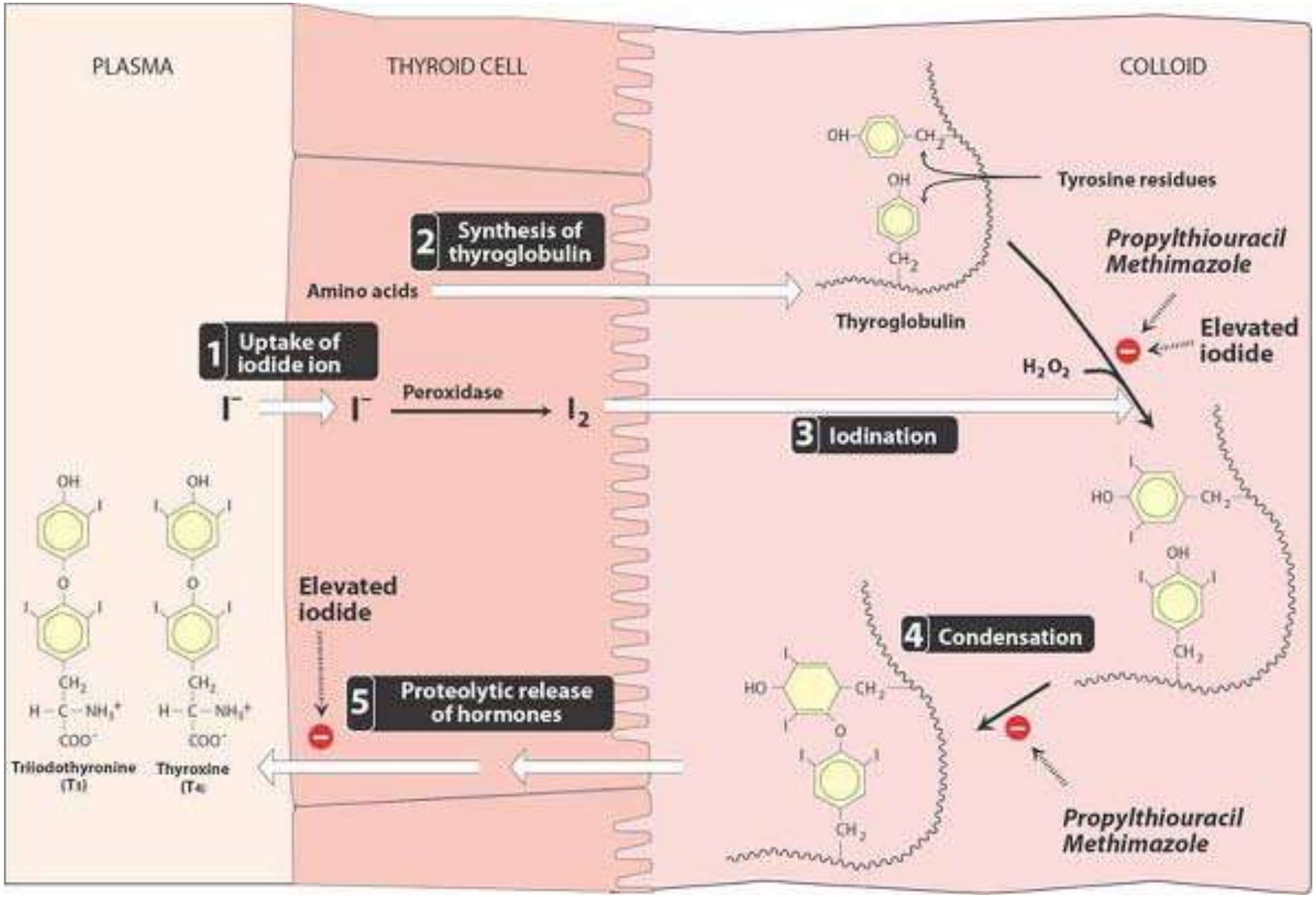
Thyroid hormones and anti-thyroid drugs



Synthesis of T3 and T4

Thyroid hormones

Mechanism of action of T3 and T4

- In the cell, T4 is enzymatically deiodinated to T3, which enters the nucleus and attaches to specific receptors.
- T4 is converted to T3 by deiodinases.
- Both T4 and T3 **<u>are absorbed after oral administration</u>**.
  Food, calcium preparations, and aluminum-containing antacids can decrease the absorption of T4 but not of T3.

Thyroid hormones

- The hormones are metabolized through the microsomal P450 system >>> Drugs that induce the P450 enzymes, such as phenytoin, rifampin, and phenobarbital, accelerate metabolism of the thyroid hormones.

- levothyroxine (T4) is used to treat hypothyroidism.

- Toxicity manifests itself as nervousness, heart palpitations and tachycardia, intolerance to heat, and weight loss.(sympathetic sympotms) >>> beta- blockers are used to reduce the sympathetic ativation.

- **Why is levothyroxine the treatment of choice?**
- **Why should levothyroxine be taken on an empty stomach?**
- **Which laboratory test is most commonly used to monitor the adequacy of levothyroxine therapy?**
- **What are major side effects of levothyroxine?**

Anti-thyroid drugs

Radioactive iodine

- Destruction of the gland by beta particles emitted by radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells.
- Normal thyroid follicular cells and most differentiated thyroid cancer cells express the sodium-iodide symporter on their cell membrane.

- **Side effect:** hypothyroid as a result of this drug >>> require treatment with levothyroxine.

- Is used for the treatment of thyroid cancer.

- **Which thyroid cancers respond?**

Papillary and follicular carcinoma responses well because cancer cells retain iodine uptake, while anaplastic carcinoma does NOT response; poorly differentiated, usually lacks sodium-iodide symporter expression.

Does medullary carcinoma response to radioactive iodine? Why?

Anti-thyroid drugs

propylthiouracil (PTU) and methimazole

- Are concentrated in the thyroid.

MOA:

1. Inhibit the oxidative processes required for iodination of tyrosyl groups
2. Inhibit the coupling of iodotyrosines to form T3 and T4.
3. **PTU** can also block the conversion of T4 to T3.

- These drugs have no effect on the thyroglobulin already stored in the gland >>>> **observation of any clinical effects of these drugs may be delayed until thyroglobulin stores are depleted.** مهم

Anti-thyroid drugs

propylthiouracil (PTU) and methimazole

- Are well absorbed from the gastrointestinal tract >>>> Taking orally.

- **Adverse effects include:**

1. Agranulocytosis (is the most serious adverse effect. Patients should immediately report fever, sore throat, or signs of infection, and the drug should be stopped while obtaining a complete blood count.)
2. Rash
3. Edema.

- Why is propylthiouracil preferred over methimazole during the first trimester of pregnancy and in the treatment of thyroid storm?

Anti-thyroid drugs

Beta blockers

- β-Blockers that **lack sympathomimetic activity (Pindolol and acebutolol)**, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism.
- Intravenous administration is effective in treating thyroid storm.
- An alternative in patients suffering from severe heart failure or asthma is the calcium channel blocker, diltiazem.

Other agents used in the treatment of thyroid storm include :

1. PTU (WHY?!) because it inhibits the peripheral conversion of T4 to T3 but methimazole does not)
2. Iodides
3. Glucocorticoids (to protect against shock).

Anti-thyroid drugs

Iodide

- Inhibits the iodination of tyrosines (so-called acute **Wolff-Chaikoff effect**).
- This effect lasts only a few days.
- Iodide inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood.
- Today, iodide is rarely used as the sole therapy.
- However, it is employed to treat potentially fatal thyrotoxic crisis (thyroid storm) or prior to surgery, **because it decreases the vascularity of the thyroid gland.**

- **What are the main clinical indications for iodide in patients with hyperthyroidism?**

1) Before thyroid surgery to reduce thyroid vascularity and intraoperative bleeding.
2) Thyroid storm.
3) After administration of thionamides (e.g., PTU or methimazole) to rapidly inhibit thyroid hormone release.

Anti-thyroid drugs

Iodide

- Iodide is not useful for long-term therapy, (why?!) because the thyroid ceases to respond to the drug after a few weeks.

Adverse effects are relatively <u>minor</u> and include:

1. Sore mouth and throat
2. Swelling of the tongue or larynx
3. Rashes (Iodide can trigger hypersensitivity reactions in the skin.)
4. Ulcerations of mucous membranes
5. Metallic taste in the mouth.

Iodide is concentrated in the salivary glands and secreted into saliva. This causes local irritation and inflammation of the oral and pharyngeal mucosa, leading to soreness.