral protamine Hagedron.

③ long acting → Insulin + Zinc.

Hexamer form

stable hexagon form.

↓ slowly release active monomers form.

↑ D.O action

- addition of Zinc increases stability of Insulin and ↑ duration of action
- Insulin + Zn preparation is called.

Lente.

Short acting - Semi Lente.

Int - Lente.

Long - ultra Lente

Insulin Analogue

- Same function different structure.

- ultra short acting → rapid acting

- Insulin LISPRO
- Insulin ASPART
- Insulin GLULISINT

ultra-long acting.

- Insulin GLARGINE
- Insulin DETEMIR
- Insulin DEGLUDEL

↳ longest acting.

• long acting

• when given Subcutaneously they are present in S.C area in stable hexagonal form.

• and they are only released slowly into blood.

• they are only slowly released to blood so there is no plasma peak and always remains in same LVl

↓

peakless Insulin

↓

plasma LVl remain stable

↓

low chance of hypoglycemia.

• Glargine acidic pH=4 rest → neutral pH

• Glargine is not mixed with any other Insulin, while rest can be mixed.

Route

① Subcutaneous: all Insulin can be given S.C.

why?
sely administrable.

site → abdomen
ant, lateral thigh
arm.

abdomen → any area other than periumbilical region Cause skin thickness isn't uniform, so it can affect absorption

• also, rotate the site, don't give on same area of abdomen always

• if continuously given at one site

↓

Lipoatrophy at that site.

② Intravenous

• only regular Insulin.

• used in Ketoacidosis Emergency.

③ Inhalational.

• Exubera. – removed now
↓
due to s/e
lung fibrosis.

• Insulin Afrezza
-short acting.

• given before meals.

ie,
for a patient who absolutely requires Insulin

• In morning →
long acting: Injection

• then to control glucose spike after meals

↓

use short acting ones like.

Insulin Afrezza.

{ It's not a stand alone one i.e, it alone can't treat, it's used along with others }

Side effects

① hypoglycemia.

• most dangerous s/e
• easily preventable.

② Hypokalemia.

③ Lipoatrophy.

Oral Anti-Diabetic Drugs.

Dm

FBS > 126 mg/dL. (60-110).

PPBS > 200.

RBS

HbA_1C > 6.5

Oral Drugs.

- Insulin Secretagogues {Insulin secretors}
- other MOA.

Insulin Secretagogues {Insulin secretors}

- they make β cells release Insulin.
- If there is no enough β cells then there is no point in using them.

requirement:

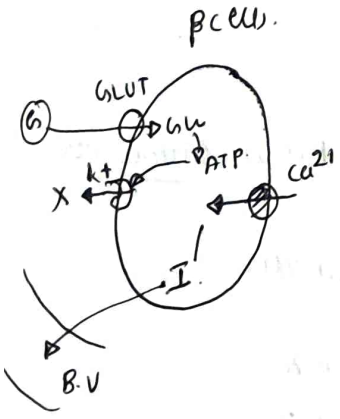
1. min 30% β-cells.
2. can cause hypoglycemia as they cause Insulin release.

other MOA

doesn't require β cells.

doesn't cause hypoglycemia

① Insulin Secretagogues



- most potent stimulant for Insulin release?
  ↓
  hyperglycemia.
- when glucose ↑ in blood glucose enters β cells.

with help of GLUT

- Glucose is metabolized to form ATP.
- there are potassium channels in β cells that are blocked by ATP.
- ATP sensitive K^+ channel.
- K^+ can't go out.
- depolarization occurs
- which leads to Ca^{2+} channel opening & Ca^{2+} entry.
- Complete depolarization
- Insulin released to blood stream.

K, due to K^+ channel blocking, ultimately Insulin is secreted.

- so, Insulin secretagogues are K^+ channel blockers.
- thus they lead to Insulin secretion

kinase are phosphorylation which leads to ⊕ & ⊖ of certain enzymes

- those processes that generate glucose are ⊖.
- those process that ↓ glucose are ⊕

- Glycogenolysis Inhibition ⊖
- Gluconeogenesis Inhibition ⊖
- Glycogenesis activation ⊕
- Glycolysis activation ⊕

Side effect of Biguanides

① Megaloblastic anemia

② lactic acidosis

Mefformin → megaloblastic anemia is more.

phenformin → lactic acidosis is more.

- lactic acidosis is dangerous and with use of phenformin, there is high Risk of lactic acidosis

↓

so not used ✗.

Only mefformin is used.

See, mefformin also causes lactic acidosis.

- normally it's low.
- But in
  - Liver
  - Kidney
  - Lung
  - disorders

  } lactic acidosis ↑↑↑.

so C/I of mefformin.

↓

- Liver, kidney, lung disorders

- anaerobic glycolysis. caused lactic acid ↑.
- lactic acid is usually metabolized in Gluconeogenesis to form glucose.
- But they ⊖ Gluconeogenesis
- so lactic acid is not metabolized

- Kidney → Excrete L.A
- Liver → L.A metabolism
- lung → ↑ anaerobic disease metabolism.

Mefformin.

- they are not insulin secretors.
- 80% β cell not req.
- don't cause hypoglycemia.
- max. HbA1C control drug.
- wt loss or wt neutral.
- never cause weight gain
- so used in obese

MOST
- M - mefformin
- O - obese
- S - sulfonylurea
- T - Thin

DOC in Type II DM

↓

Metformin.

② PPAR-γ ⊕

- peroxisome proliferator activated receptor-γ.

↓

PPAR-γ ⊕

↓

reverse insulin resistance.

- Troglitazone.
- Rosiglitazone.
- Pioglitazone.

↓

- they are PPAR-γ activators

↓

- reverse insulin resistance.

- they cause Na^+, H_2O retention.

↓

worsen CHF, edema, HTN.

- so not used in Heart patients.

- Cause weight gain due to H_2O retention

- Cause Hepatotoxicity. {Troglitazone is not used}.

- Cause osteoporosis.

S/E

- Na^+, H_2O retention.
- Hepatotoxic.
- Osteoporosis.
- Rosi → ↑ MI risk.
  ↓
  so also not preferred.

Pioglitazone ↑ risk of urinary bladder carcinoma in patients were already risk factors are present.

③ α-glucosidase ⊖

↓

- ACARBOSE.

- diet has complex carbs mainly.
- complex carbs are broken down to absorbable forms by α-glucosidase.
- ACARBOSE ⊖ α-glucosidase
- so complex carbs can't be absorbed.
- these complex carbs will be trapped in GIT.
- Bacteria utilize these.
- fermentation of these carbs occurs.
- Gas generates.
- main S/E of acarbose FLATULENCE

- Normally, it's okay.
- But in patients with IBD

↓

it's life threatening. Intestinal rupture

↓

C/I in IBD

If hypoglycemic drug + acarbose is given

ie, Glipizide + acarbose

if hypoglycemia occurs in this case..

- will have to take glucose
- not complex carbs.

- Voglibose
- Miglitol.

Newer Anti Diabetic Drugs.

① Incretin Mimetic Drugs.

- what are incretins?
- while eating food, for preventing glucose spike, Incretin that ↑ insulin release will be released.

K^+ ATPase Blockers) Both.

Sulfonyl ureas

1st Generation

- Chlorpropamide ✓
- Tolbutamide. ✓

2nd Gen

Glipizide

Gliclazide.

Glibenclamide.

Glimepiride.

Sulfonyl ureas

- K_{ATP} blocker
- 30% β cell req
- Causes hypoglycemia
- Cause weight gain so not used in obese patients.

- 1st gen: less potent
- 2nd gen: more potent.

Chlorpropamide.

- Side effect:

① Cholestatic jaundice.

② ↑ ADH release from post pituitary.
↓
Cause dilutional hyponatremia.

Meglitinides. → Both.

D phenyl alanine analogue.

- requires 30% β cell
- Causes hypoglycemia

Nateglinide	Nausea, dizz.
Repaglinide.	

↓
Hepatotoxicity

Exam Question

- what all causes hypoglycemia?

all ending in ide.

causes hypoglycemia

- So we can use it in diabetes insipidus.

- which drug can be used in both DM & DI
↓
chlorpropamide.

③ Cause Disulfiram like reaction.
↓
so don't drink alcohol

- they have normal lvl, but only after meal → hyperglycemia.

so. they are used here!

Tolbutamide.

- follows zero order kinetics.

Meglitinides

- they are short acting. ~ 1 hr.
- so can't be used in sugar control in DM.
- So where is it used?

– In post prandial hyperglycemia.

Other mechanism

AMP kinase ⊕

PPAR-γ ⊕

α glucosidase ⊖

AMP Kinase stimulators
↓
Biguanides

metformin
phenformin.

MOA.

they stimulate AMP Kinase enzyme.

- Glucagon like peptide GLP
- Gastric inhibitory peptide

GLP / GIP

↓

- naturally produced incretin

↓

1. causes Insulin release
2. ↓ gastric emptying → weight loss.
3. activate satiety centre

- good for increasing no. of β cells

↓

↑ formation

↓ apoptosis.

GLP-1 → ↓ glucagon ⊖ — beneficial

GIP → ↓ ⊕ glucagon. — nullify effect.

- mostly we use GLP drugs.

metabolism

GLP-1 → DPP-IV → breakdown.

- we can ↑ GLP 1
- ⊖ DPP-IV.

(a) GLP-1 analogue.

- Exenatide.
- Lixeglutide
- Semaglutide.
- Albiglutide
- Dulaglutide (GLP-2 too.)

- they are secrete Insulin while eating food.
- only meal induced.
- so they don't generally cause hypoglycemia

even though they end in de.

Liraglutide - approved in obesity.

- since they are ↑ they can't be given orally.
- IV given.

- Only peptide that can be given orally

↓

Semapeptide.

GLP-1

↓

GLP-1 receptor ← Glp1 analogues

- **pancreas**
  - ↑ insulin
  - ↓ glucagon
- **Hypothalamus**
  - ↓ apetite
- **Stomach**
  - ↓ gastric emptying

- Increase glucose uptake by muscle
- decrease glucose synthesis by liver.