بسم الله الرحمن الرحيم

Thyroid hormones & anti-thyroid drugs

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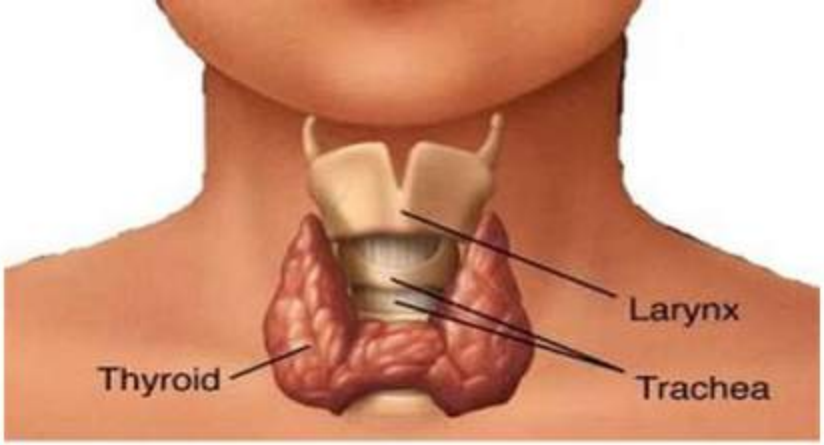
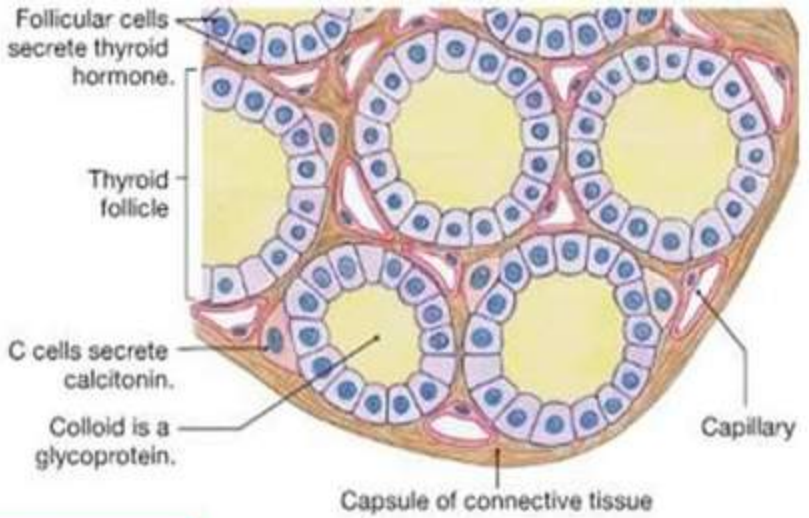
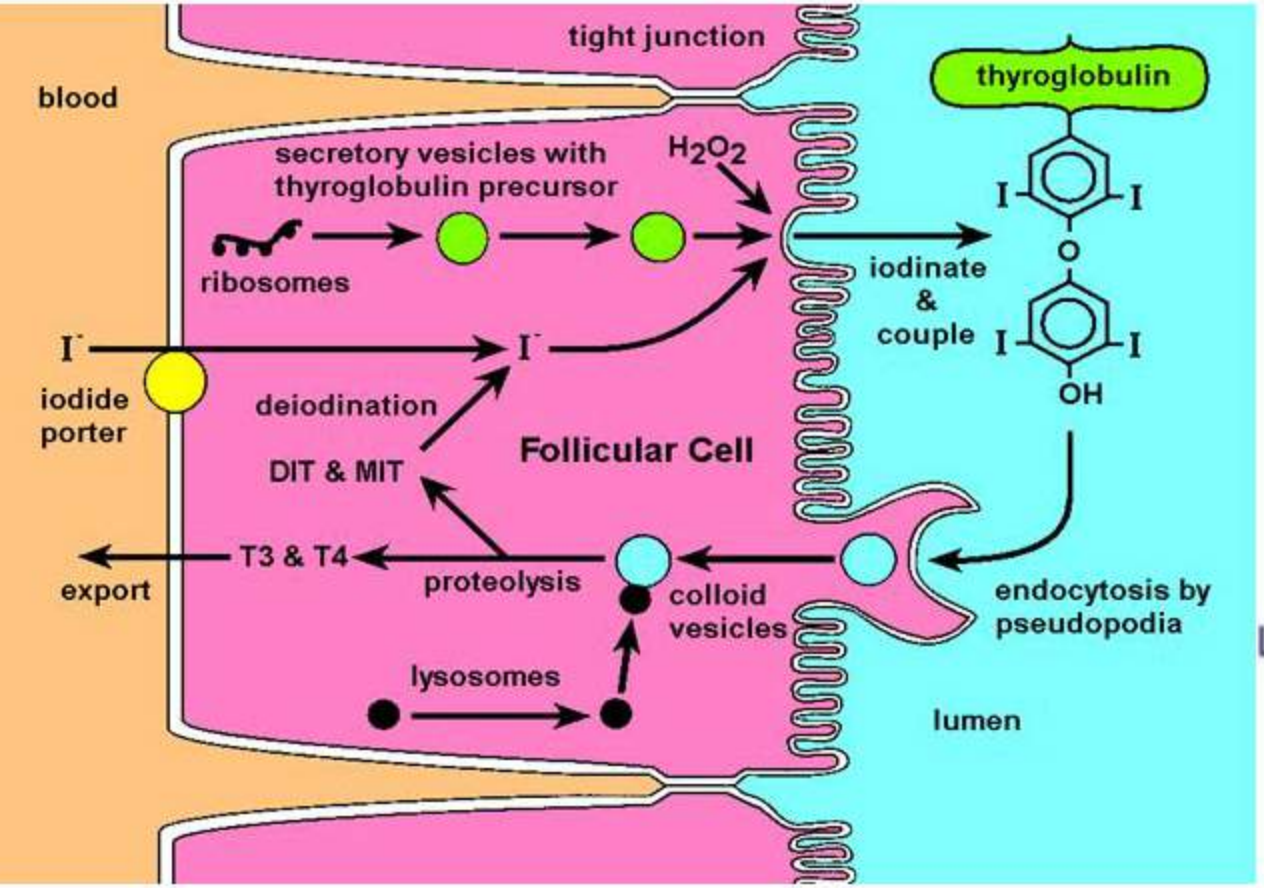
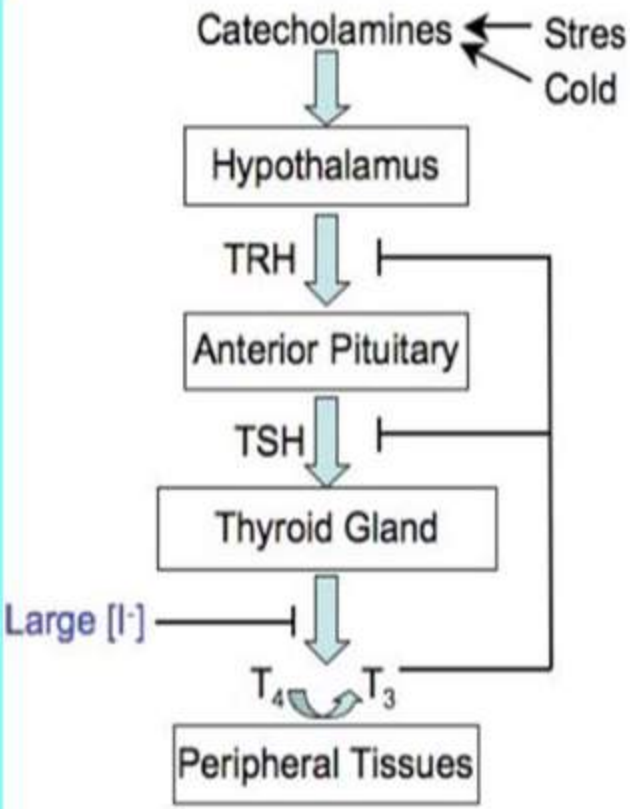
2025


Larynx
Thyroid
Trachea


Follicular cells secrete thyroid hormone.
Thyroid follicle
C cells secrete calcitonin.
Colloid is a glycoprotein.
Capillary
Capsule of connective tissue


tight junction
blood
thyroglobulin
secretory vesicles with thyroglobulin precursor
H_2O_2
ribosomes
iodinate & couple
I^-
iodide porter
deiodination
DIT & MIT
Follicular Cell
T3 & T4
export
proteolysis
colloid vesicles
endocytosis by pseudopodia
lysosomes
lumen
OH


Catecholamines
Stres
Cold
Hypothalamus
TRH
Anterior Pituitary
TSH
Thyroid Gland
Large [I-]
T_4
T_3
Peripheral Tissues

Regulation of thyroid hormone

1- TRH

- The Hypothalamic Thyrotropin-releasing hormone (**TRH**) acts on the anterior pituitary to stimulates synthesis and secretion of the **TSH**.
- Neurogenic inputs cause pulsatile secretion of TRH.
- **Alpha-adrenergic agonists** & **ADH** are **stimulatory**, while **Alpha-adrenergic blockers** are **inhibitory** for TRH secretion.
- The most important regulator of TRH is the negative feedback by **T3.**

- **Exogenous TRH** can promote secretion of **TSH, GH** & **prolactin**.
- **Endogenous TRH** is not a physiologic releasing factor for GH or prolactin (except during pregnancy).

2-TSH

- TSH secretion exhibits a **circadian rhythm** (**higher at night).**
- **T3** only (not T4) produces negative feedback to TSH.
- Pituitary TSH secretion is also **inhibited by dopamine** & **somatostatin**.

3-Other regulators of thyroid hormone

1-Glucocorticoids can:

- ↓ synthesis of TRH & ↓ responsiveness of thyrotrophic cells to TRH.
- ↓ plasma T3 levels by ↓ cellular deiodinase activity

2- Excess iodide:

Wolff-Chaikoff Effect: Inhibition of thyroid hormone release & synthesis in response to acute iodine excess; it is a transient effect, lasting **26-50 hours**.

This inhibition wears off (escape) when the gland adapted the high iodide I (through ↓ Na+/I- symporter production→ ↓amount of iodide transported into the thyroid follicle regardless of the high serum iodide levels).

In **Graves' disease**, **minimal iodide excess** will trigger Wolff-Chaikoff inhibition of hormone synthesis and release **without** inducing the subsequent escape-from-inhibition response (so treatment with high iodide provides **dramatic recovery).**

Synthesis of thyroid hormones: Iodination of tyrosine and coupling.

Release of thyroid hormones (under TSH control):

The released thyroxin (T4) to triiodothyronine (T3) ratio is **(4:1).**

Transport of T3 and T4:

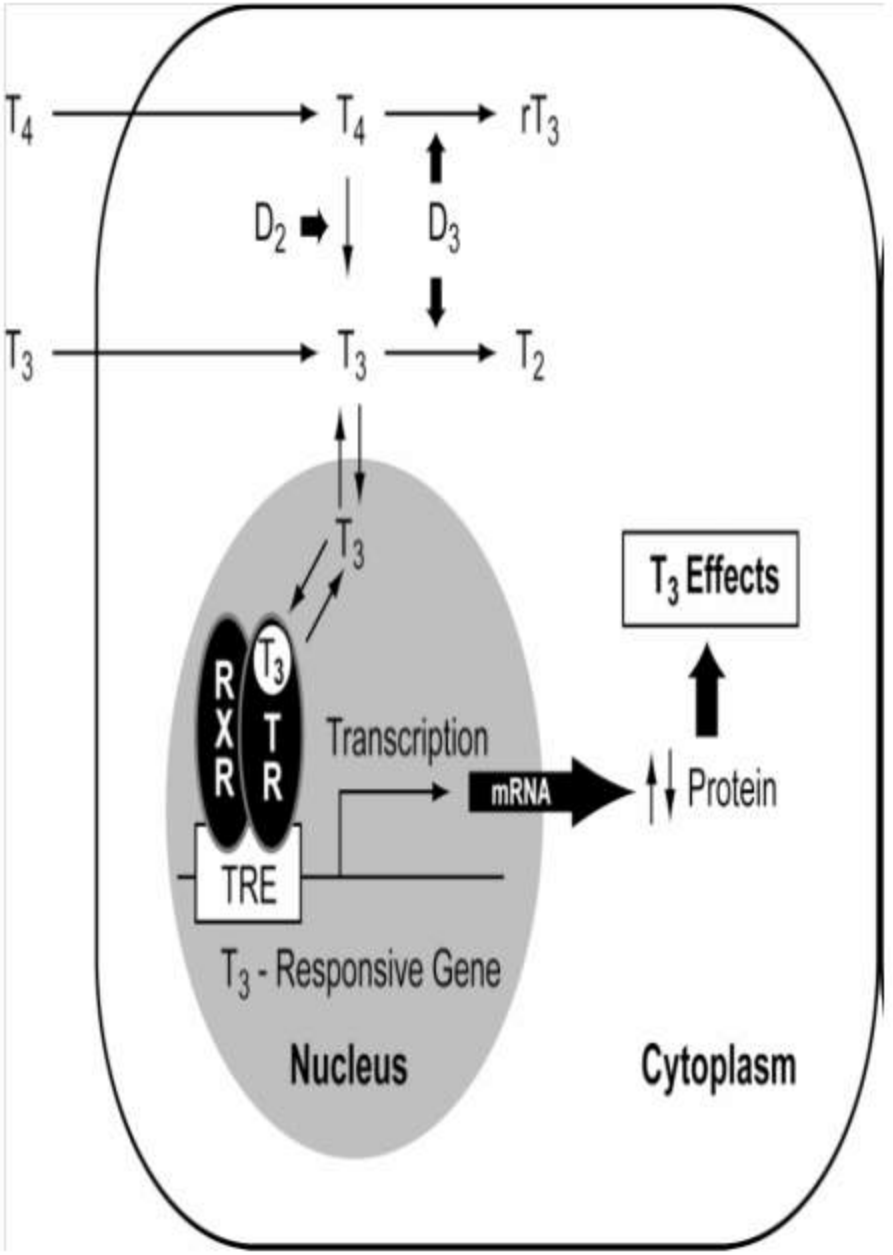
1. Thyroxin binding globulin (TBG).
2. Thyroxine binding pre-albumin (forT4 only) & albumin (for both T3 & T4).

- ❑ Affinity of T4 for TBG & albumin is much higher than T3.
- ❑ More free (unbound) T3 exist.
- ❑ Only the free hormone molecules are biologically active.

- ➢ Liver disease can decrease plasma protein concentration.
- ➢ pregnancy and estrogen can ↑ plasma proteins and increased TBG
- ➢ testosterone and glucocorticoids decrease TBG levels.
- ➢ Phenytoin displaces T3 & T4 from TBG leading to hyperthyroid state.
- ➢ Salicylates displace T3 and T4 from albumin.

- Biological **t1/2 of T3** is **1 day**, while **t1/2of T4** is **7 days**
- **T3 is more potent than T4.**
- Most of the **circulating** pool of **T3 (80%)** is produced from T4 by **deiodinase** (e.g. in the liver), rather than biosynthesis.
- All T4 is produced by the thyroid gland.

The body adjusts its metabolic rate downward by **shunting T4 to reverse T3 (inactive) rather than to T3 during times of stress, illness and caloric deprivation** as a protective mechanism.



Physiological Role of Thyroid Hormone

1. Calorigenesis.

Increase metabolic rate, oxygen consumption and appetite. Heat intolerance.

2. Growth and Development

Essential for CNS development (critical for normal fetal and neonatal development),regulates growth as it increases growth hormone and IGF secretion.

Essential for skeleton and dental development.

3. Cardiovascular

Increase rate and strength of heart beat, increase cardiac output and increase in myosin Ca^{2}+ ATPase as well as β-adrenoceptors numbers.

Hypersensitivity to catecholamines.

4. Intermediary Metabolism

Stimulate glycogenolysis and gluconeogenesis (increase blood glucose).

Increased lipid catabolism (lower plasma cholesterol levels).

Net loss of protein mass.

Hypothyroidism

1. **Primary thyroid deficiency**: usually referred as **myxedema**. Goiter is obvious and Iodine deficiency is a major risk factor here.
2. **Hashimoto's thyroiditis:** autoimmune disorders that destroy the thyroid
3. **Decrease peroxidase** may lead to **congenital goiter** and **cretinism**.
4. **Drug induced**: by antithyroid and other drugs (e.g. amiodarone)
5. **Secondary thyroid deficiency** due to pituitary disease or irradiation.

➢ Treatment of **hypothyroidism** is achieved by pharmacological **preparations** of **thyroid hormone** (T4 or T3 or combination)

➢ Treatment of drug-induced hypothyroidism (stop the offending drug).

❑ Thyroid hormone preparations can also treat **sick euothyroid syndrome** in patients with liver cirrhosis and renal diseases.

❑ the use of thyroid hormone in treatment of **unipolar depression** is questionable.

Thyroid hormone preparations

1. Levothyroxine (T4) or L-troxin

- Absorption is decreased by cholestyramine, iron & Calcium supplements, Al(OH)3, and Soy products.
- **It may take several weeks to obtain steady-state levels.**
- Monitoring of serum T4 and TSH levels is needed to ensure efficacy.
- Thyroxin ↑ the effect of **warfarin, antidepressants & amiodarone.**
- Elimination of T4 is ↑ by drugs that induce hepatic CYP enzymes like **rifampicin**, **phenytoin**, **carbamazepine**, **oral contraceptives.**

2. Liothyronine Sodium (T3)

used for rapid onset of action as in treatment of **Myxedema coma.**

3. Mixture of T3 and T4 **(liotrix)**

In which T3:T4 = 4:1

Adverse effects of thyroid hormone therapy:

These are dose related adverse effects and produce symptoms similar to hyperthyroidism and some immunological reactions.

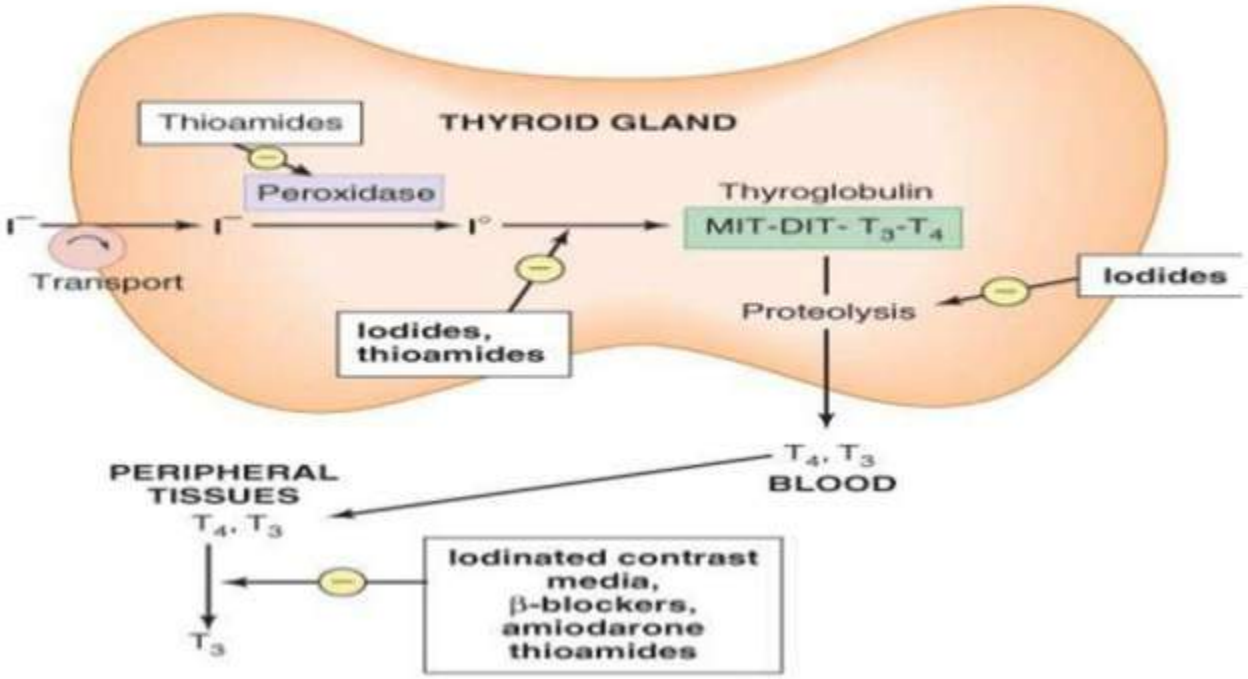
Hyperthyroidism:

1. **Grave's disease** (exophthalmic goiter); an autoimmune thyroid disease.
2. **Toxic nodular goiter** (carcinoma).

Treatment of hyperthyroidism is complex and may include:

1. **Surgery.**
2. **Radioactive Iodine (It is considered one of the anti-thyroid drugs).**
3. **Anti-thyroid drugs.**

Mechanism of action of anti thyroid drugs



1-Thioureylenes (thioamides):

Carbimazole, methimazole & Propylthiouracil (PTU)

- They **inhibit all steps in thyroid hormone synthesis.**
- PTU in addition **inhibits peripheral conversion of T4 to T3** and has some immunosuppressive effects.

Pharmacokinetics and properties:

- Thionamides are rapidly absorbed from the GIT.
- Carbimazole is a **prodrug** and converted to methimazole.
- PUT has a shorter plasma half-life (75min) than methimazole (4-6h).
- **Methimazole** is 10 times more potent than PTU
- Both methimazole and PTU crosses the placental barrier and are concentrated in the fetal thyroid, but **PTU** is preferred in pregnant patients or nursing mothers because of restricted placental transfer and limited excretion in milk.

Therapeutic uses of thionamides:

1. In **hyperthyroidism**, it is used alone to control the symptoms of hyperthyroidism within 3-4 weeks.
2. **Preoperative preparation** for thyroidectomy to control symptoms preoperatively.
3. In **conjunction with radioactive iodine** to control symptoms until the onset of action of iodine.

Adverse effects of Thionamides

1. **Agranulocytosis** (sore throat as early sign), leukocyte count is recommended.
2. **Hypersensitivity**: skin rash, fever, hepatitis, nephritis.
3. **Hypothyroidism** may occur in prolonged therapy.
4. With chronic use, there is hyperplasia and enlargement of thyroid gland (**goiter**) due to excess TSH.

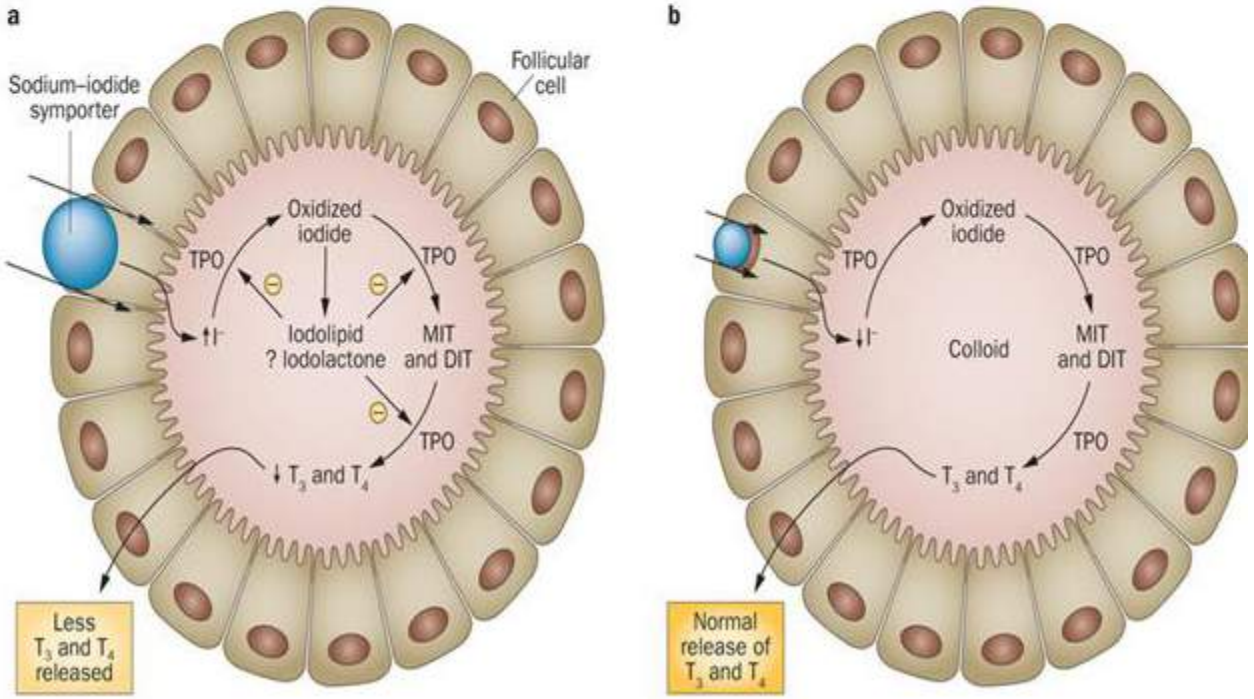
2-Iodide (Lugol's iodine)

It is also known as aqueous iodine or strong iodine solution.

It is used as a medication and as a disinfectant.

Mechanism of action and pharmacological effects:

- At high concentrations; it causes **Wolff-Chaikoff effect** → **inhibit the hormone release** & **inhibits its synthesis.**
- It inhibits iodine uptake by the gland.



Therapeutic uses:

- It is used to protect the thyroid gland from accidental exposure to radioactive iodine (as it inhibits the uptake of radioactive iodine).
- It is used to treat iodine deficiency.

- It is used **orally** to treat thyrotoxicosis until surgery can be carried out.
- It is used as **pre-operative drug** before thyroidectomy (as it **decreases vascularity**, **size**, and **fragility** of the hyperplastic gland)
- It is valuable in treatment of **thyroid storm**.
- It should not to be used prior to radioactive iodide treatment.
- It must be used in **conjunction with other drugs (like thionamides or beta blockers)** since the patient may overcome the iodide block (escape of Wolff-Chaikoff effect) resulting in therapeutic failure.

Adverse effects:

1. With chronic use **iodism** occur: **gastritis**, **conjunctivitis**, **bronchitis**, **salivary gland inflammation**, mucus membrane ulceration & metallic taste.
2. **Recurrence of symptoms of hyperthyroidism**, (so it is not used alone)
3. Dangerous to the **fetus**, so not used during pregnancy.
4. **Hypersensitivity reactions** and rarely anaphylaxis.
5. **Metallic taste** and **bleeding disorders** may occur.

3- β-adrenergic Receptor Blockers

It is known that T3 increases the number & sensitivity of β-adrenergic receptors in the heart leading to **increased hear rate & angina** in hyperthyroid states.

Propranolol not only helps against the adverse cardiac side effects of hyperthyroidism, but also can decrease peripheral deiodination of T4 to T3.

4-Radioactive iodine (I^{131})

Iodine-131 (^{131}I) is an important radioisotope of iodine. It is administered orally and concentrated in the thyroid gland, where **β** and γ radiation will, then in several weeks, destroy all or part of the tissue.

Biological t ½ is **8 days** and 99 % of radiant ion is expended after **56 days.**

There is no evidence of any radiation-induced damage to any other tissues.

It can be used in adults 35 years and older, but not in women of child bearing age. The major disadvantage is **delayed hypothyroidism.**

Therapeutic uses:

1. **Treatment of hyperthyroidism** (but propranolol or anti-thyroid drugs or both are used till the actions occur).
2. **Destroy malignant thyroid** tissues (after surgery or metastatic tumor)

3.Diagnosis of disorders in thyroid function (used for scanning procedures). The isotope I^{123} which has short half-life (13 hours) is used because it is primarily a γ-ray emitter.

Adverse effects of radioactive iodine:

1. High incidence of **delayed hypothyroidism**.
2. **Delayed** antithyroid effect (several weeks)
3. May cause **worsening of ophthalmopathy** after its treatment.
4. Cross placenta and excreted in milk (may **destroy fetal thyroid gland**), so not used in pregnant and lactating women and children.

5-Anion Inhibitors

Due to their toxicity and uncertain effects these are only used for diagnosis..

1. **Thiocyanate** (inhibit the organification of iodine).

2.Potassium Perchlorate blocks the entrance of iodide into the thyroid.

The major clinical use for potassium perchlorate is to block thyroidal reuptake of I^- in patients with iodide-induced hyperthyroidism (e.g. **amiodarone-induced hyperthyroidism**). However, it is rarely used clinically because it is associated with aplastic anemia.

6-Iodinated contrast agents

➢ **Diatrizoate** orally and **iohexol** orally or intravenously.

- These drugs rapidly inhibit the conversion of T_4 to T_3 and inhibit hormone release.
- Fortunately, these agents are relatively non-toxic.
- They provide useful adjunctive therapy in the treatment of thyroid storm and offer valuable alternatives when iodides or thioamides are contraindicated.

- these agents may not interfere with ^{131}I uptake (unlike iodide)

- Their toxicity is similar to that of the iodides, and their safety in pregnancy is undocumented.

Thyroid Storm

It is an acute; life threatening hyper-metabolic state in patients suffering from **thyrotoxicosis** (may be initial presentation in undiagnosed patients).

Symptoms: Heat intolerance, diaphoresis (sweating), hyperpyrexia, diarrhea, vomiting, jaundice, and abdominal pain, tachycardia, high output heart failure, cardiac arrhythmias, irritability, restlessness, severe agitation, delirium, seizure, and coma.

Treatment of thyroid storm

1. Antipyretics (**acetaminophen**) to control fever.
2. **Hydrocortisone** (i.v.) as it blocks T4 toT3 conversion.
3. **β-blockers** which block T4 toT3 conversion and cardiac actions.
4. **PTU** is the preferred thionamide since it blocks T4 toT3 conversion.
5. High doses of **iodide** to block thyroid hormone release.
6. **Iodinated contrast agents.**


Thank
You