Thyroid drugs

Introduction

- The thyroid gland facilitates normal growth and maturation by maintaining optimum levels of metabolism in tissues for their normal function

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

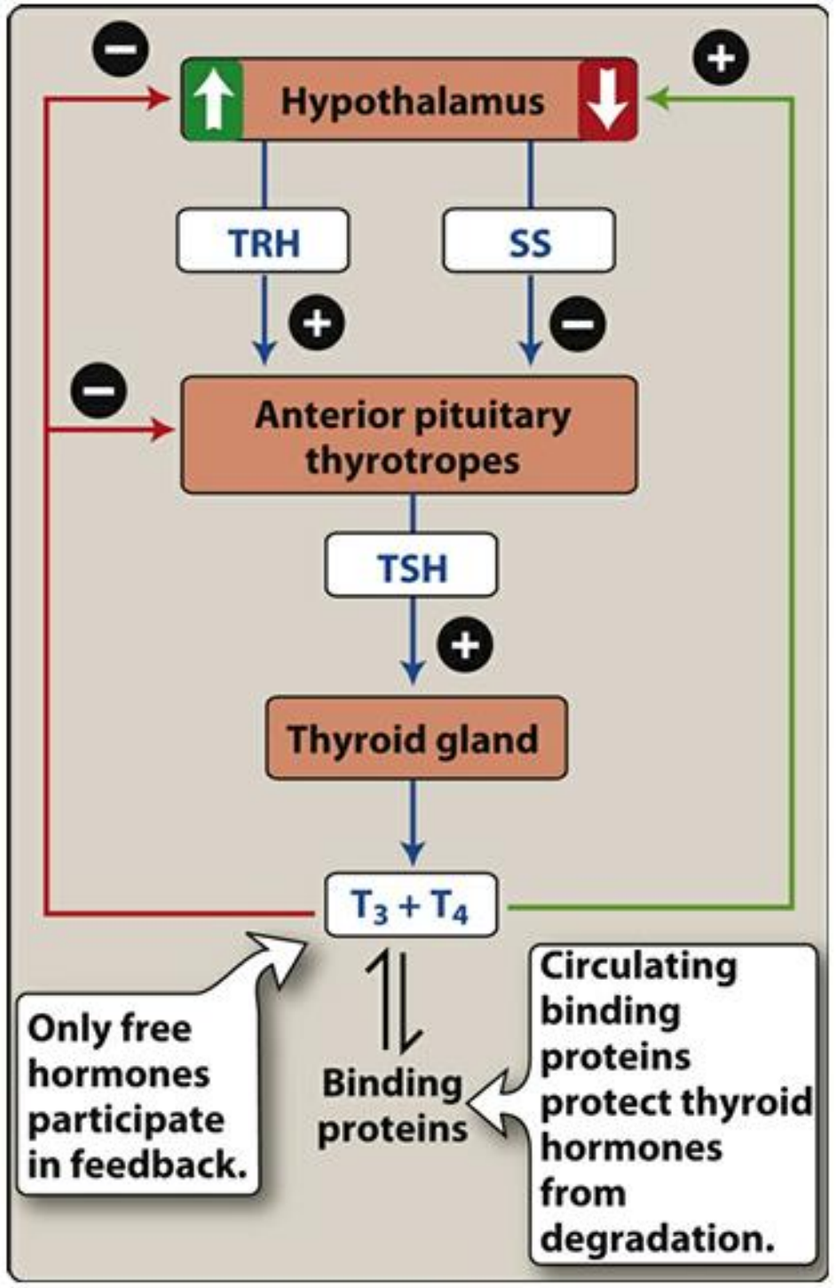
- The two major thyroid hormones are triiodothyronine (T3) and thyroxine (T4)

Introduction

- **Euthyroidism**: normal thyroid function

- **Hypothyroidism**, inadequate secretion of thyroid hormone, results in:
  - Bradycardia, poor resistance to cold, and mental and physical slowing
  - In children, this can cause mental retardation and dwarfism

- **Hyperthyroidism**, an excess of thyroid hormones secretion, causing:
  - Tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess heat production



Thyroid hormones: synthesis and secretion

1. Regulation of synthesis:

- Thyroid function is controlled by TSH (thyrotropin)
- TSH action is mediated by cAMP and leads to stimulation of iodide (I–) uptake
- Oxidation to I2 by a peroxidase is followed by iodination of tyrosines on thyroglobulin
- Condensation
- The hormones are released following proteolytic cleavage of the thyroglobulin

Thyroid hormones: synthesis and secretion

2. Regulation of secretion:

- Secretion of TSH by the anterior pituitary is stimulated by hypothalamic 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
- Most of the hormone (T3 and T4) is bound to thyroxine-binding globulin in the plasma

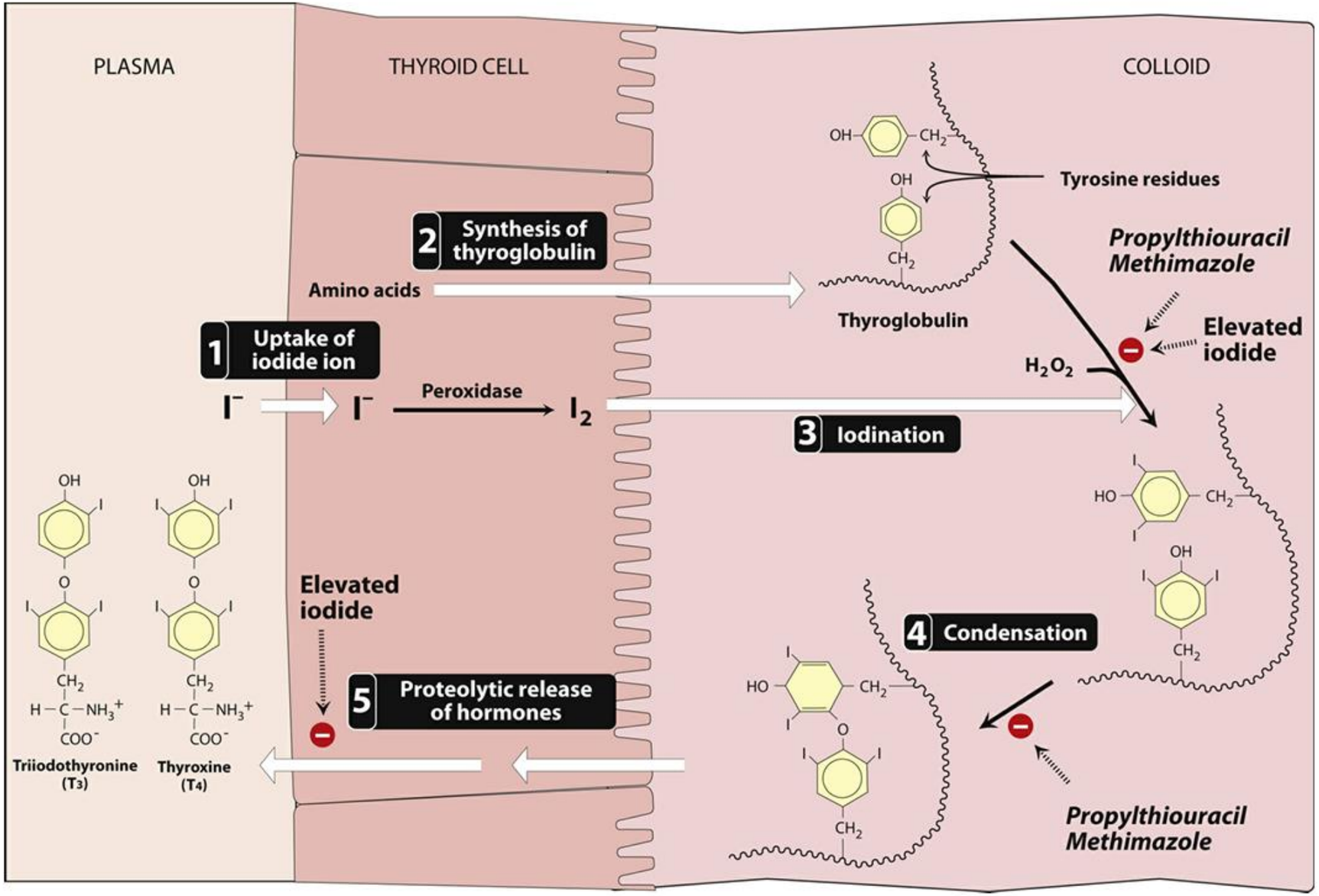


Figure 23.9 Biosynthesis of thyroid hormones.

Thyroid hormones: Mechanism of action

- 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 the effects of T4

Thyroid hormones

- Both T4 and T3 are absorbed after oral administration
- Food, Ca, Al can decrease the absorption of T4 but not of T3
- T4 is converted to T3 by deiodinases
- 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

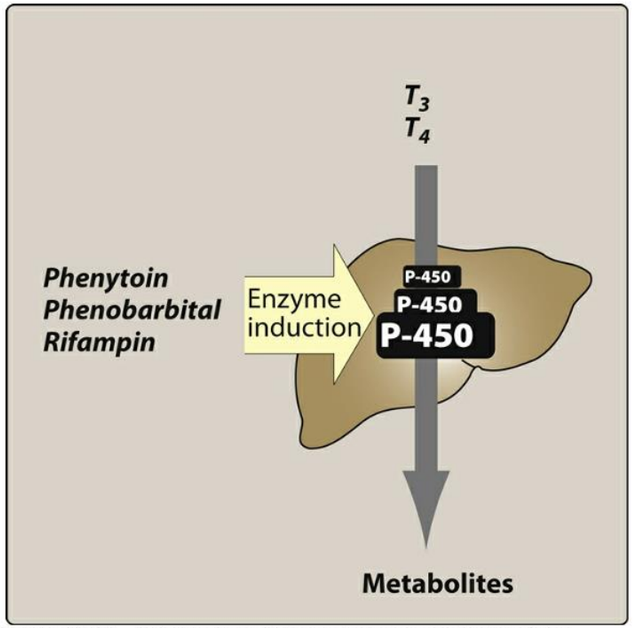


Figure 23.10 Enzyme induction can increase the metabolism of the thyroid hormones. T_3 = triiodothyronine; T_4 = thyroxine.

Thyroid hormones: actions

- General metabolic effects: Increase oxygen consumption, metabolic rate, heat production (thermogenesis)
- Increase glucose utilization and oxidation by muscles, increase hepatic gluconeogenesis
- CNS: Influence growth and development, axon proliferation, mylein sheath formation
- CVS: Increase cardiac output and heart rate, decrease peripheral resistance
- G.I. tract and kidneys: Important for function, increases intestinal motility

Hypothyroidism: treatment

- Hypothyroidism usually results from autoimmune destruction of the gland or the peroxidase
- Diagnosed by elevated TSH
- Condition presented at birth: Cretinism: Impaired mental and skeletal development
- Condition presented at adulthood: Myxedema: Muscle weakness, decreased appetite, fatigue, and lethargy

Hypothyroidism: treatment

- Levothyroxine (T4) is used for hypothyroidism treatment
  - Given once daily because of its long half life
  - Steady state is achieved in 6 to 8 weeks
  - Toxicity is directly related to T4 levels
    - Nervousness
    - Heart palpitations
    - Tachycardia
    - Intolerance to heat
    - Unexplained weight loss
- Levothyroxine is preferred over liothyronine (T3) or liotrix (T3/T4 combination)

Hyperthyroidism (Thyrotoxicosis): treatment

- 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 due to negative feedback

Hyperthyroidism (Thyrotoxicosis): treatment

- The goal of therapy is to decrease synthesis and/or release of additional hormone by:
  - Removing part or all of the thyroid gland
  - Inhibiting synthesis of the hormones
  - Blocking release of the hormones from the follicle

Hyperthyroidism (Thyrotoxicosis): treatment

1. Removal of part or all of the thyroid:

- Can be accomplished either surgically or by destruction of the gland by beta particles emitted by radioactive iodine (131I), which is selectively taken up by the thyroid follicular cells
- Younger patients are treated with the isotope without prior pretreatment with methimazole, the opposite is done in elderly patients
- Most patients become hypothyroid and require treatment with levothyroxine

Hyperthyroidism (Thyrotoxicosis): treatment

2. Inhibition of thyroid hormone synthesis:

- The thioamides: propylthiouracil (PTU) and methimazole
- Inhibit oxidative processes for iodination of tyrosyl groups and the condensation (coupling) of iodotyrosines to form T3 and T4
- PTU can also block the conversion of T4 to T3
- Clinical effects of these drugs may be delayed

Hyperthyroidism (Thyrotoxicosis): treatment

2. Inhibition of thyroid hormone synthesis:

- PTU, methimazole
- Adverse effects include agranulocytosis, rash, edema
- PTU can cause liver toxicity or liver failure and should be reserved for patients who are intolerant of methimazole
- PTU is safer in first trimester of pregnancy

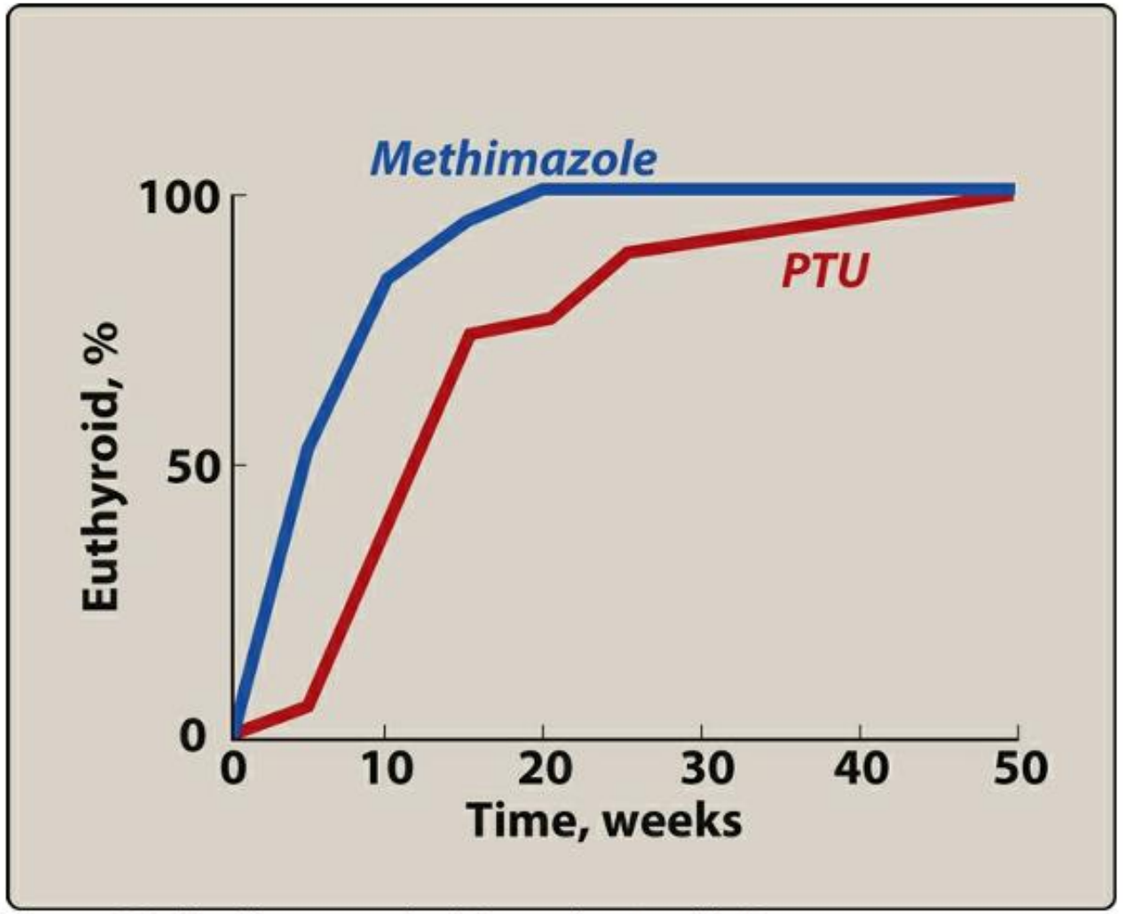


Figure 23.11 Time required for patients with Graves hyperthyroidism to become euthyroid with normal serum T_4 and T_3 concentrations.Modified from K.Okamura , H.Ikenoue , and A.Shiroozu . Reevaluation of the effects of methylmercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. *J. Clin. Endocrinol. Metab*. 65: 719 (1987).

Hyperthyroidism (Thyrotoxicosis): treatment

3. Blockade of hormone release:

- A pharmacologic dose of iodide inhibits the iodination of tyrosines "acute Wolff-Chaikoff effect" but this effect lasts only a few days
- Iodide inhibits the release of thyroid hormones from thyroglobulin by unknown mechanisms
- Iodide is rarely used as the sole therapy
- It is employed to treat potentially fatal 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 ceases to respond to the drug after a few weeks

Hyperthyroidism (Thyrotoxicosis): treatment

3. Blockade of hormone release:

- It is administered orally

- **Adverse effects**
  - Sore mouth and throat
  - Swelling of the tongue or larynx
  - Rashes
  - Ulcerations of mucous membranes
  - Metallic taste in the mouth

Hyperthyroidism (Thyrotoxicosis): treatment

4. Thyroid storm:

- Presents with extreme symptoms of hyperthyroidism
- Same therapy as hyperthyroidism, given in higher doses and more frequently
- β-Blockers that lack sympathomimetic activity, such as propranolol, are effective in blunting the sympathetic stimulation
- An alternative in patients suffering from severe heart failure or asthma is the calcium-channel blocker, diltiazem

Hyperthyroidism (Thyrotoxicosis): treatment

- Other agents used in the treatment of thyroid storm include:
  - PTU
  - Iodides
  - Iodinated contrast media (which rapidly inhibits the conversion of T4 to T3)
  - Glucocorticoids (to protect against shock)