Thyroid disorders

Pharmacology
SEM III

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Learning objectives:

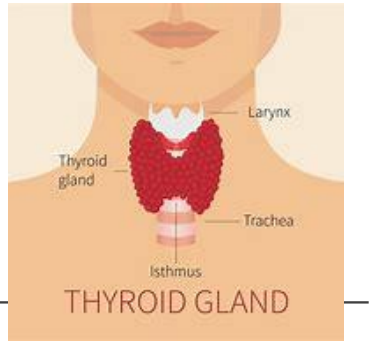
By the end of this lecture, the student will be able to:

- Describe major pathways involved in the biosynthesis & control of thyroid hormones.
- List the main therapeutic options used for treating hyperthyroidism
- Understand & Compare between of different antithyroid drugs (MOA and side effects)
- List indications & contraindications of RAI.
- Understand and compare between T3 & T4 as replacement therapies for hypothyroidism (MOA & kinetics).
- list main lines of treatment of hyper/hypo-thyroid crises.

Lecture outline:

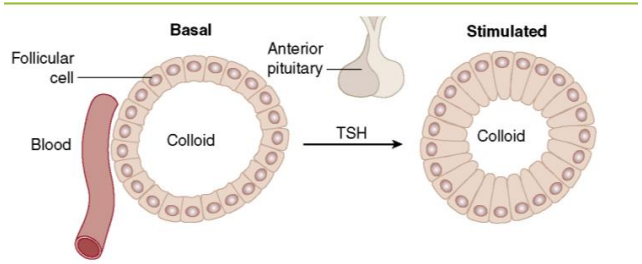
- Overview:
  - Control, biosynthesis & secretion of thyroid hormones.
- Hyperthyroidism
  - Case study: Graves's disease
  - Antithyroid drugs

Overview

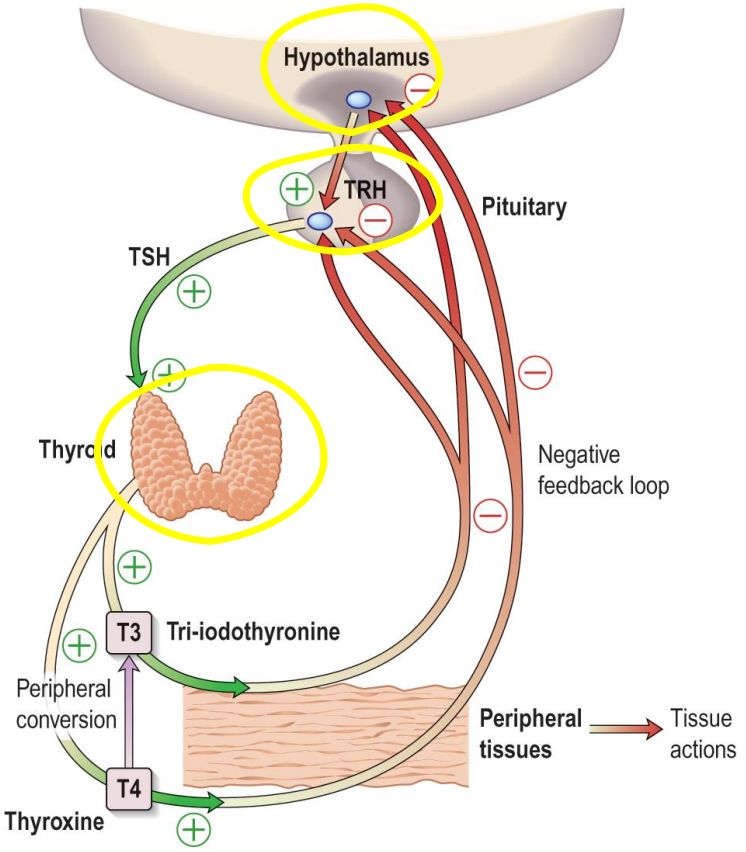


1. The thyroid gland <u>controls level of tissue metabolism</u> → facilitates normal growth and maturation
2. The two major thyroid hormones are **<u>triiodothyronine (T3; the most active form) and thyroxine (T4).</u>**
3. ↓ secretion of thyroid hormone → **<u>hypothyroidism</u>** → results in bradycardia, cold intolerance, and mental and physical slowing.
4. ↑ secretion of thyroid hormones → **<u>hyperthyroidism</u>** → can cause tachycardia, loss of body weight, nervousness, tremors, and heat intolerance.

Overview

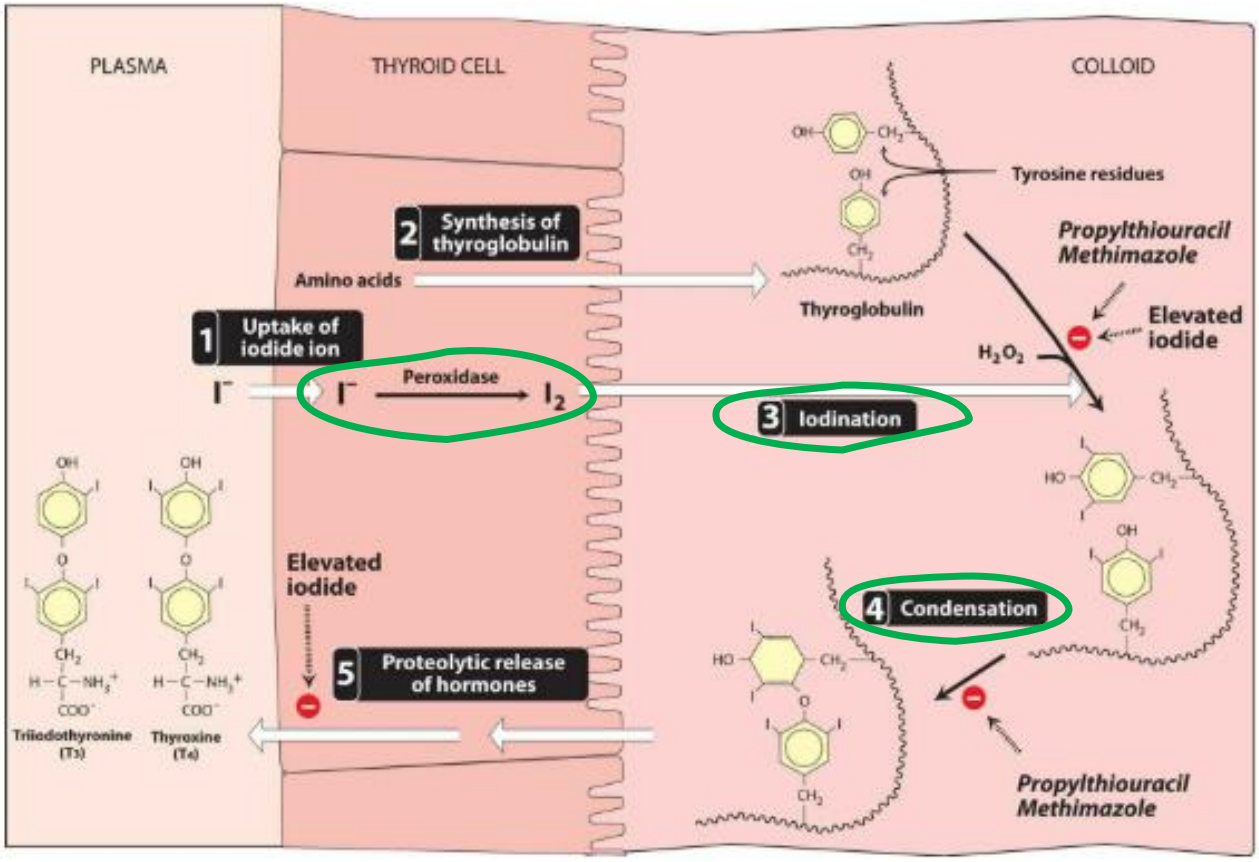


1. The thyroid gland is made up of multiple follicles → each follicle consist of a single layer of epithelial cells surrounding a lumen filled with colloid; **thyroglobulin** (the storage form of thyroid hormone).
2. Thyroid function is controlled by the thyroid stimulating hormone (TSH), which is synthesized by the anterior pituitary.
3. TSH secretion is controlled by the hypothalamic thyrotropin-releasing hormone (TRH)
4. TSH action → stimulation of **iodide (I–) uptake** by the thyroid gland.



Overview

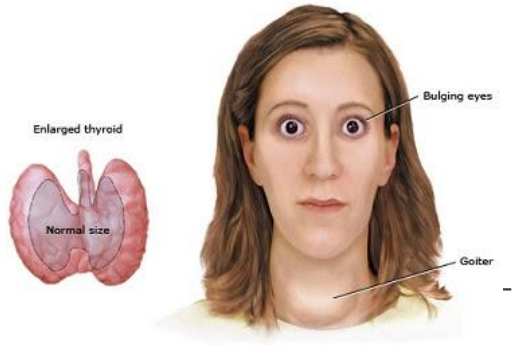
1. Iodide (I^-) is up taken from the circulation by the thyroid follicular cells
2. **Peroxidase → catalyzes oxidation of iodide (I^-) to iodine (I^2).**
3. Iodine (I^2) then crosses into the colloid; thyroglobulin.
4. **Peroxidase → catalyzes iodination of tyrosine residues of thyroglobulin** → monoiodothyronine & diiodothyronine
5. **Peroxidase → catalyzes coupling of mono- & diiodotyrosine** → form triiodothyronine (T3) and tetraiodothyronine (T4, thyroxine).
6. Thyroglobulin is stored as colloid in thyroid follicles
7. When stimulated by TSH → thyroglobulin undergoes proteolysis → release of T4 (80%) and T3 (20%)
8. In peripheral tissues → **T4 is converted to T3 (more active)** by 5'-deiodinase enzyme



Hyperthyroidism/Thyrotoxicosis

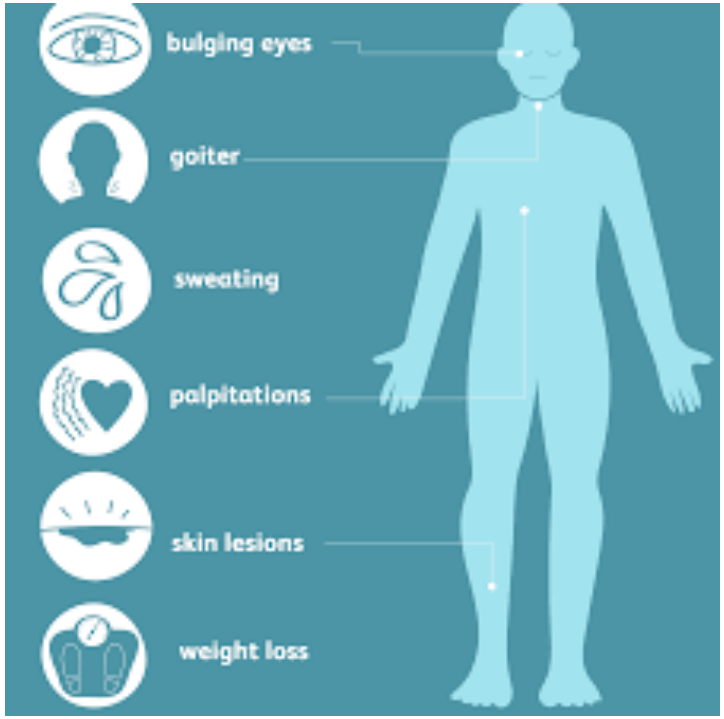
Hyperthyroidism/Thyrotoxicosis

Graves' disease → An autoimmune disease → The most common cause of thyrotoxicosis



The clinical manifestations resulting from:

1. ↑ Secretion of the thyroid hormones → ↑ physiologic effects of T3 &T4 (a generalized ↑ of all metabolic processes).
2. Sympathetic overactivity.
3. ↓ TSH levels are due to negative feedback.



3 treatment modalities → used to control hyperthyroidism of Graves' disease

Antithyroid drugs

→ are the favored therapy

- **Thioamides (Methimazole and propylthiouracil)**
- Administered for a prolonged period → **1 to 2 years**
- **+ propranolol** → at the onset of treatment → β-adrenergic receptor blocker → ↓ symptoms of sympathetic overactivity → ↓ tachycardia and hypertension in symptomatic patients.

Radioactive iodine therapy (I^{131})

In the US, radioactive iodine → the main therapy

SE → 80% to 90% of patients become **hypothyroid** → require lifelong thyroid hormone replacement.

CI →

- **Pregnant/breast feeding** women
- Ptns with **thyroid cancer**
- Ptns with **moderate to severe Graves-related eye disease**
- Ptns with **heart disease (unless controled)**

Surgery

Subtotal or total thyroidectomy
Least favored therapy

Treatment of choice for →

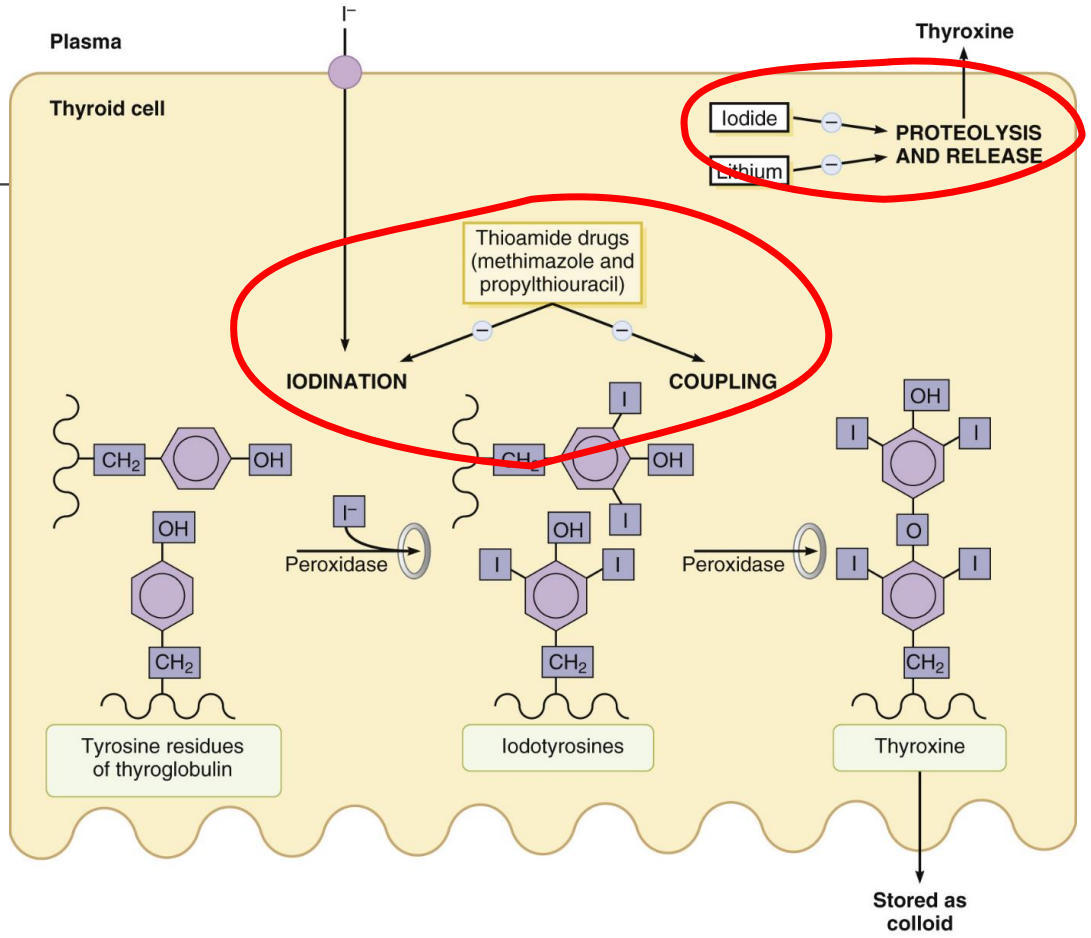
- ptns with **very large** gland causing pressure symptoms
- ptns with **large multinodular** glands
- sometimes in females who **desire pregnancy** within the next year
- Ptns with **thyroid cancer**
- Ptns with **moderate to severe Graves-related eye disease**

SE →

- **Hypothyroidism**
- Transient/Permanent **hypoparathyroidism**
- **Recurrent laryngeal nerve paralysis**

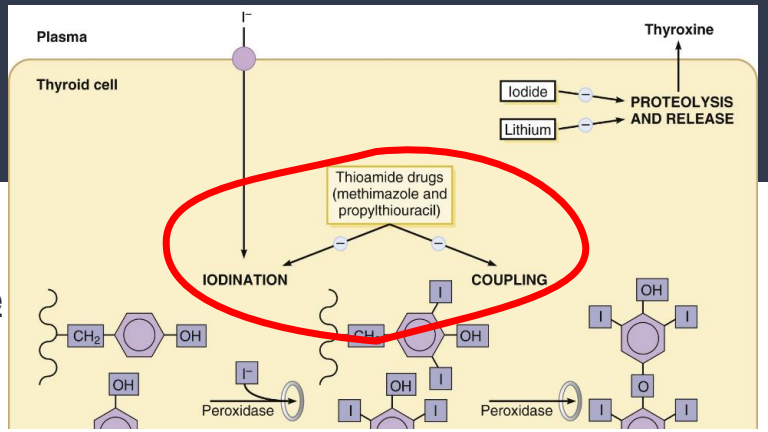
Antithyroid drugs

1. **Thioamide drugs** → ↓ synthesis of thyroid hormones
2. **Iodide salts** → ↓ release of thyroid hormones
3. **Beta (β)-blockers** → ↓ symptoms of sympathetic overactivity → control CVS symptoms of hyperthyroidism



Thioamides

Methimazole & propylthiouracil (PTU)



MOA →

- **Methimazole & PTU** → accumulated in thyroid gland → **inhibit peroxidase enzyme** → inhibit **iodination of tyrosine and coupling iodotyrosine** → block synthesis of T4 & T3
- **PTU** (but NOT methimazole) → **inhibits peripheral conversion of T4 to T3**

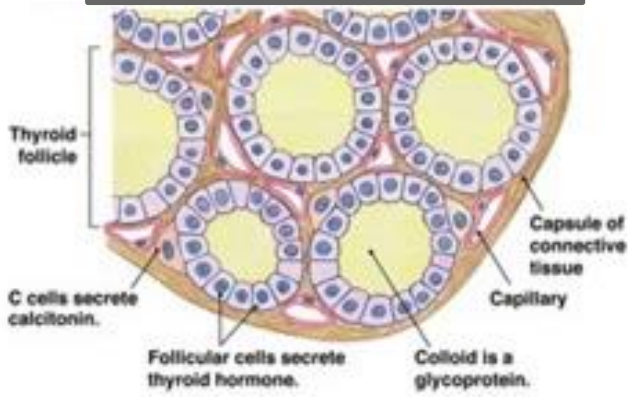
  N.B. Effects of thioamides are **delayed** → **takes 4 - 8 weeks** till the circulating T3 & T4 levels return to normal

  Start with higher doses → patient is euthyroid (remission of Graves' disease) → then ↓ gradually at monthly intervals to reach the steady-state dose

  Duration of treatment → **12 to 24 months**

  About 45% of patients → achieve a permanent remission.

Time needed for glandular hormone stores to deplete



Indications →

- **To induce remission** in Graves' disease
- **Preoperative** → to ↓ T4 & T3 levels before surgery or RAI treatment.

Thioamides

Methimazole & propylthiouracil (PTU)

Preferred line of therapy

	Methimazole →	***PTU →***
MOA	• Block T4 & T3 synthesis	• Same + ***inhibits the peripheral conversion of T4 to T3.***
Efficacy	• ***More effective***	• Less effective
t1/2	• ***Longer → 8 h*** → ***once*** daily	• Short → 2 h → 2-3 times/day
Plasma protein binding	• Not bound → ***crosses placenta*** and appears in breast milk →	• ***80% bound***
Use in pregnancy	• x3 more likely to cause birth defects (esp. during 1st trimester of pregnancy)	• ***Drug of choice*** just before and ***during 1st trimester of pregnancy.***
Liver toxicity	• Lower risk	• ***Higher*** risk
Leukopnea	• Lower risk	• ***Higher*** risk

Thioamides

Methimazole & propylthiouracil (PTU)

SE →

1. **Rash, arthralgia, and fever** → in up to 5% of ptns.
2. **Lupus erythematosus–like syndrome, hepatitis, or GIT distress** → less frequently
3. **Benign and transient leukopenia** → mild ↓ in WBCs count
4. **Severe agranulocytosis** → granulocyte count < 250/μL.

- Reversible → managed by stopping treatment
- **PTU > methimazole**
- **Rare** → 0.1-0.3% of patients
- Develops **during the first 3 months** of therapy
- Monitor with complete blood count
- Advice patient to contact physician if he experiences fever, malaise, sore throat, or other flu like symptoms

5. **Hepatotoxicity and fatal liver failure**

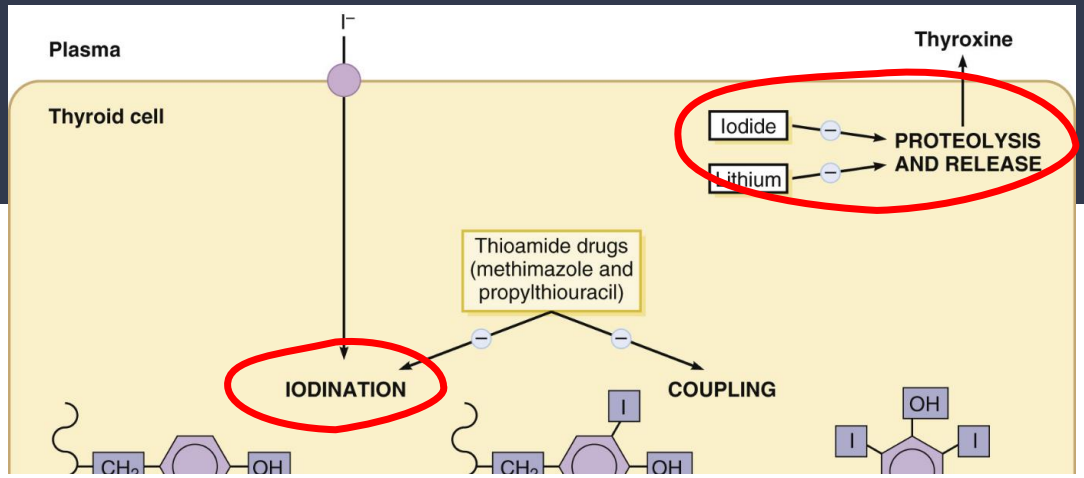
- **PTU > methimazole**
- 1% of ptns
- Monitor for liver toxicity for **the first 6 months.**

FDA recommends that **PTU be reserved for patients who are allergic or intolerant of methimazole** except in pregnant lady ?????.

Iodide salts

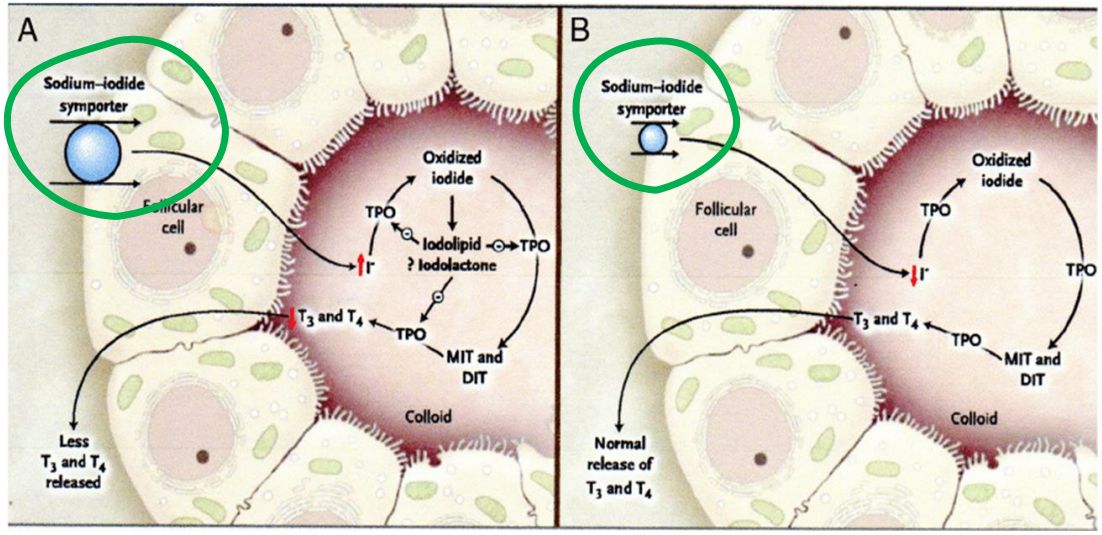
Potassium iodide (KI)

Lugol's solution (5% KI & 5% elemental iodine)



MOA →

- Rapidly ↓ **iodination** of tyrosine residues of thyroglobulin (Acute Wolff-Chaikoff Effect)
- ↓ **Release of T4 & T3** from thyroid gland → most important effect.
- **Rapid** symptomatic improvement → **within 2 to 7 days** after starting iodide
- Effect is **limited to several weeks** → the thyroid gland escapes from the inhibitory effects of iodides



Indications → a short-term therapy to →

- Treat patients with **thyroid storm**
- **Preoperative** → for 7 - 14 days → to ↓ size & vascularity of thyroid gland
- **After RAI** treatment → KI for 3 - 7 days

Iodide salts

Potassium iodide and Lugol's solution

SE →

Usually mild

- Skin rashes and other **hypersensitivity** reactions
- **Salivary & lacrimal gland swelling**, **sore gums & teeth** → **iodism**
- **Metallic taste**
- **Ulcerations of mucous membranes**

β-adrenergic receptor blockers

N.B → ***Drugs that ↓ peripheral conversion of T4 to T3***
→ 2 Ps → **propranolol & PTU + corticosteroids**

Hyperthyroidism (↑ T3 & T4) →

- ↑ density of β receptors
- ↑ conversion of T4 to T3

This leads to a generalized state of sympathetic overactivity (Tachycardia, Palpitaions, sweating, anxiety & tremors)

MOA of β-blockers in hyperthyroidism →

- β-blockers → **propranolol & atenolol** → used to **↓ CVS symptoms** associated with hyperthyroidism
- **Propranolol**, but **NOT** other beta blockers → **↓ peripheral conversion of T4 to T3**
- If beta blockers are CI → **Calcium channel blockers** can be used → ***diltiazem***

Q1

Which option is most appropriate for a patient with newly diagnosed hyperthyroidism **in the first trimester of pregnancy**?

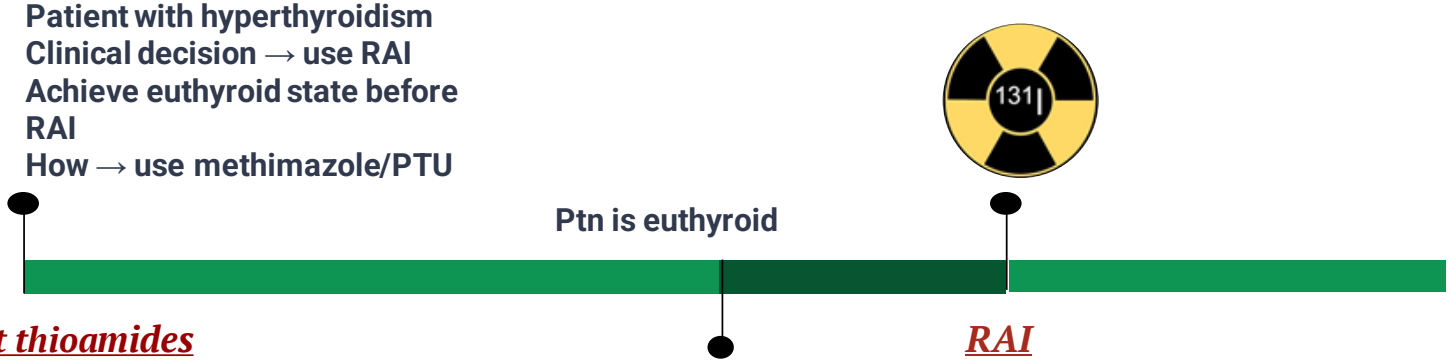
A. Methimazole
B. Propylthiouracil (PTU)
C. Radioactive iodine
D. Surgical removal of the thyroid

Radioactive iodine (I^{131}).. (RAI)

Single dose → safe, effective & cheap

Treatment with RAI is ABSOLUTELY CI in pregnant women → it destroys fetal thyroid tissue.

1. Patient with hyperthyroidism
2. Clinical decision → use RAI
3. Achieve euthyroid state before RAI
4. How → use methimazole/PTU



MOA→

I^{131} → colourless & tasteless → **orally** administered → rapidly absorbed from the gut and **selectively concentrated in the thyroid gland** → **emits low penetration radiation that destroy thyroid tissue** → T4 & T3 levels gradually return to normal ***over several weeks (4-8 weeks).***

Adjunctive therapy to I^{131} →

1. **Thioamide drugs** → **(before & after)** → should be **stopped *3-7 days*** before RAI & reinstituted 3-7 days after it.
2. **Beta blockers** → to control **symptoms** of hyperthyroidism till full effect to RAI is achieved.
3. **Iodide salts (KI)** → used **after** RAI to ↓ radioactive thyroid hormone release

   should **NOT be used before** RAI → because nonradioactive iodide would compete with I^{131} for uptake by thyroid gland.

Radioactive iodine (I 131).. (RAI)

SE →

- 80% to 90% of ptns become **hypothyroid** → require lifelong thyroid hormone replacement.

CI→

- **Pregnant** women → but it is NOT teratogenic if pregnancy occurs after I^{131} therapy.
- **Young children**
- Ptns with **thyroid cancer**
- Ptns with moderate to severe **Graves-related eye disease**
- Ptns with **heart disease** (unless controlled)

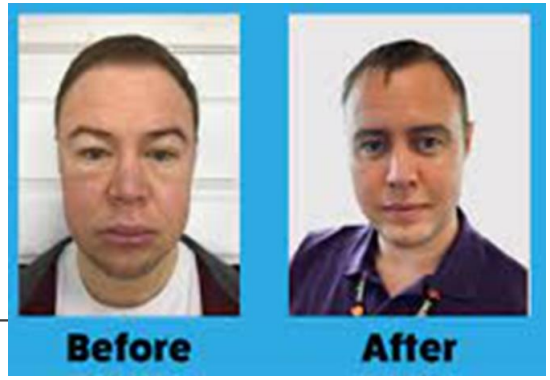
Severe hyperthyroidism (Thyroid storm)

An acute, life-threatening complication of hyperthyroidism.

1. **Inhibition of thyroid hormone synthesis:**
   - **PTU** 800 mg initially → followed by 200 - 300 mg 4 times daily.
   - **PTU is preferred over methimazole** → has the added benefit of blocking peripheral conversion of T 4 to T 3
2. **Inhibition of stored thyroid hormone release:**
   - **KI** → important to **administer PTU/methimazole 1 hr before the iodide** → to prevent iodide incorporation in the synthesis of additional thyroid hormone
3. **IV Corticosteroids** → to inhibit peripheral conversion of T4 to T3
4. **Suppression of CV effects of thyroid hormone:**
   - Oral/IV **propranolol**, cardioselective; metoprolol, diltiazem
5. **Fluid replacement**
6. Correct underlying precipitating event.
7. Treatment of **hyperthermia** with cooling blankets or acetaminophen

Hypothyroidism/Myxedema

Hypothyroidism/Myxedema

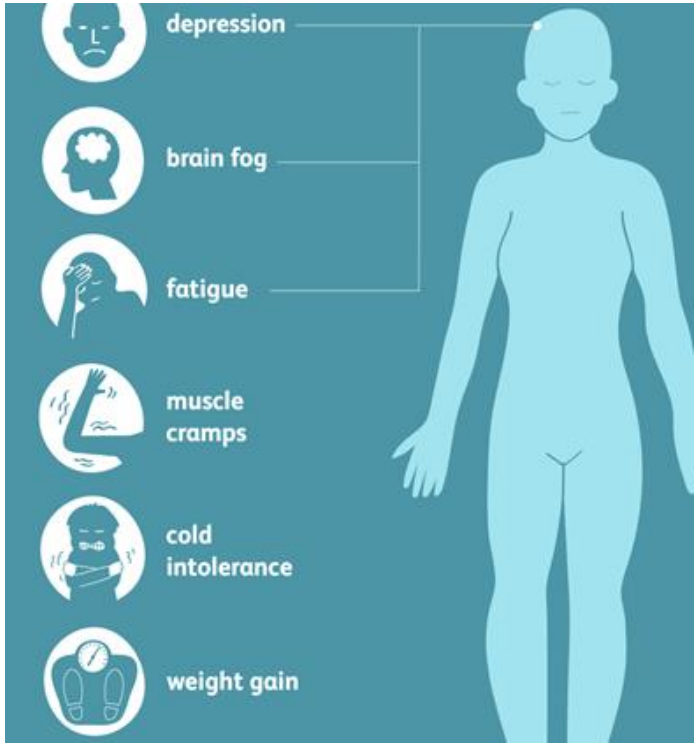


A clinical syndrome caused by deficiency of thyroid hormones

Adult-onset hypothyroidism is mostly due to auto-immune disease

Iatrogenic causes of hypothyroidism →

- I^{131} therapy
- Thyroidectomy
- Iodine deficiency/excess
- Lithium
- Amiodarone



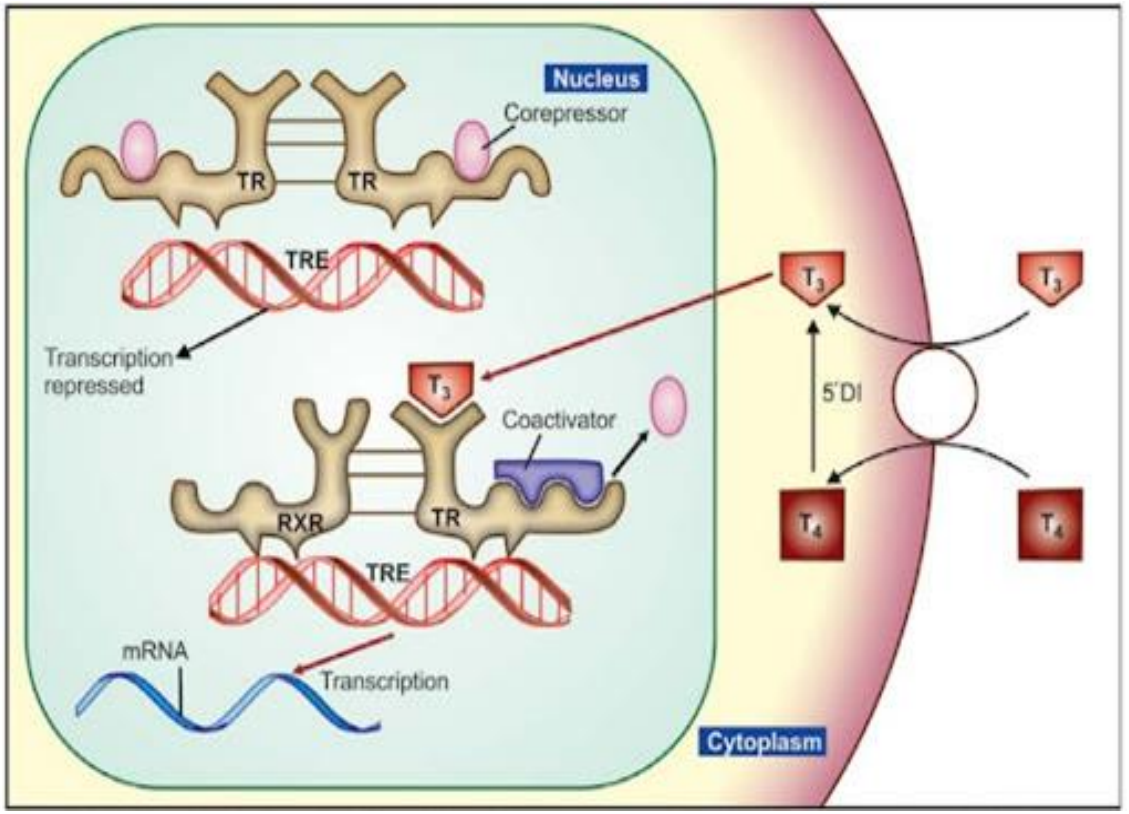
Replacement therapy

thyroid hormone preparations → levothyroxine (T4), liothyronine (T3)

MOA→

T4 → the major circulating form of thyroid hormone → in peripheral tissues → deiodinase (5'DI) enzyme convert T4 to T3 → the more biologically active form of thyroid hormone.

T3 → **bind to nuclear receptors, thyroid hormone receptors (TRs)** → **control of transcription of genes** involved in many metabolic processes → maintain normal growth & development



Replacement therapy for hypothyroidism

thyroid hormone preparations → levothyroxine (T4), liothyronine (T3)

Levothyroxine

Synthetic T4 → drug of choice for thyroid hormone replacement

- Relative potency → ***1***
- t1/2 → ***8 days***
- ***Once*** daily administration
- Coffee, Ca+2 preparations, Al+3-antacids→↓ absorption of levothyroxine → recommended to be taken on empty stomach
- Response to levothyroxine therapy → monitored after 6 - 8 weeks → ***clinical improvements & ↓ serum TSH levels***

Liothyronine

Synthetic T3

- Relative potency → ***4***
- t1/2 → ***1 day***
- ***1-3*** times daily

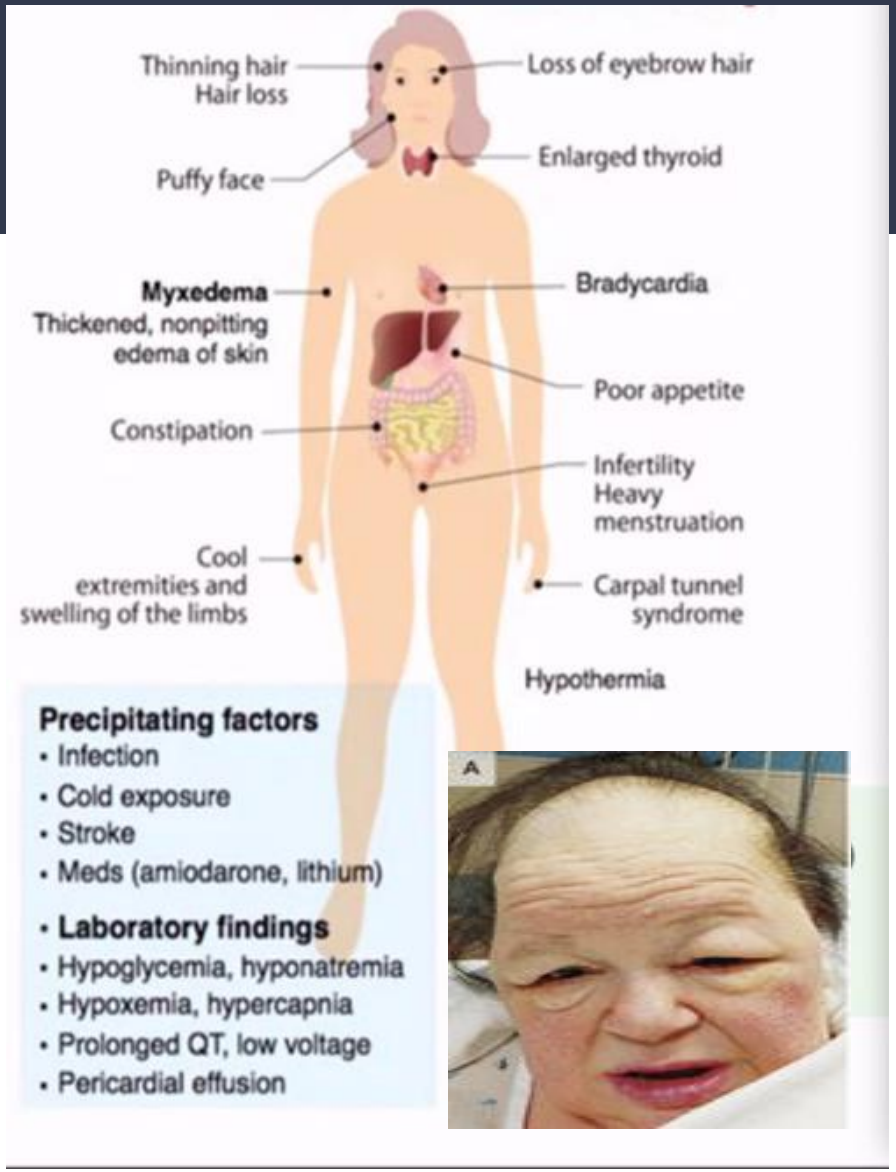
Levothyroxine → often start with lower dose, esp. in old ptns & those with long-standing/severe hypothyroidism → then gradually increase dose → to prevent excessive stress on the CVS

Myxedema coma

Severe hypothyroidism → metabolic decompensation & mental status change

Carries ***a high mortality rate*** despite treatment

1. High dose (500 - 800 µg ***IV***) ***levothyroxine*** → loading dose → followed by 100 µg/day of levothyroxine
2. ***Hydrocortisone*** (100 mg ***IV*** three times daily)
3. ***IV fluids.***
4. Correct underlying precipitating event.
5. Supportive →
   a. ***Respiratory*** assistance
   b. Treatment of ***hypothermia*** with warming blankets



Q2

A 29-year-old female has **a TSH of 13.5 mIU/L** (normal 0.5 to 4.7 mIU/L). Which agent is most appropriate to treat the TSH abnormality?

A. Levothyroxine
B. Liothyronine
C. Liotrix
D. Propylthiouracil

Q3

A patient was recently placed on levothyroxine. Which of her medications may affect the levothyroxine dosage requirements?

A. Bromocriptine
B. Calcium carbonate
C. Metoprolol
D. Vitamin D

References:

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