Thyroid & Antithyroid Drugs

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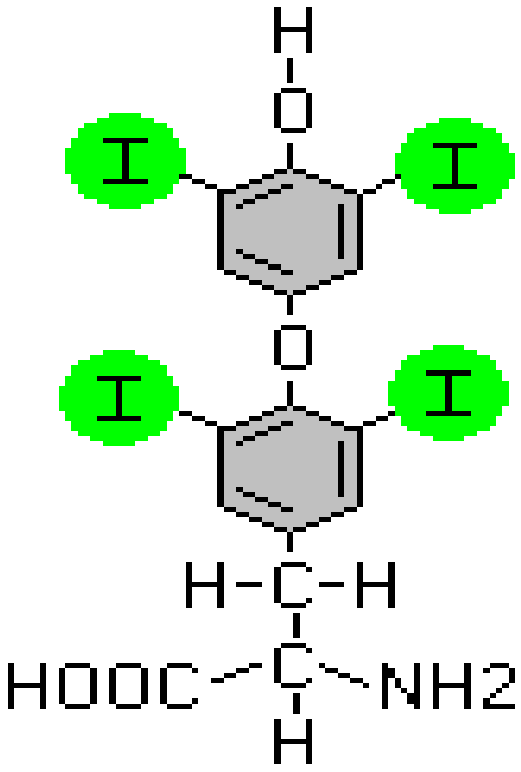
The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues for their normal function(normalize growth and development, body temperature, and energy levels).

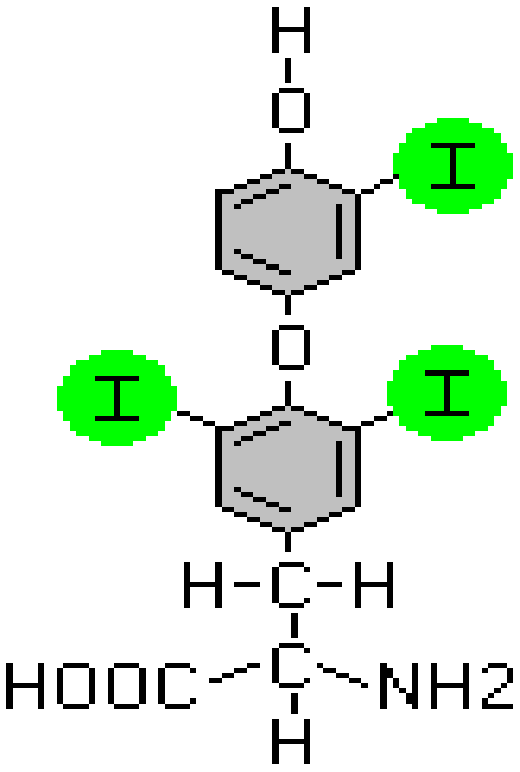
Two major Thyroid hormones are:

1. Triiodothyronine (T3, the active form) contain 59% of iodine
2. Tetraiodothyronine (thyroxine) (T4) contain 65% of iodine .

The thyroid gland also secretes Calcitonin serum calcium lowering hormons



Thyroxine (T4)

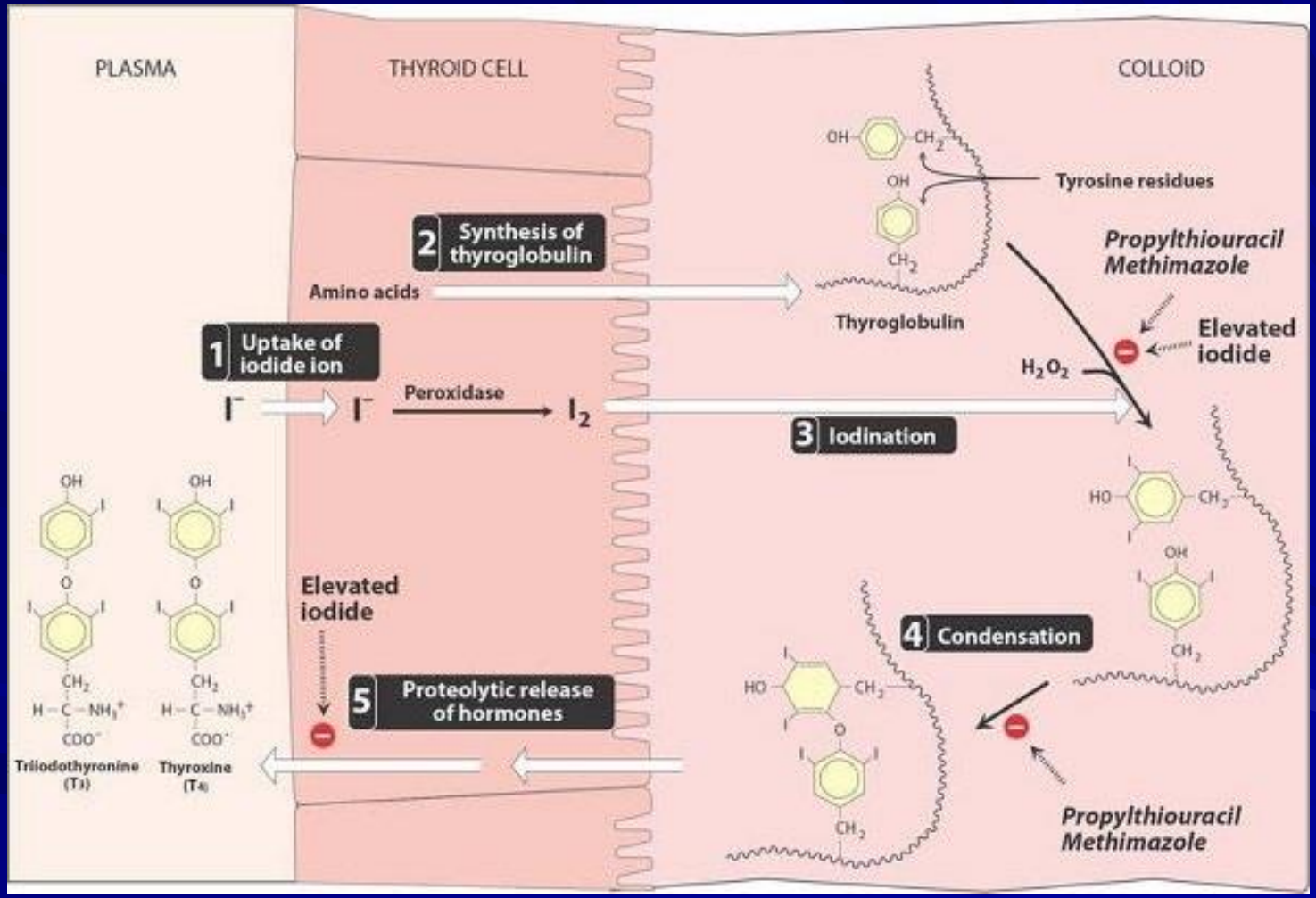


Triiodothyronine (T3)

Thyroid Hormone Synthesis and Secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with colloid (thyroglobulin), which is the storage form of thyroid hormone.

Biosynthesis of Thyroid Hormones

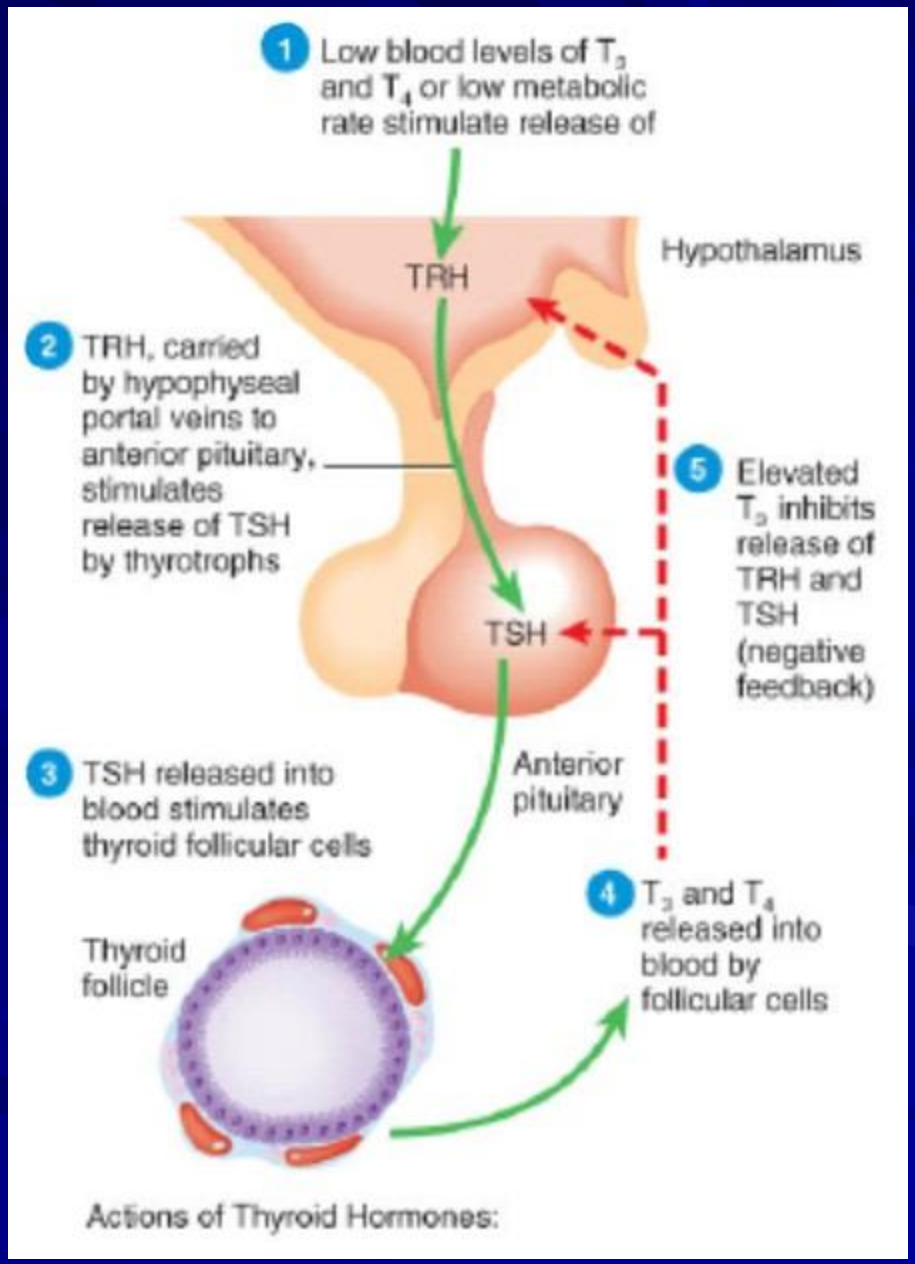


Secretion of Thyroid Hormone

- Secretion of thyroid hormone under the control of TSH which is secreted by the anterior pituitary, TSH is stimulated by the hypothalamic TRH.
- Most of the hormone (T3 and T4) is bound to thyroxine-binding globulin in the plasma.

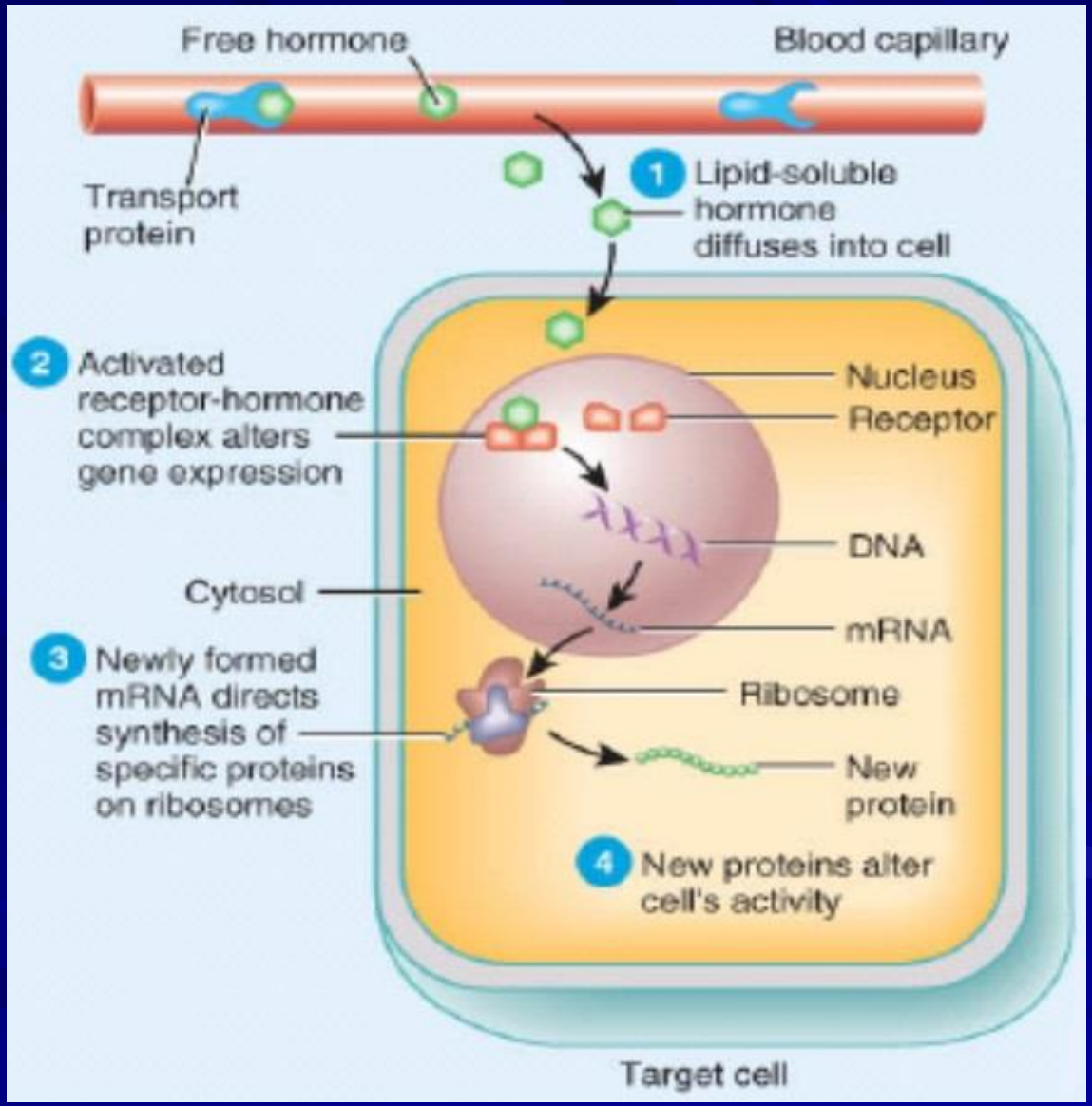
Inhibition of TRH

- Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone.
- At pharmacologic doses, dopamine, somatostatin, or glucocorticoids can also suppress TSH secretion.


1 Low blood levels of T_3 and T_4 or low metabolic rate stimulate release of
Hypothalamus
TRH
2 TRH, carried by hypophyseal portal veins to anterior pituitary, stimulates release of TSH by thyrotrophs
5 Elevated T_3 inhibits release of TRH and TSH (negative feedback)
TSH
Anterior pituitary
3 TSH released into blood stimulates thyroid follicular cells
4 T_3 and T_4 released into blood by follicular cells
Thyroid follicle
Actions of Thyroid Hormones:

Mechanism of Action

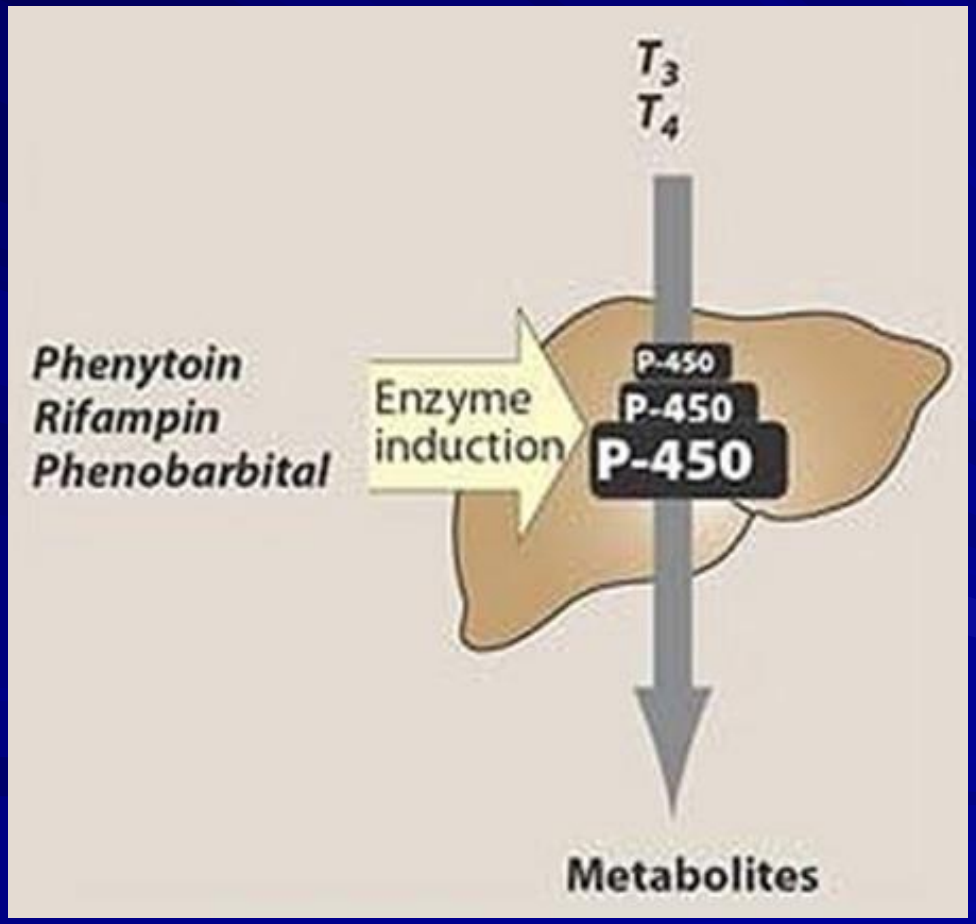
- Both T4 and T3 must dissociate from thyroxine-binding plasma proteins prior to entry into cells, either by diffusion or by active transport.
- In the cell, T4 is enzymatically deiodinated to T3, which enters the nucleus and attaches to specific receptors.
- The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for normal physiological action .


Free hormone
Blood capillary
Transport protein
1 Lipid-soluble hormone diffuses into cell
2 Activated receptor-hormone complex alters gene expression
Nucleus
Receptor
DNA
Cytosol
mRNA
3 Newly formed mRNA directs synthesis of specific proteins on ribosomes
Ribosome
New protein
4 New proteins alter cell's activity
Target cell

Pharmacokinetics

- Both T4 and T3 are absorbed after oral administration.
- Food, calcium preparations and aluminum-containing antacids can decrease the absorption of T4 but not of T3.
- T4 is converted to T3 by one of two distinct deiodinases, depending on the tissue.
- Metabolized byP450 enzymes. (enzyme inducer such as phenytoin, rifampin and phenobarbital, accelerate metabolism of the thyroid hormones

Enzyme induction can increase the metabolism of the thyroid hormones.



Hypothyroidism

- Inadequate secretion of thyroid hormone due to autoimmune destruction of the gland or the peroxidase
- It is diagnosed by elevated TSH
- Hypothyroidism results in bradycardia, poor resistance to cold and mental and physical slowing (in children, this can cause mental retardation and dwarfism).

Treatment (Replacement Therapy)

Preparation of T4 levothyroxine sodium

Preparation of T3 liothyronine sodium

Mixture of T3, T4 liotrix

Levothyroxine

Synthetic levothyroxine is the preparation of choice for thyroid replacement and suppression therapy because of:

- Stability
- Content uniformity,
- Low cost
- Lack of allergenic foreign protein
- Easy laboratory measurement of serum levels
- Long half-life (7 days) Steady state is achieved in 6 to 8 weeks
- Once-daily administration.

Side Effects of Levothyroxine

- Nervousness
- Heart palpitations and tachycardia
- Intolerance to heat
- Unexplained weight loss.

Liothyronine (T_3)

- Three to four times more potent than levothyroxine,
- Not recommended for routine replacement therapy because of
  - Its shorter half-life (24 hours)
  - Requires multiple daily doses
  - Higher cost
  - The greater difficulty of monitoring its adequacy of replacement by conventional laboratory tests.
  - Greater risk of cardiotoxicity,

Note: It is best used for short-term suppression of TSH.

Hyperthyroidism (Thyrotoxicosis)

- An excess secretion of thyroid hormone
- Hyperthyroidism cause tachycardia and cardiac arrhythmias body wasting, nervousness, tremor, and excess heat production
- Excessive amounts of thyroid hormones in the circulation are associated with a number of disease states, including Graves' disease, toxic adenoma, and goiter.
- TSH levels are reduced.

Treatment of Hyperthyroidism

The goal of therapy is to decrease synthesis and/or release of additional hormone.

1. By removing part or all of the thyroid gland
2. By inhibiting synthesis of the hormones
3. By blocking release of the hormones from the follicle.

Removal of Part or all of the Thyroid

1. Surgically
2. Destruction of the gland by beta particles emitted by radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells.
3. Younger patients are treated with the isotope without prior pretreatment with methimazole whereas the opposite is the case in elderly patients.

Note: Most patients become hypothyroid as a result of this drug and require treatment with levothyroxine

Inhibition of Thyroid Hormone Synthesis:
Thiourylenes
Thioamides
Propylthiouracil (PTU)
Methimazole

- These drugs are concentrated in the thyroid, inhibit both the oxidative processes required for iodination of tyrosyl groups and the coupling of iodotyrosines to form T3 and T4
- Propylthiouracil can also block the conversion of T4 to T3

These drugs have no effect on the thyroglobulin already stored in the gland; therefore, observation of any clinical effects of these drugs may be delayed until thyroglobulin stores are depleted

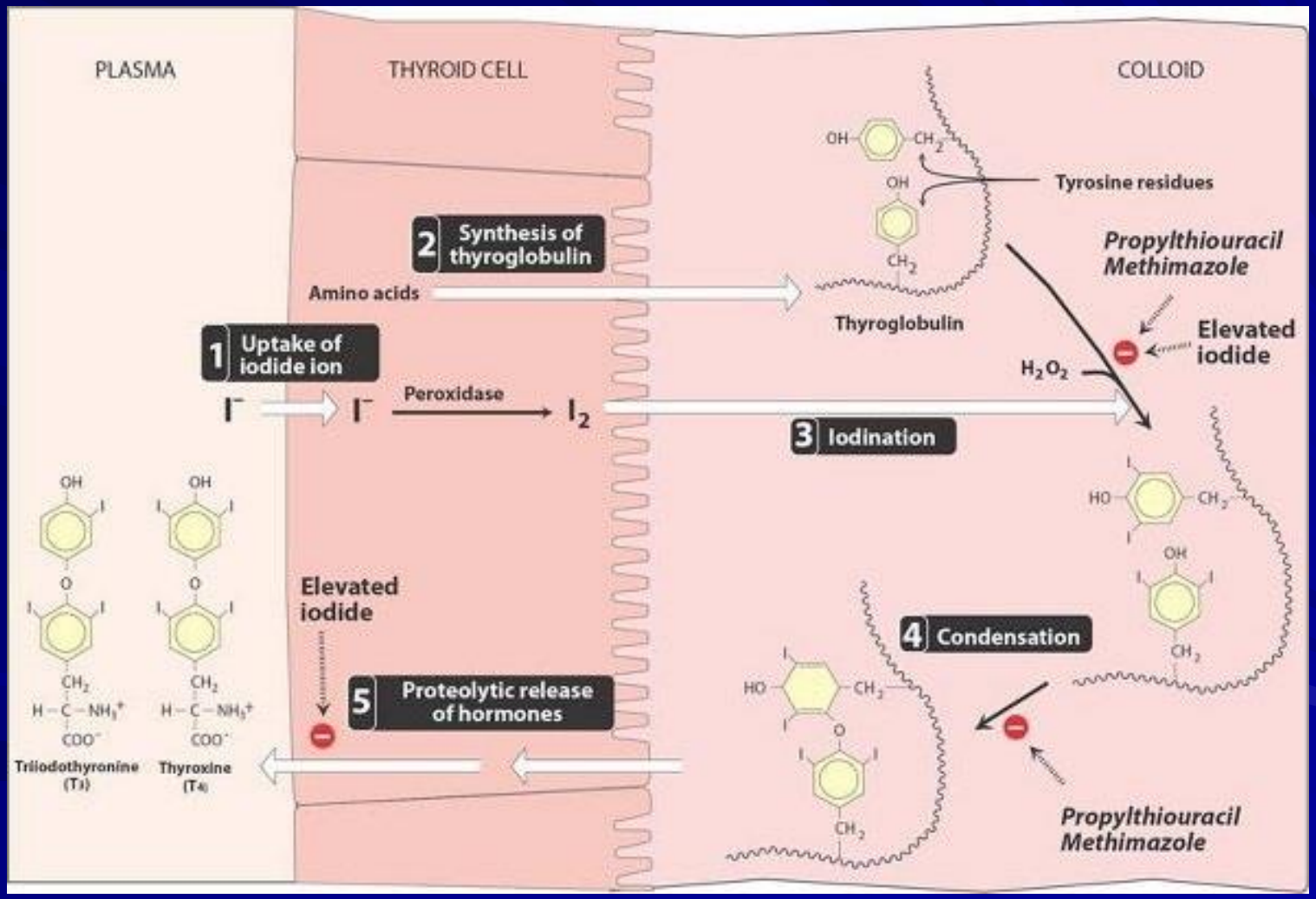
Pharmacokinetics of Propylthiouracil

- Rapidly absorbed
- Short plasma half-life of 1.5 hours
- The bioavailability of 50-80%
- Accumulatied in the thyroid gland
- Excreted by the kidney within 24 hours
- A single 100 mg dose can inhibit iodine organification by 60% for 7 hours
- Giving the drug every 6-8 hours

Pharmacokinetics of Methimazole

- Short plasma half-life of 6 hours
- A single 30 mg dose of methimazole exerts an antithyroid effect for longer than 24 hours
- A single daily dose is effective in the management of mild to moderate hyperthyroidism.

Biosynthesis of thyroid hormones



Adverse Effects of Thiourylenes

1. Agranulocytosis
2. Pain, stiffness in joint
3. Paraesthesia
4. Loss of hair pigment
5. Rash
6. Cross the placental barrier & concentrated by the fetal thyroid

Thyroid Storm

- B-Blockers such as propranolol, blunts the sympathetic stimulation that occurs in hyperthyroidism(IV administration)
- Calcium-channel blocker, diltiazem is the alternative in patients suffering from severe heart failure or asthma .
- Other agents used in the treatment of thyroid storm include Propylthiouracil (because it inhibits the peripheral conversion of T_4 to T3) but methimazole does not), iodides and glucocorticoids (to protect against shock).

Blockade of hormone release:

Iodide

Administered orally.

- Inhibits the iodination of tyrosines(lasts only a few days)
- Inhibits the release of thyroid hormones from thyroglobulin
- It is rarely used as the sole therapy. However, it is employed to treat thyroid storm or prior to surgery, because it decreases the vascularity of the thyroid gland.
- Iodide is not useful for long-term therapy, because the thyroid not respond to the drug after a few weeks

Adverse effects

Sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and a metallic taste in the mouth.