Thyroid & Antithyroid drug

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Thyroid gland secretes thyroid hormones—

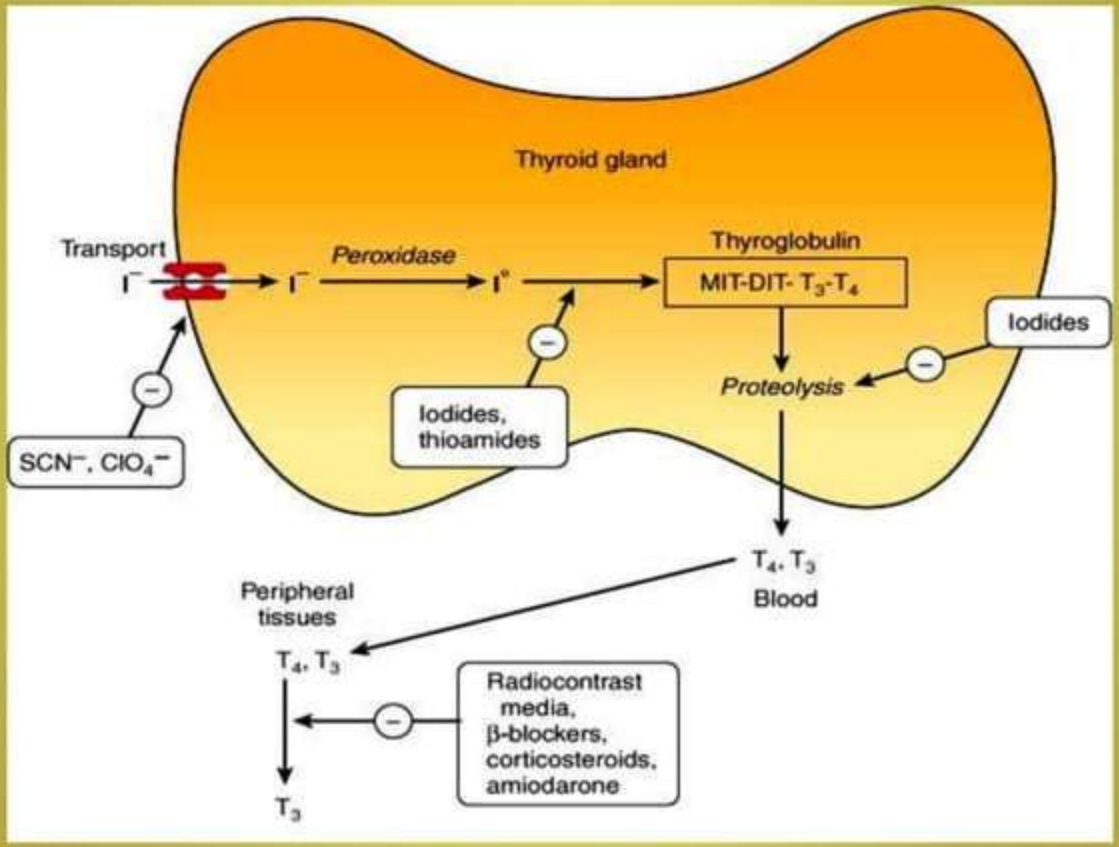
- Triiodothyronine (T_3)
- Tetraiodothyronine (T_4, thyroxine)
- Calcitonin

Pharmacological actions of thyroid hormone

- Metabolic function –
  - CHO metabolism:
    - ↑ glycogenolysis
    - Increase gluconeogensis
    - ↑ glucose absorption from GIT
    - Enhance glycolysis – rapid uptake of glucose by the cell.
  - Net result - ↑ blood glucose level
  - On protein metabolism: ↑ protein catabolism
  - On fat metabolism:
    - ↑mobilization of fat,
    - oxidation of FA → ↑ FFA
  - On BMR: ↑ BMR

- Growth : ↑ growth
- On GIT:
  - ↑ appetite & food intake.
  - ↑ rate of secretion of digestive juice.
  - ↑ motility of GIT → diarrhea often result in hyperthyroidism
- On CVS:
  - Enhance tissue sensitivity to catecholamines
  - ↑cardiac output
- On nervous system:
  - excitable effect.
  - Has role on development of brain in fetal & 1st few weeks of postnatal life
- Muscle weakness due to protein catabolism

Biosynthesis of thyroid hormones



- Synthesis Of Thyroid hormone

Steps

1. Transport of iodide into the thyroid gland by sodium-iodide symporter
2. Iodide is oxidized by thyroidal **peroxidase** to iodine
3. Tyrosine in thyroglobulin is iodinated and forms MIT & DIT- **iodide organification** (MIT- monoiodotyrosine, DIT- Diiodotyrosine)
4. Iodotyrosines condensation within thyroglobulin molecule

   MIT+DIT→T3; DIT+DIT→T4

Cont'd

5. T_4, T_3, MIT & DIT - released from thyroglobulin by exocytosis & proteolysis of thyroglobulin .

6. The MIT and DIT are deiodinated within the gland, and the iodine is reutilized.

- T_4 & T_3 ratio within thyroglobulin - 5:1
- Most of the T_3 circulating in the blood is derived from peripheral metabolism of thyroxine.
- T_3 is three to four times more potent than T_4
- receptor affinity of T_3 about ten times higher than T_4

- **Transport of Thyroid Hormones**

- T_4 and T_3 in plasma - bound to protein - thyroxine-binding globulin (TBG) – Reversibly

- Only about 0.04% of total T_4 & 0.4% of T_3 exist in the free form.

Variable	T_4	T_3
Vd	10L	40L
Extrathyroidal pool	800 mcg	54 mcg
Daily production	75 mcg	25 mcg
Half-life	7 days	1 day
Total Serum level Free Serum level	5-12 mcg/dl 0.7-1.86 ng/dl	70-132 ng/dl 0.23-0.42 ng/dl
Amount bound	99.96%	99.6%
Biologic potency	1	4
Oral absorption	80%	95%
Metabolic clearance/d	1.1L	24L
Daily secretion	93% (80 μg/d)	7% (4 μg/d)

Disease of Thyroid gland

- Hyperthyroidism/Thyrotoxicosis/Grave's disease

- Hypothyroidism –
    - Cretinism (in children)
    - Myxoedema (in adult)

Thyroid drugs

- **DRUGS**

  levothyroxine (L-T4)

  liothyronine (T3)

  liotrix (T4 plus T3)

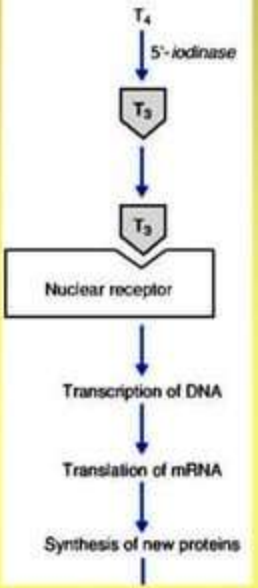
- Pharmacokinetics

Orally easily absorbed; the bioavalibility of T4 is 80%, and T3 is 95%.

Drugs that induce hepatic microsomal enzymes (e.g., rifampin, phenbarbital, phenytoin, and etc) improve their metabolism.

- Mechanism of actions of thyroid hormones

T3, *via its nuclear receptor, induces new proteins generation which produce effects*



GROWTH	CNS	BMR	METABOLISM	CARDIOVASCULAR
Growth formation Bone maturation	Maturation of CNS	↑ Na^+-K^+ ATPase ↑ O_2 consumption ↑ Heat production ↑ BMR	↑ Glucose absorption ↑ Glycogenolysis ↑ Gluconeogenesis ↑ Lipolysis ↑ Protein synthesis and degradation (net catabolic)	↑ Cardiac output

- Synthetic levothyroxine --thyroid replacement and suppression therapy.
- Adv:

  -high stability

  -uniform

  -low cost

  -lack of allergenic foreign protein

  -easy laboratory measurement of serum levels

  -long half-life -7 days (once-daily administration)

  -In addition, T_4 is converted to T_3 intracellularly; thus, administration of T_4 produces both hormones.

  -Generic levothyroxine preparations provide comparable efficacy and are more cost-effective than branded preparations.

- liothyronine (T_3) is 3 to 4 times more potent than levothyroxine.

- Use:

  short-term suppression of TSH.

- Disadv:
  - Shorter half-life -24 hours (not recommended for routine replacement therapy which requires multiple daily doses)
  - Higher cost
  - Difficulty of monitoring.
  - Its greater hormone activity and consequent greater risk of cardiotoxicity- avoided in patients with cardiac disease. It is best.

- Liotrix - Mixture of thyroxine and liothyronine
  .

  -Expensive

  - Oral administration of T_3 is unnecessary ,so combination is not required (levothyroxine preferable)

Clinical use

- Hypothyroidism:

  cretinism & myxedema

Adverse reactions

Overmuch leads to thyrotoxicosis

Angina or myocardial infarction usually appears in aged

Antithyroid drugs

Class	Representative	
Thioamides	propylthiouracil	Inhibitors of thyroxine synthesis
	methylthiouracil	
	methimazole	
	carbimazole	
Anion inhibitors	perchlorate Thiocyanate	inhibitors of iodide trapping
Iodinated contrast media	diatrizoate, iohexol	
Iodides	KI, NaI	inhibition of hormone release
Radioactive iodine β-R blockers	^{131}I propranolol	
Miscellaneous	sulphonamides, phenylbutazone, thiopental sodium, lithium, amiodarone, domarcaprol	

Thioamides

- Prevent hormone synthesis by inhibiting the thyroid peroxidase-catalyzed reactions and blocking iodine organification.
- Block coupling of the iodotyrosines.
- Propylthiouracil and methimazole inhibit the peripheral deiodination of T_4 and T_3 .
- Since the synthesis of hormones is affected, their effect requires 4 weeks.

- Carbimazole cross the placental barrier & are concentrated by the fetal thyroid - caution in pregnancy
- Methimazole associated with congenital malformations
- Secreted in low concentrations in breast milk- safe for the nursing infant.
- Propylthiouracil is preferable in pregnancy:
  - It crosses the placenta less readily
  - Is not secreted in breast milk

Adverse reactions

- Nausea & GI distress
- An altered sense of taste or smell may occur with methimazole
- Maculopapular pruritic rash – most common
- Hepatitis & cholestatic jaundice can be fatal
- The most dangerous – agranulocytosis (granulocyte count < 500 cells/mm^2).

- Use:
  - Thyrotoxicosis: life long
  - Pre operatively to make euthyroid

- Advantage –
  - Less surgical complication
  - If hypothyroidism develops then therapy can be stopped → normal function

- Disadvantage –
  - Long term therapy
  - Not practicable in unconscious patient
  - Toxicity specially in pregnancy

Propylthiouracil	Carbimazole
Thiourea derivative	Imidazole derivative
Less potent	More potent
Highly plasma protein bound	Not so
Less transported across placental barrier & milk	Can cross placental barrier
t½ → 1-2 hours	6-10 hours
Multiple dose needed	Single dose needed
No active metabolite	Methimazole is the active metabolite
$T_4 \rightarrow T_3$ is inhibited	Not inhibited

Anion inhibitors

- Perchlorate, Thiocyanate - block uptake of iodine by the gland through competitive inhibition of the iodide transport mechanism.

- Potassium iodide- block thyroidal reuptake of I^- in patients with iodide-induced hyperthyroidism.

- Potassium perchlorate is rarely used, associated with aplastic anemia

Iodides – inhibitors of hormone release

- M/A:

  They inhibit organification

  Hormone release

  Decrease the size & vascularity of the hyperplastic gland.

- Use:
  - Thyrotoxic crisis
  - Preparation for thyroidectomy(decrease the size & vascularity of the hyperplastic gland)
  - Prophylaxis in endemic goiter

- Adverse effect:
  - Acute : swelling of lip, eye lid, face, angineurotic edema of larynx, fever, joint pain, lymphadenopathy, thrombocytopenia
  - Chronic : ulceration of mucous membrane of mouth, salivation, lacrimation, burning sensation in the mouth, rhinorrhoea, GI intolerance

Iodinated contrast media

- These drugs rapidly inhibit the conversion of T_4 to T_3 in the liver, kidney, pituitary gland, & brain.

- relatively nontoxic.
- Adjunctive therapy in the treatment of thyroid storm
- use as alternatives when iodides or thioamides are contraindicated.

- Their toxicity is similar to that of iodides.
- safety in pregnancy is undocumented

Radioactive iodine

- ^{131}I is - used for treatment of thyrotoxisis

- Administered orally in solution as sodium ^{131}I, it is rapidly absorbed, concentrated by the thyroid, & incorporated into storage follicles → emits β particles & X rays → β particles damage the thyroid cells → thyroid tissue destroyed by piknosis → replaced by fibrosis

- Use
  - Diagnostic purpose → 25-100μ curies in thyroid function test
  - Therapeutic use → 3-6 milli curies in toxic nodular goiter, graves disease, thyroid Ca.

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- Advantage :
  - Easy administration
  - Effectiveness
  - Low expense
  - Absence of pain
  - In patient who have indication of operation but want to avoid operation
  - Once treated no chance of recurrence
- Disadvantage :
  - Hypothyroidism
  - Latent period of getting response (8-12 weeks)

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- C/I : Pregnancy
  Young patients
  Hyperdynamic circulation

- Adverse effect :
  - Hypothyroidism
  - crosses the placenta to destroy the fetal thyroid gland & is excreted in breast milk (baby become hypothyroid)

Adjuncts to Antithyroid Therapy

- Hyperthyroidism resembles sympathetic overactivity
- Propranolol, will control tachycardia, hypertension, and atrial fibrillation
- Diltiazem, can control tachycardia in patients in whom beta-blockers are contraindicated
- Barbiturates accelerate T_4 breakdown (by enzyme induction) and are also sedative

Thyroid malfunction and Pregnancy

- In a pregnant hypothyroid patient- dose of thyroxine should be adequate.
- This is because early development of the fetal brain depends on maternal thyroxine.
- If thyrotoxicosis occurs, propylthiouracil is used and an elective subtotal thyroidectomy performed.

Class	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
Antithyroid Agents			
Thioamides			
Propylthiouracil (PTU)	Inhibit thyroid peroxidase reactions block iodine organification inhibit peripheral deiodination of T4 and T_3	Hyperthyroidism	Oral duration of action: 6–8 h delayed onset of action *Toxicity:* Nausea, gastrointestinal distress, rash, agranulocytosis, hepatitis,hypothyroidism
Iodides			
Lugol solution Potassium iodide	Inhibit organification and hormone release reduce the size and vascularity of the gland	Preparation for surgical thyroidectomy	Oral acute onset within 2–7 days *Toxicity:* Rare (see text)
Beta blockers			
Propranolol	Inhibition of adrenoreceptors inhibit T4 to T_3 conversion (only propranolol)	Hyperthyroidism, especially thyroid storm adjunct to control tachycardia, hypertension, and atrial fibrillation	Onset within hours duration of 4–6 h (oral propranolol) *Toxicity:* Asthma, AV blockade, hypotension, bradycardia
Radioactive iodine ^{131}I (RAI)			
	Radiation destruction of thyroid parenchyma	Hyperthyroidism patients should be euthyroid or on blockers before RAI avoid in pregnancy or in nursing mothers	Oral half-life 5 days onset of 6–12 weeks maximum effect in 3–6 months *Toxicity:* Sore throat, sialitis, hypothyroidism

Class	Mechanism of Action	Indications	Pharmacokinetics, Toxicities, Interactions
Thyroid Preparations			
Levothyroxine (T4) Liothyronine (T_3)	Activation of nuclear receptors results in gene expression with RNA formation and protein synthesis	Hypothyroidism	maximum effect seen after 6–8 weeks of therapy

Thank you for your attention