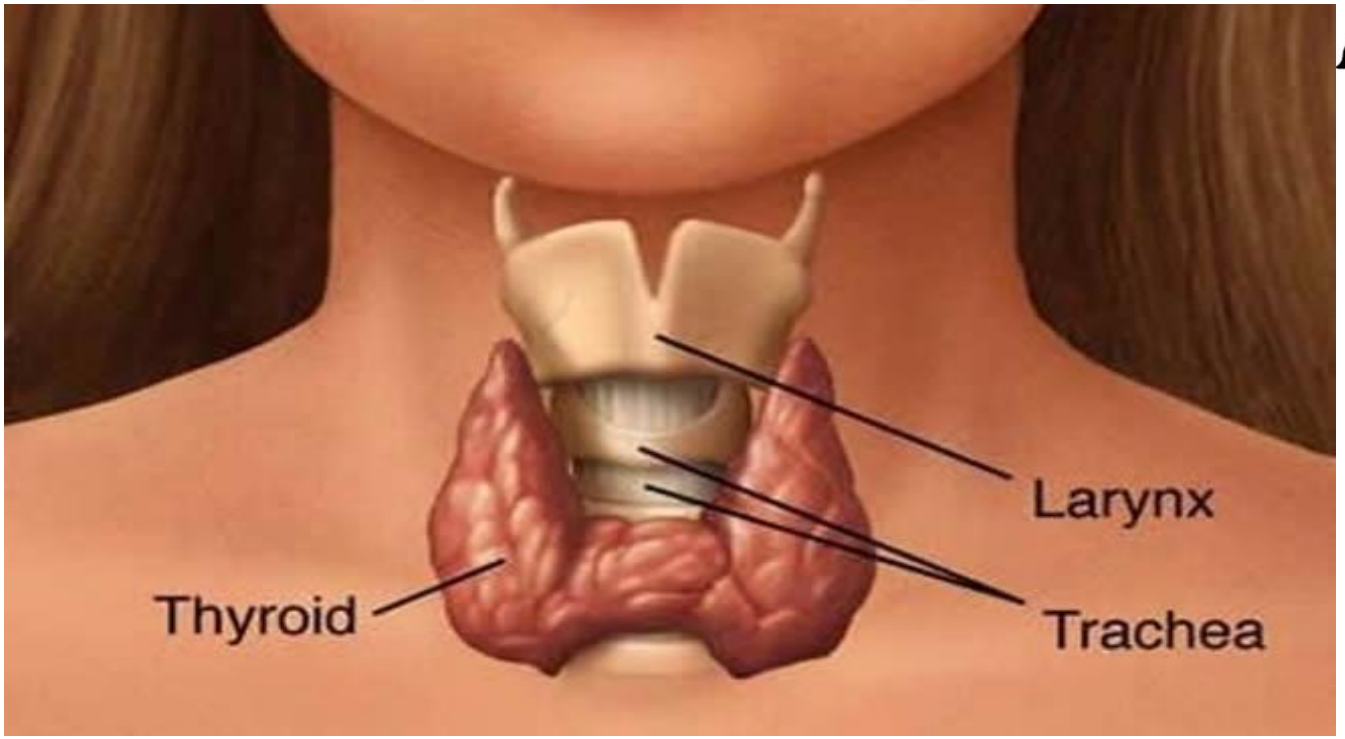
Thyroid hormones and anti-thyroid drugs



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- The thyroid gland facilitates **normal growth** and **maturation** by maintaining a level of metabolism in the tissues that is optimal for their normal function.

- Two major thyroid hormones:

1) triiodothyronine (T3), the more active form

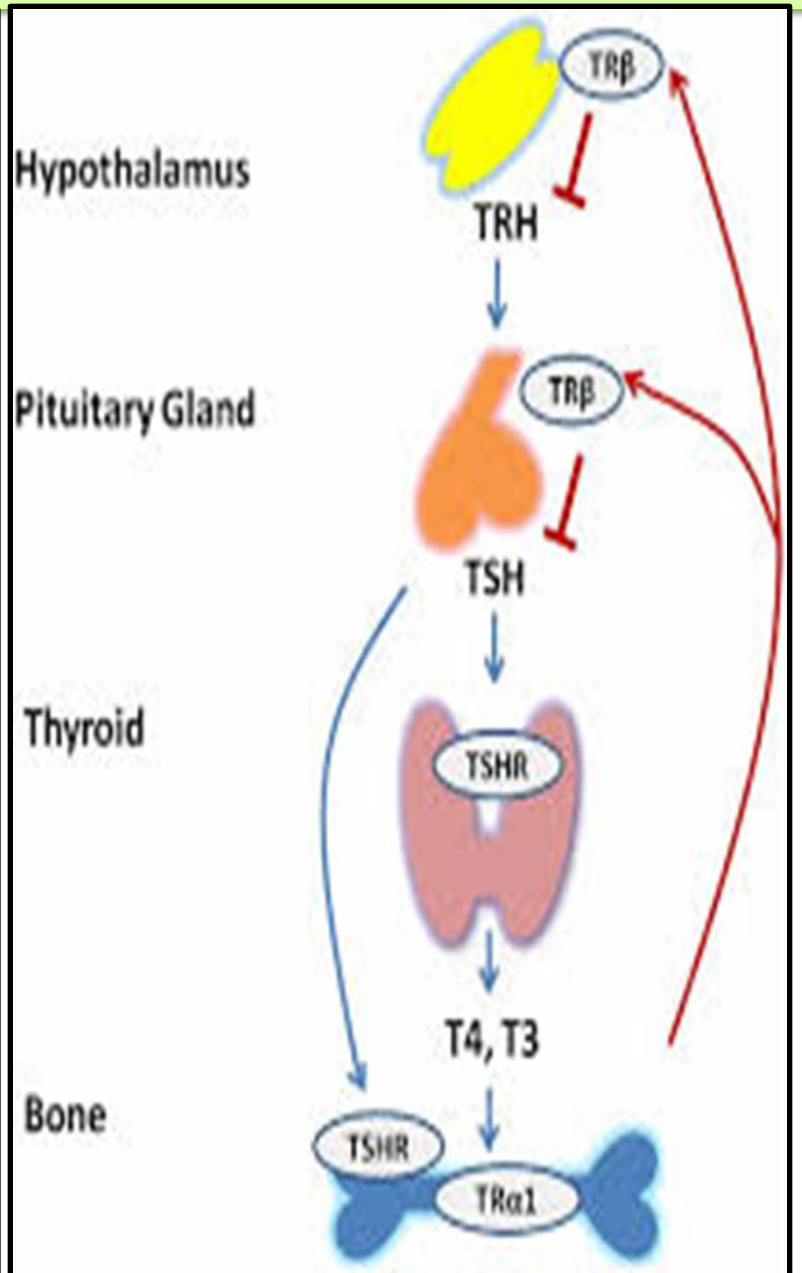
2) thyroxine (T4).

1-Hypothyroidism

2- hyperthyroidism

Control of thyroid hormones

- Hypothalamus produces (**TRH**) that releases **TSH** from the pituitary gland.
- TSH helps in trapping of iodine, increasing the size and vascularity of the gland.
- **Autoregulation**: via regulation of iodine uptake.
- **Thyroid-stimulating immunoglobulins,** as in Graves' disease



Formation of thyroid hormones

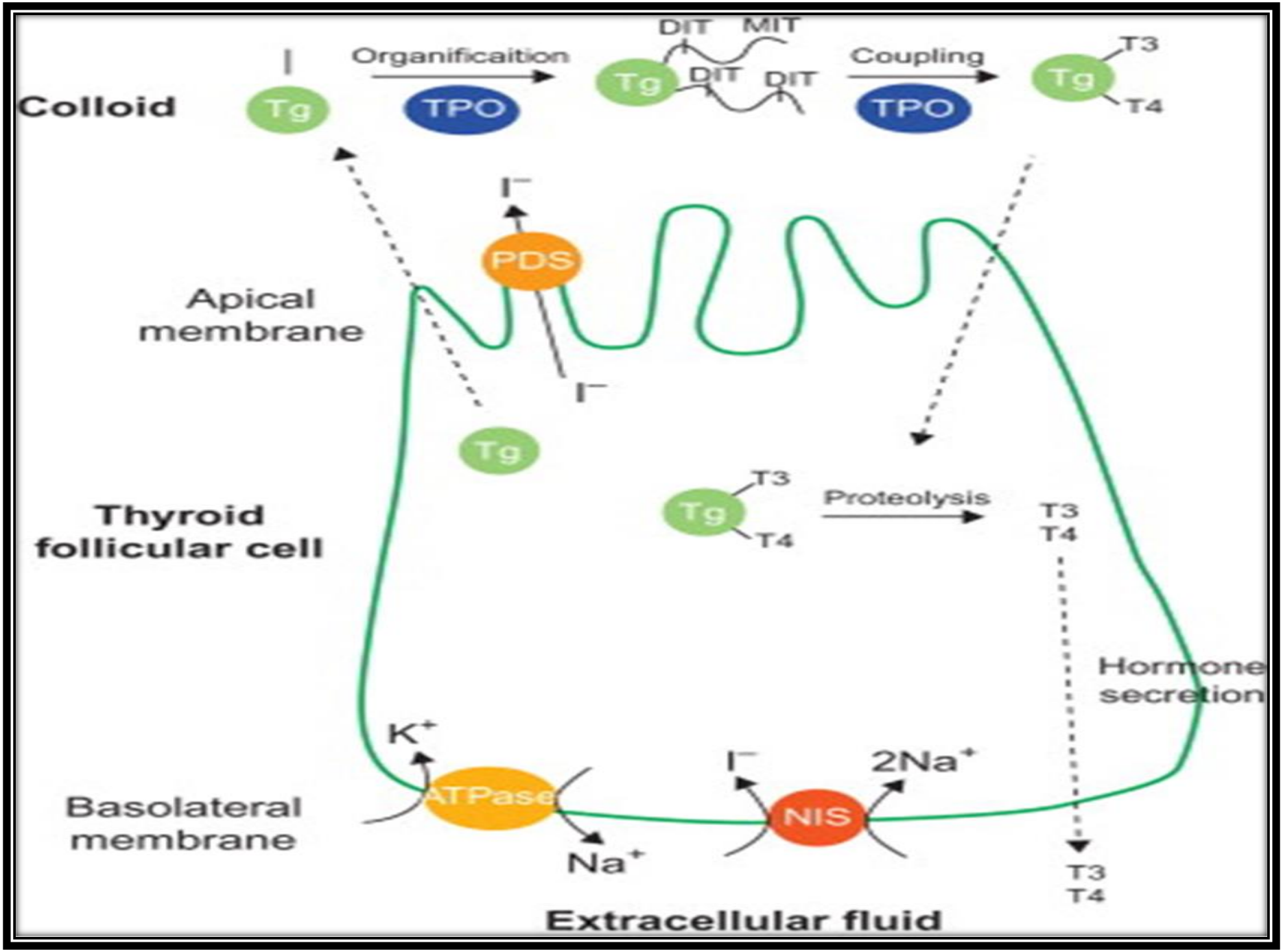
1 . T.S.H. stimulates iodide **trapping**. This process requires energy obtained from ATP and is decreased by anaerobic conditions and digitalis.

2 . Iodide is converted into iodine by the **peroxidase enzyme (oxidation),** then iodine is added to tyrosine to form mono and di-iodotyrosine (MIT& DIT) →**organification**.

3 . **Coupling** of iodotyrosines will form Tetra-iodothyronine (T4) and Tri-iodothyronine (T3).

4 . T4 and T3 are linked with thyroglobulin **(storage** in gland follicles). Then the proteolysis of thyroglobulin **by the protease enzyme** releases T3 and T4.

5 . In the blood and peripheral tissues, T4 is converted to **T3 (more active).**


Colloid
I
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Organificaition
TPO
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DIT
DIT
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TPO
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T3
T4
I⁻
PDS
Apical membrane
I⁻
Tg
Thyroid follicular cell
Tg
T3
T4
Proteolysis
T3
T4
Hormone secretion
K⁺
ATPase
Basolateral membrane
Na⁺
I⁻
2Na⁺
NIS
T3
T4
Extracellular fluid

HYPOTHYRODISM

Diagnosis

Symptoms

Level of free T4, T3

TSH

Preparations and dosage

1 . d-Thyroxin (synthetic): potent hypocholesterolemic

The dextrorotary isomer of the thyroid hormone, known for its ability to lower cholesterol without significantly raising metabolism.

2 . Levothyroxin sodium (L-thyroxine) (T4): 100 ug/day

- Long duration and slow onset
- absorption orally is complete and stable (non-peptide hormone).
- **Used in myxoedema and cretinism**.
- The dose increased in pregnancy up to **150 ug/day**

3 . Liothyronine sodium (T3): 25 ug/day.

- It is highly potent
- short duration, and a more rapid onset than T4.
- It is mainly **used in myxoedema coma**

4 . Liotrix:

T4 + T3 (4:1) **similar to** normal thyroid hormone.

Uses of thyroid hormones

1 . Hypothyroidism due to: Prolonged use of anti-thyroid drugs, after thyroidectomy, Destruction of the gland by a radioactive isotope, or Hashimoto's disease.

2 . Cretinism (hypothyroidism in early infancy):

L-Thyroxin 10µg/kg daily if under 6 months. The dose differs according to age.

3 . To suppress T.S.H. secretion, which causes thyroid enlargement in:

Simple goiter and Thyrotropin-dependent carcinoma

4 . Hypercholesterolemia:

- Use d-thyroxin in an euthyroid patient.
- Use L-thyroxin in a hypothyroid patient

5. Infertility and amenorrhea

6. Resistant depression

1. Before starting treatment: Serum TSH, Free T4 (± Free T3), Weight, age, cardiac status, Pregnancy status, and History of coronary artery disease or arrhythmia.

2. Treatment protocols:

	Dose	Precautions
Primary hypothyroidism in healthy adults	• 1.6 µg/kg/day orally once daily	• Take on an empty stomach 30–60 minutes before breakfast, Same time every day, avoid iron, calcium, and antacids within 4 hours.
Elderly patients or cardiac disease	• Initial dose: 12.5–25 µg/day • Increase: By 12.5–25 µg every 4–6 weeks according to TSH	• Start low to avoid precipitating angina or arrhythmia.
Congenital hypothyroidism (cretinism)	• Start immediately after diagnosis : 10–15 µg/kg/day	• Rapid normalization of T4 and TSH to prevent neurodevelopmental delay
Pregnancy	• Requirement increases during pregnancy. Increase total dose by 25–30% once	• pregnancy confirmed Keep TSH in trimester-specific normal range

3. Monitoring protocol: TSH after 6–8 weeks of starting or changing dose, Then every 6–12 months once stable

Desired target: TSH ≈ 0.5–4 mIU/L

Side effects
(The manifestations of hyperthyroidism)

1 . Intolerance to heat: warm flushed patient

2 . Precipitation of angina pectoris: as it increases H.R, BP, and may lead to extrasystoles and atrial fibrillation.

3 . Weight loss: **Due** to the increased basal metabolic rate.

4 . Tremors: fine tremors of the hand due to increased neuromuscular excitability.

5 . GIT: diarrhea and increased appetite.

6 . Eye signs: lid retraction, exophthalmos.

HYPERTHYRODISM

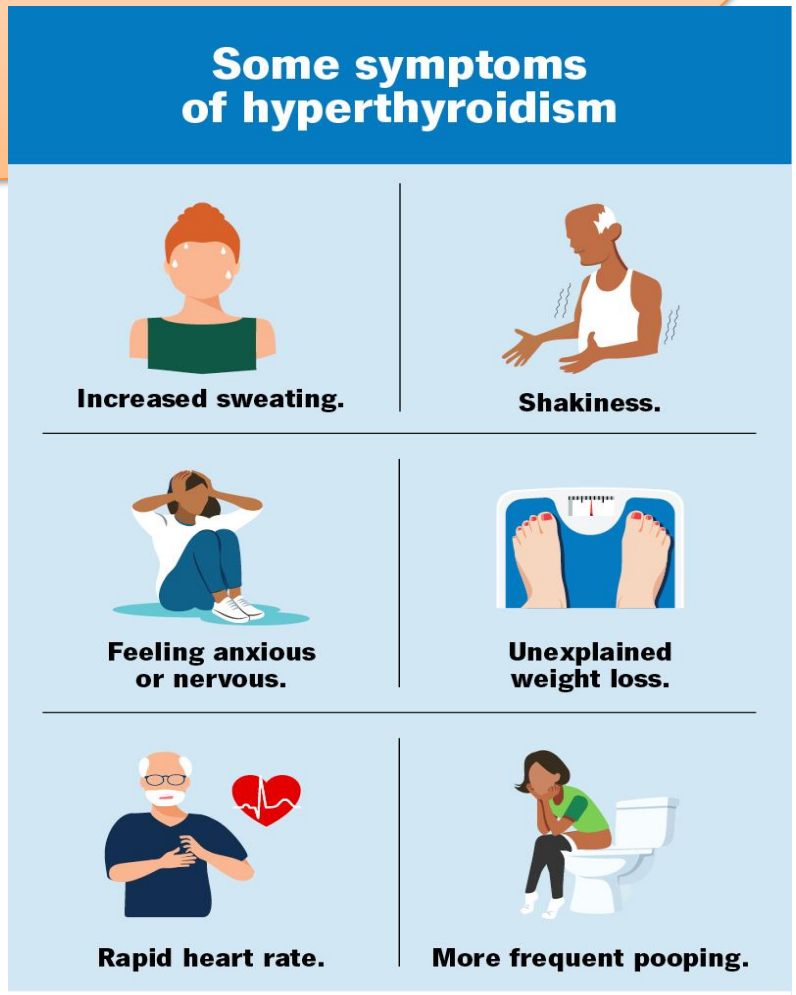
Diagnosis

Symptoms

Level of free T4, T3

TSH

Scan tch 99



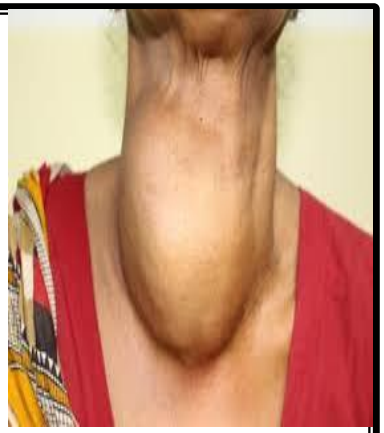
(A)Medical treatment

Indications

1. Primary cases (young), Thyrotoxic pregnant ladies
2. Premedication before thyroidectomy, Complicated cases: H.F.

Contraindications:

1. Huge goiter.
2. Suspicion of malignancy.



(B) Surgery (thyroidectomy)

Indications:

Very large goiter, Suspicion of malignancy, Failure of medical therapy, Compression symptom.

Preoperative preparation:

- Carbimazole: till euthyroid state.
- Lugol's iodine (5% I2 in 10% KI 15 drops t.d.s for 10-15 days): ↓size & vascularity of the gland.
- Propranolol.

Medical Treatment of Hyperthyroidism

I. Anti-thyroid drugs:

1. **Thioamides**
2. **Ionic inhibitors,** e.g., K+ perchlorate
3. **Iodide in high concentration**:e.g., Lugol's iodine. It can suppress the thyroid
4. **Radioactive iodine,** which emits B-rays and damages the gland.

II. sympathetic depressants:

1. propranolol
2. Guanethidine (eye drops)

(1) Thioamides

- **Propylthiouracil:** 100 mg t.d.s. (4-8 weeks) till control of symptoms, then 50 mg once for 12-18 months. Onset 1h, duration 1.5, highly bound to plasma protein, does not pass the placenta, not secreted in milk.
- **Methimazole:**10 mg t.d.s (4-8 weeks) then 5 mg once for 12-18 months.
- **Carbimazole (drug of choice):** 5-10 mg t.d.s. (prodrug which is converted to methimazole) 12-18 months.

Pk:

- Rapidly **absorbed** and reaches the peak plasma level after 1 hour.
- **Distributed** all over the body can pass the placental barrier (contraindicated in pregnancy) and the BBB.
- **Carbimazole** is **metabolized** in the liver → **Methimazole** (active)
- **Excreted** in urine and milk (contraindicated in lactation).

Inhibit the formation of thyroid hormones by

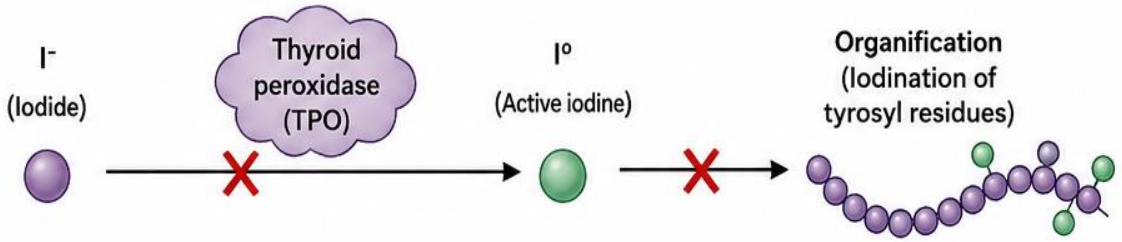
1. Interfere with the oxidation of iodide ion by inhibiting the peroxidase enzyme and inhibiting iodine organification.
2. Interfere with iodination of tyrosyl residues of thyroglobulin and a decrease in MIT and DIT.
3. Inhibit coupling of lodo-tyrosyi residues (MIT and DIT) to form iodothyronine (T3, T4), leading to an increase in T.S.H. release, which causes an **increase in the size and vascularity of the gland.** Also, releasing of exophthalmos-producing factor causes increasing of **exophthalmos**

4 . **Prophylthiouracil** inhibits the peripheral deiodination of T4 to T3.

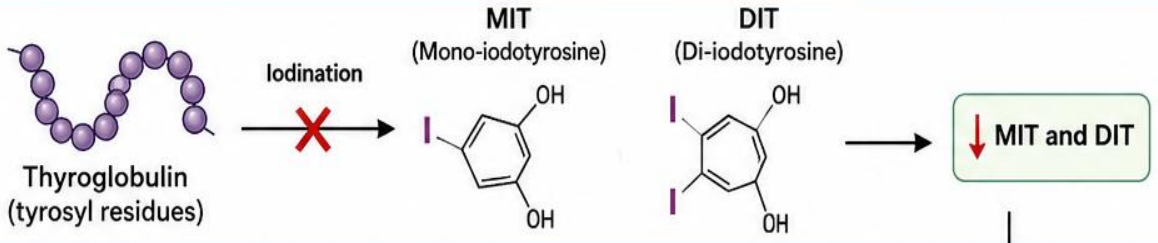
- The onset of these agents is **slow (3-4 weeks) ???.**

MOA: Inhibits the formation of thyroid hormones

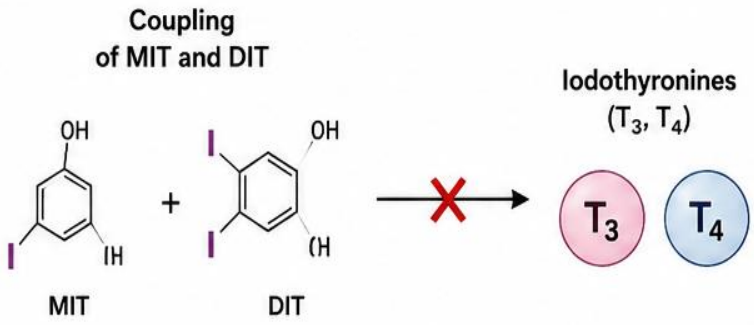
1 Interfere with the **oxidation of iodide** ion by inhibiting the peroxidase enzyme and inhibiting **iodine organification**.



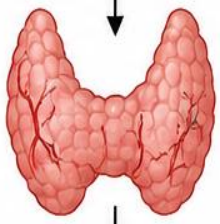
2 Interfere with **iodination** of tyrosyl residues of thyroglobulin and a decrease in MIT and DIT.



3 Inhibit **coupling** of Iodo-tyrosine residues (MIT and DIT) to form iodothyronine (T_3, T_4), leading to an increase in T.S.H. release, which causes an increase in the size and vascularity of the gland. Also, the exophthalmos-producing factor causes increasing of exophthalmos



↑ T.S.H. release

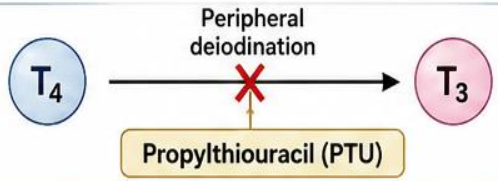


Increase in the size and vascularity of the gland (Goiter)

Exophthalmos-producing factor

Increasing of exophthalmos

4 Propylthiouracil inhibits the **peripheral deiodination** of T_4 to T_3.



The onset of these agents is slow (3–4 weeks)

Uses:

1. Treatment of mild hyperthyroidism.
2. With radio-iodine to hasten recovery.
3. **Propylthiouracil** in thyroid crisis

Toxicity and side effects

1 . **Agranulocytosis**: Usually, during the first few months of therapy, a sore throat or fever **most dangerous**. So, a frequent blood count may be needed.

2 . **Allergy:** skin rash, fever.

3 **. Pain**, headache, and stiffness in joints: sometimes nausea

4 . Hepatitis, nephritis, hepatotoxic (PTU).

5 . In lactation and pregnancy: they cause cretinism (Not used in pregnancy and lactation).

Propylthiouracil is the only thioamide allowed during **pregnancy**.

6 . **Increase the** size and vascularity of the gland and sometimes increase exophthalmos.

(2) Iodide

Preparations:

- Lugol's solution = 5% iodine + 10% potassium iodide
- Sodium and potassium iodide tablets
- Potassium iodide solution

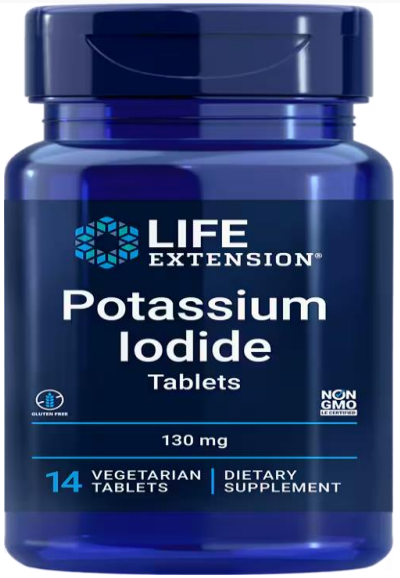
Rapid onset &short duration (The maximal effects are obtained after 10-15 days)

- **Mechanism of action:** (High iodide concentration)

a. "Acute Wolff–Chaikoff effect": Excess iodide enters thyroid cells, inhibits thyroid peroxidase, ↓ iodide oxidation↓ organification, ↓ MIT and DIT formation, ➞ So hormone synthesis drops immediately.

b. Reduces endocytosis of thyroglobulin, Inhibits proteolytic enzymes (lysosomal proteases) inside thyroid cells → This inhibit of T3 and T4 release into blood

c. Decreases the responsiveness of thyroid cells to TSH ↓, cAMP signaling inside thyroid cells. Further suppresses hormone synthesis and release.



The result will be:

1) The B.M.R. may fall

2) Reduction of size and vascularity of the gland

3)Accumulation of the colloids (thyroglobulin) in the follicle.

d. Escape phenomenon:

After ~10–14 days: The thyroid "escapes" from inhibition.

It reduces iodide uptake by downregulating NIS, so hormone synthesis may return to near normal. This is why iodine is only a short-term treatment.

Uses (**short-term only)**

1. **Preoperative** before thyroidectomy to reduce the size and vascularity of the gland (7-10 days).

2. In the treatment of **thyroid crisis** after Propylthiouracil and Propranolol.

3. Saline expectorant in **chronic bronchitis**

Side effects

1. Iodism.

Metallic taste in the mouth, Excessive salivation, Burning sensation in the mouth/throat, Rhinitis (runny nose), Conjunctivitis (red eyes, tearing), Cough / bronchial irritation, Skin rash.

- **Management**

Stop iodine exposure immediately

Supportive treatment:

- Antihistamines for skin/mucosal symptoms
- Symptomatic care (eye drops, hydration)
- In thyroid dysfunction: Treat hypo- or hyperthyroidism as needed

2. With continuous treatment, the **Hyperthyroidism may return** due to increasing of T.S.H., so, restricted only to preoperative

(3) Radioactive Iodine

Pharmacokinetics:

- **I-131** is rapidly trapped by the thyroid gland and deposited in the colloid of the follicles, from which it is slowly liberated

Action

- The effect appears 6-12 weeks after administration.
- Two types of radiation are emitted
  - **β-rays** in large doses: destructive with low penetration
  - **Gamma rays** in small doses: non-destructive with high penetration.

Preparations:

- Sodium iodide I131 (Iodotope), Solution (oral or IV.), Capsules (oral)
- I132 is used for diagnosis of disorders of thyroid (t1/2 = 2 h).

Indications:

1. Failure of medical treatment.
2. Patient unfit for surgery.
3. Age above 40 years.
4. Recurrence after thyroidectomy.
5. Malignant thyroid secreting excess T4

5. Propranolol or antithyroid drugs may be given with radio I-131 to **hasten recovery**.

6. **I-131** (used in thyroid cancer – testing thyroid function).

Side effects:

1. Hypothyroidism.

Contraindications:

1. During pregnancy, lactation & childhood.
2. Huge goiter & retrosternal goiter.

N.B. Give anti-thyroid drugs for the next 2-3 months. Why?

(4) Ionic Inhibitors
[Potassium perchlorate]

•They block the **uptake of iodide (NIS)** into the gland → ↓**synthesis** of thyroid hormones (T3 and T4), is not used nowadays because cause aplastic anemia, agranulocytosis, and nephrotoxicity.

II- Sympathetic depressant

(1) Beta-blockers: Propranolol (Oral & IV)

Advantages:

1. No **I.S.A.**
2. **Protects the heart** from tachycardia, angina & arrhythmia of hyperthyroidism.
3. **Pass BBB** ↓anxiety & tremors of hyperthyroidism.
4. **↓ Conversion** of T4 to the more active T3

Uses

- Orally in **temporary relief** of manifestations till control of hyperthyroidism by anti-thyroid drugs or thyroidectomy, or radioactive iodide.
- IV in the **emergency treatment** of **hyperthyroidism crisis**

(2) Guanethidine

It decreases sympathetic stimulation to muscles that cause eyelid retraction.

Treatment of exophthalmos

- **Guanethidine eye drops**→↓exophthalmos.
- **Corticosteroids & surgical decompression** may be needed.

Drugs used in the treatment of thyroid crisis (thyroid storm): (rare life-threatening increase in severity of hyperthyroidism)

1. **Propyl thiouracil.**
2. **Lugol's iodine↓ release of T4 & T3**
3. **Propranolol. (i.v)**
4. **Hydrocortisone (i.v)→↓release of T4, T3&↓ conversion T4→ T3.**
5. **<u>Symptomatic</u>: antipyretic, sedative.**
6. **<u>Treatment of the cause</u>: e.g. stress, infection**


Thank You