Lec. 5: Thyroid Hormones

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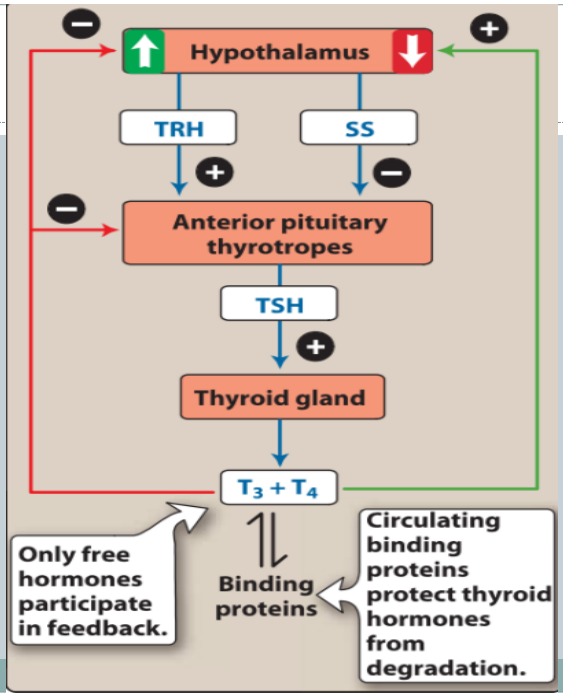
The Thyroid Gland

- **The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for normal function.**
- **The two major thyroid hormones are triiodothyronine (T3; the most active form) and thyroxine (T4).**
- **Normal TH concentration called Euthyroid.**
- **High TH concentration called hyperthyroidism or Graves ' disease or thyrotoxicosis.**

- **Low TH concentration called cretinism in children.**
- **Low TH concentration called myxoedema in adults.**
- **NOTE: Hyper or hypothyroidism may or not associated with goiter formation.**
- **The t1/2 of T3 is 2 days, while the the t1/2 of T4 in euthyroid is 7 days.**
- **The t1/2 of T4 in hyperthyroidism is 3 days The t1/2 of T4 in hypothyroidism is 14 days .**

A. 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 thyroglobulin (the storage form of thyroid hormone).**
- **Thyroid function is controlled by TSH (thyrotropin), which is synthesized by the anterior pituitary.**
- **[Note: The hypothalamic thyrotropin-releasing hormone (TRH) governs the generation of TSH.]**
- **TSH action is mediated by cAMP and leads to stimulation of iodide.**



Steps of TH synthesis:

- **1- Iodide trapping: active uptake of iodide from circulation into thyroid cells.**
- **The concentration of iodide in the thyroid gland is 25 times more than concentration in the blood.**
- **2- Oxidation of iodide to iodine**

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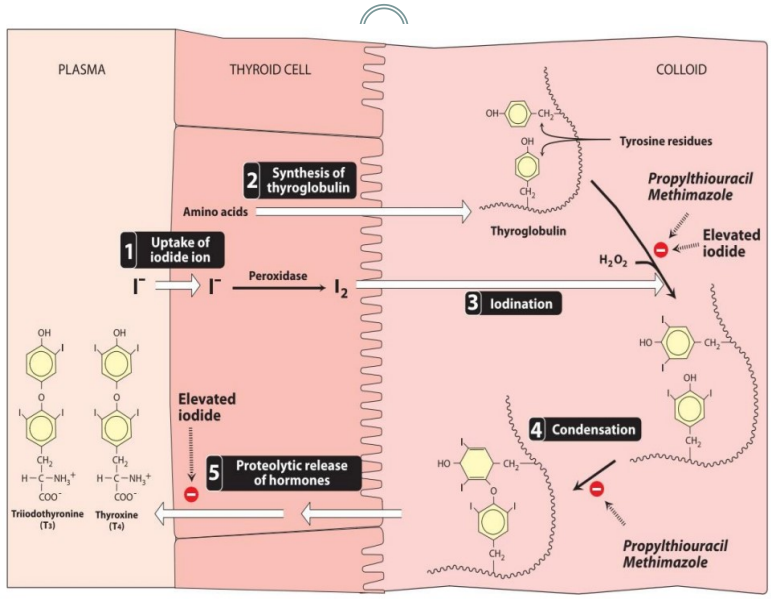
- **3- Coupling of iodide with tyrosine (a.a): forming mono iodic tyrosine in the presence of peroxidase enzyme.**

- **4- Condensation of 2 molecules of mono iodic tyrosine forming di-iodic tyrosine and then tri iodic tyrosine and tetra-iodic tyrosine in the presence of peroxidase enzyme.**
- **About 80% of T4 converted to T3 which is biologically 5 times more active than T4.**
- **Both T3 and T4 are highly protein binding forming thyroglobulin (TG), especially T4.**
- **Both are metabolized by cytochrome p-450 in the liver so they affected by enzyme inducers and inhibitors.**



B. Mechanism of action

- Most circulating T3 and T4 is bound to thyroxine binding globulin in the plasma.
- The hormones must dissociate from thyroxine binding globulin prior to entry into cells.
- In the cell, T4 is enzymatically deiodinated toT3, 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.

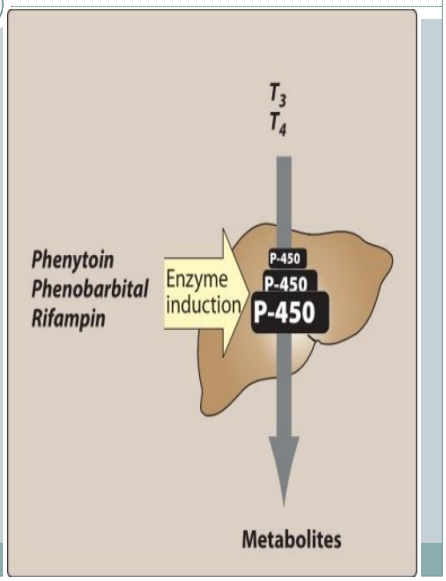
- C. Pharmacokinetics Both T4 and T3 are absorbed after oral administration. Food, calcium preparations, iron salts, and aluminum-containing antacids can decrease the absorption of T4.
- Deiodination is the major route of metabolism of T4. T3 also undergoes sequential deiodination. The hormones are also metabolized via conjugation with glucuronides and sulfates and excreted into bile.

D. Treatment of hypothyroidism

- Hypothyroidism usually results from autoimmune destruction of the gland and is diagnosed by elevated TSH.
- Levothyroxine (T4) is preferred over T3 (liothyronine) or T3/T4 combination products (liotrix) for the treatment of hypothyroidism.
- Levothyroxine is better tolerated than T3 preparations and has a longer half-life.
- It is dosed once daily, and steady state is achieved in 6 to 8 weeks.

Toxicity is directly related to T4 levels and manifests as nervousness, palpitations and tachycardia, heat intolerance, and unexplained weight loss.

Drugs that induce the cytochrome P-450 enzymes, such as phenytoin, rifampin, and phenobarbital, accelerate metabolism of thyroid hormones and may decrease the effectiveness.



E. Treatment of hyperthyroidism (thyrotoxicosis)

- **Graves' disease, an autoimmune disease that affects the thyroid, is the most common cause of hyperthyroidism.**
- **In these situations, TSH levels are low due to negative feedback.**
- **[Note: Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone, which, in turn, decreases secretion of TSH.]**
- **The goal of therapy is to decrease synthesis and/or release of additional hormone.**
- **This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of hormones from the follicle.**

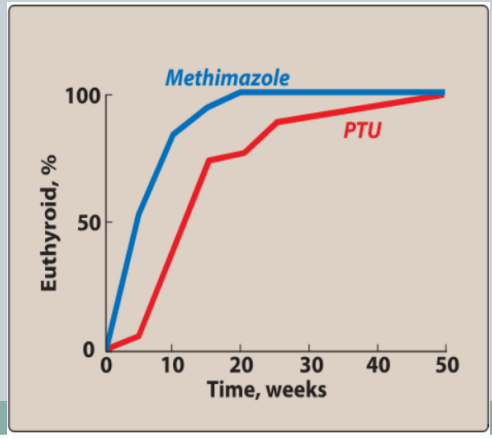
1. Removal of the thyroid:

- This can be accomplished surgically or by destruction of the gland with radioactive iodine (131I), which is selectively taken up by the thyroid follicular cells.
- Most patients become hypothyroid after radioactive iodine and require treatment with levothyroxine.

2. Inhibition of thyroid hormone synthesis:

- The thioamides (propylthiouracil (PTU) and methimazole), are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the condensation (coupling) of iodotyrosines to form T3 and T4.
- PTU also blocks the peripheral conversion of T4 to T3.
- [Note: These drugs have no effect on thyroglobulin already stored in the gland.

- **Therefore, clinical effects may be delayed until thyroglobulin stores are depleted.**



- **Methimazole is preferred over PTU because it has a longer half-life, allowing for once-daily dosing, and a lower incidence of adverse effects.**
- **However, PTU is recommended during the first trimester of pregnancy due to a greater risk of teratogenic effects with methimazole.**
- **PTU has been associated with hepatotoxicity and, rarely, agranulocytosis.**

3. Blockade of hormone release:

- A pharmacologic dose of iodide inhibits the iodination of tyrosine ("Wolff-Chaikoff effect"), but this effect lasts only a few days.
- More importantly, iodide inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood.
- Iodide is employed to treat thyroid storm or prior to surgery, because it decreases the vascularity of the thyroid gland.

- Iodide, administered orally, is not useful for long-term therapy; the thyroid ceases to respond to the drug after a few weeks.
- Adverse effects include sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and metallic taste.

4. Thyroid storm:

- Thyroid storm presents with extreme symptoms of hyperthyroidism.
- The treatment of thyroid storm is the same as for hyperthyroidism, except that the drugs are given in higher doses and more frequently.

- β-blockers, such as metoprolol or propranolol, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism.
- but beta blockers can't be considered as anti- hyperthyroid drugs because:
- 1- B-Blockers don't change the lab-biochemical test results.
- 2- B-Blockers don't treat or block all metabolic effects of TH.
- 3- B-Blockers don't change the course of disease.


Thank You