ENDOCRINE
PHARMACOLOGY

03

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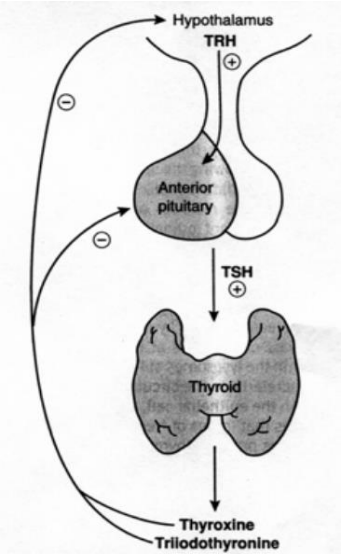
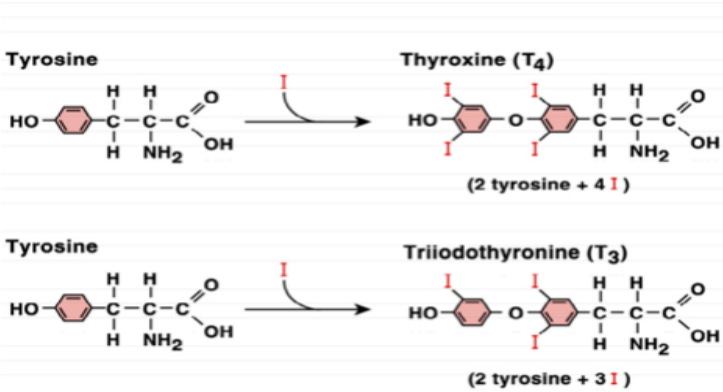
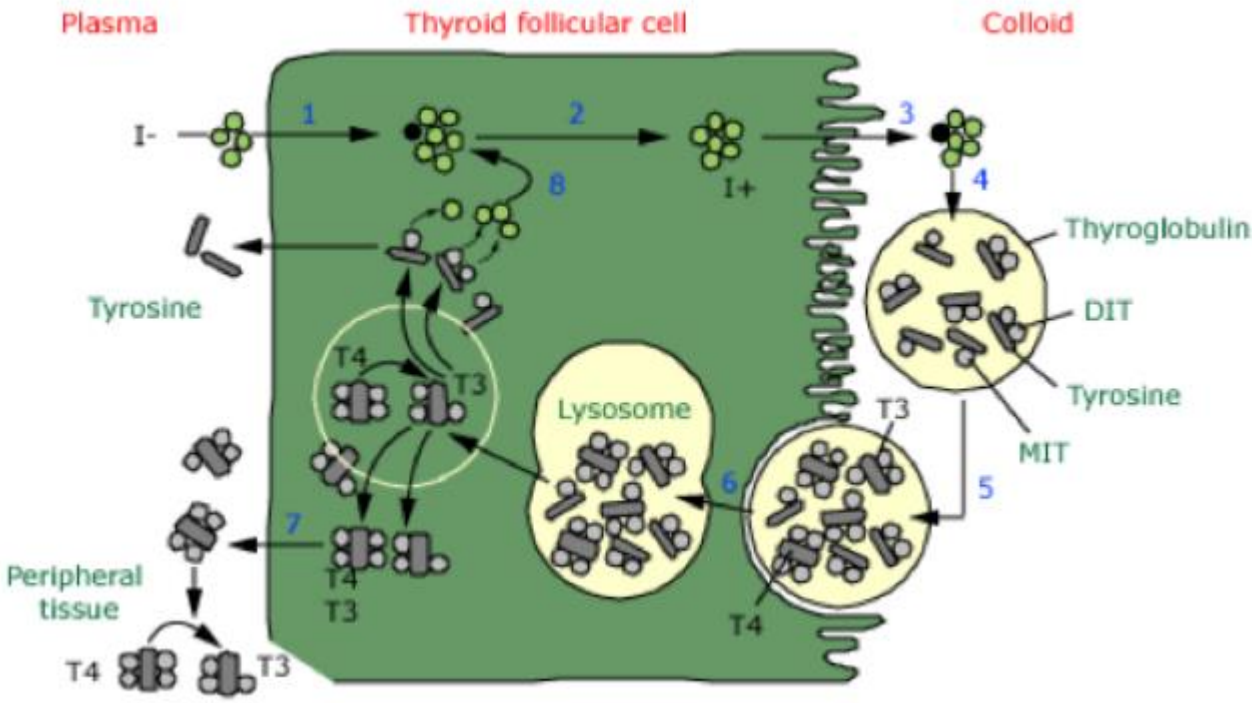
THYROID GLAND HORMONES:

- Hypothalamus release TRH → Anterior pituitary release TSH → thyroid (follicular cell release T3 & T4 that negatively feedback at the level of pituitary (mainly) & little bit on the hypothalamus + parafollicular cell release calcitonin involved in regulation of calcium metabolism.



- T3 & T4: amino acid derivatives (iodinated tyrosine)
- T4 produces little effect. The main action of T4 is to be transported to peripheral tissue then converted to T3.





- The machinery of formation starts by:

1- uptake of iodide by thyroid follicle from the blood.

2- Enter the thyroid follicle.

3- Oxidation iodide to iodine.

4- Iodination (addition of iodine to tyrosine residues on thyroglobulin).

5- Coupling reaction. (DIT & MIT)

6- Endocytosis & cleavage by lysosomal enzymes to produce T3 & T4 that are stored in special pool.

7- Release to blood.

8- T4 is converted to T3 in periphery.

IODIDE:

Needed for synthesis of thyroid hormones.

- **Sources:**
  1. **Iodized salt**
  2. **Iodated bread**
  3. **Dairy products**
  - **Daily requirement: 75 micrograms which is about 10g of iodized salt.**
  - **The oxidation, iodination, and coupling reactions are catalyzed by iodine or thyroid peroxidase enzyme.**
  - **Lysosomal enzymes hydrolyze thyroglobulin.**
  - **Most of released T4 is converted in periphery to T3 by deiodinase enzyme.**
  - **Thyroid hormones travel in blood bound to a specific thyroxine binding globulin (TBG).**

-- a quick sort of comparison--

- **Thyroid content:**

T4 (Thyroxine) > T3 (4:1)

- **Source:**

T4 = thyroid gland

T3 = deiodination of T4 (80% of T3 is formed by deiodination of T4 in peripheral tissues).

- **Potency:**

  T3 > T4 (Free T3 is 3-5 times more active than free T4).

- **Protein binding:**

  T4 > T3 (T4 99.97% bound; T3 99.5% bound)

- **Half-life:**

  T4 = 1 wk

  T3 = 1 day

THYROID HORMONES MOA:

- **Thyroxine reaches target cells with the aid of the carrier protein. Thyroxine easily passes plasma membrane (highly lipophilic).**
- **Most of T4 is converted to T3 in target cells.**
- **Only the T3 form enters the nucleus and binds nuclear receptor protein.**
- **The hormone-receptor protein complex binds specific response elements on DNA leading to a direct effect on the level of transcription.**
- **The mRNA produced then codes for specific proteins that mediate effects of thyroid hormones.**

GENERAL EFFECTS OF THYROID HORMONES:

- Promote growth & development (essential for growth in childhood).

- Calorigenic effect: ↑ BMR; ↑ O2 consumption; ↑ general metabolism; ↑ CHO metabolism.

- ↑ lipolysis; ↑ lipid breakdown.

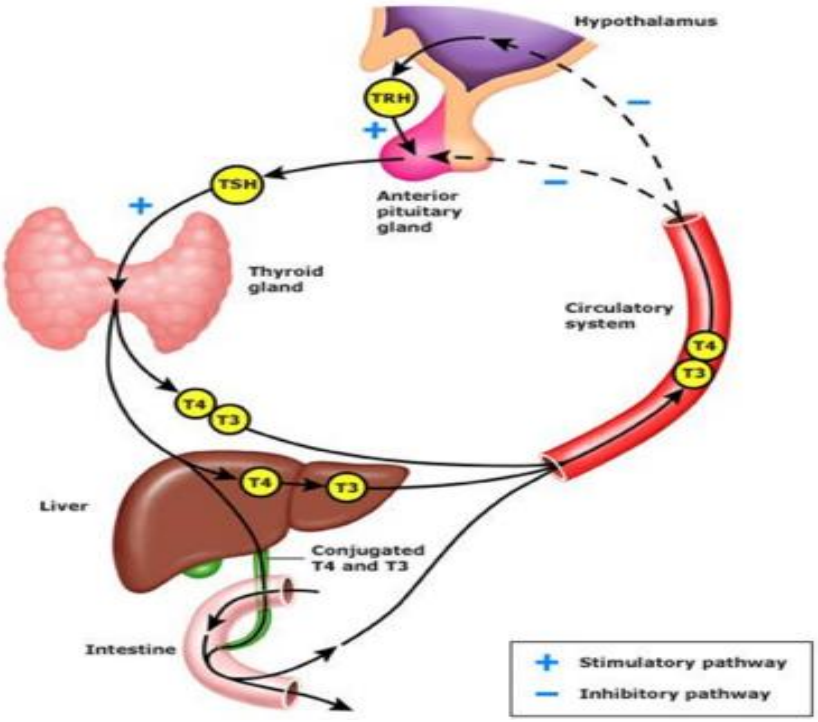
- ↓ Cholesterol blood level.

- ↑ β-adrenergic receptors in most tissues. (Especially the CVS)

- ↑ GIT motility…cause diarrhea**.**

-Pathways of thyroid hormone metabolism:

Mainly metabolized in the liver by conjugation.



DISORDERS AFFECTING THE THYROID GLAND:

I.HYPOTHYROIDISM:

In Children → Cretinism **In adults → Myxedema**

- **Causes:**
  1) **Surgical removal of thyroid.**
  2) **Thyroiditis (Hashimoto's= chronic lymphocytic thyroiditis= an AI inflammatory disease-causing atrophy of thyroid; infectious; transient; postpartum hemorrhage…).**
  3) **Severe deficiency or excess of iodine.**
  4) **Severe deficiency of one or more of the synthesis enzymes** Involved in synthesis of thyroid hormones**.**
  5) **Severe pituitary or hypothalamic dysfunction.**
  6) **Drug induced…**
- **symptoms:**
  1) **Cold intolerance, lethargy, constipation Slowing of mental function and motor activity Weight gain but appetite decreased, abnormal menses, dry/thick skin, hair loss, and hoarse voice.**

2) **Stroke volume and heart rate decreased; non pitting edema** (non-pitting edema occurs when excess fluid builds up in the body causing swelling that does not indent when pressure is applied. It usually occurs in the limbs, and often results from underlying medical conditions affecting lymphatic system function).

➢ **Rx:**

HRT (hormone replacement therapy).

❖ **Thyroid hormones preparations:**

Orally very safe, but for IV never use it before allergic test on skin.

a- Thyroid USP (bovine, ovine, porcine) oral.

b- Thyroid extract (Thyroglobulin) oral.

c- ℓ- thyroxine sodium; synthetic T4, oral.

d- Liothyronine sodium, synthetic T3, oral & I.V.

e- Liotrix, synthetic T4 & T3 (4:1), oral.

❖ **All have t1/2 of 1 wk except liothyronine.**

❖ **Allergies more with animal preparations.**

- Iodine in salts rarely causes allergies.
- The most widely used in management of hypothyroidism is synthetic T4.

❖ **Clinical uses to thyroid hormones:**

1. **Hypothyroidism.**
2. **Thyroid cancer** (TSH-dependent).
3. **Wt. reduction (abuse!!!).**

❖ **d- isomer as compared to l- isomer:**
d- is equipotent to the l- with respect to its effects on blood cholesterol levels but has ¼ the potency with respect to other effects (e.g., growth and development, calorigenic effect…etc).

➢ **Side effects to thyroid hormones:**

1. **Hyperthyroidism.**
2. **allergic reactions.**

II.HYPERTHYROIDISM:

- **thyrotoxicosis**
- **Grave's disease** (should be combined with hyperplasia of thyroid and exophthalmos to diagnose grave's disease)

➢ **symptoms:**

- **Heat, intolerance, Nervousness, irritability, emotional instability, Fatigue, Weight loss but increased food ingestion, Increased bowel movements (diarrhea), Abnormal menses, Tachycardia, and atrial arrhythmias (atrial fibrillation)**

➢ **Rx of hyperthyroidism:**

- **Propranolol** (B- blocker), highly effective but remember it's not an anti-thyroid drug.
- **Antithyroid drugs** (Anti thyroid drug is drug hits any step in synthetic machinery of thyroid hormone).
- **Surgery**

Propranolol controls the manifestations of thyrotoxicosis.

It has no antithyroid activity.

ANTITHYROID DRUGS:

1.THIOUREA DERIVATIVES (THIONAMIDES)

- They have no effect on the release of thyroid hormone.
- **Methimazole**
- **Carbimazole((pro-drug) is converted to Methimazole)**
- **Propylthiouracil**

➢ **Potency:**

Methi. > Carbi. > Propyl.

➢ **All effective orally**

MOA:

- **Inhibitors to thyroid peroxidase enzyme**
- **Interfere with oxidation, iodination, and coupling reactions.**
- **Propyl. also ↓ peripheral deiodination of T4**

- **Side effects to thioamides:**
  - **Allergy**
  - **Hepatic dysfunction**
  - **Agranulocytosis (also an absolute contraindication to their use)**

Agranulocytosis: extremely low number of granulocytes (a type of white blood cell) in the blood.

  - **Methimazole is teratogenic (aplasia cutis congenita** -congenital defect of skin-**); propylthiouracil is not.**

- **Disadvantages:**
  - **Delayed onset of action (12-18 hrs)** Because it doesn't work by release mechanism but affects the synthetic pathway, so it takes time.
  - **Prolong Rx (12-18 months)**
  - **Side effects**
  - **High relapse rate** (When you stop taking the drug, the condition reoccurs)

2. IODIDE (K+ OR NA+):

- **Solution and oral tab.**

MOA:

- **↓ oxidation ↓ release of T4, T3 (the Wolff–Chaikoff effect= an autoregulatory phenomenon, whereby a large amount of ingested iodine acutely inhibits thyroid hormone synthesis within the follicular cells)**

- **Major side effects:**
  - **Allergy (test for iodide hypersensitivity)**
    - **Widely used before thyroid surgeries to ↓ vascularity of the thyroid gland**

3.RADIOACTIVE IODINE=RAI (131I):

- **Sol., Caps.**
- **Diagnostic use (small dose)**
- **Rx of hyperthyroidism and Grave's disease (intermediate dose)**

- ❖ **Rx of thyroid Ca (large doses)**
- ❖ **In the US, over 60% of endocrinologists select radioiodine as first-line therapy for Grave's disease.**
- ❖ **It is the preferred therapy for women desiring pregnancy soon. After RAI therapy, they must wait 4-6 months before conceiving.**
  - ➢ **Advantages: higher remission rates - 10% will fail first treatment and require a second dose of 131I**
  - ➢ **Disadvantage: hypothyroidism - is dose dependent**
  - ➢ **Contraindications:**
    - ❖ **pregnancy (absolute)** (Because of its teratogenic activity)
    - ❖ **ophthalmopathy (relative-RAI therapy may cause or worsen this condition)**
  - ➢ **Side effects:**
    - ❖ **Pulmonary fibrosis**
    - ❖ **Teratogenicity and carcinogenicity**

4.LITHIUM CARBONATE:

- ❖ **Oral and S.R tab**
- ❖ **Has similar MOA to iodide.**
- ❖ **Has a narrow therapeutic window.**
- ❖ **Also, the drug of choice to treat manic depressive psychosis.**
  - ➢ **Side effects:**

    Nausea, diarrhea, drowsiness, blurred vision Ataxia, tinnitus, and diabetes insipidus

5. IODINATED CONTRAST MEDIA:

- ❖ **e.g., Ipodate**
- ❖ **Given orally.**
- ❖ **Contain iodine + Inhibit peripheral conversion of T4 to T3**
- ❖ **Inhibit release of T4 & T3**
- ❖ **Similar side effects to iodide**
- ❖ **Allergic reactions**

POTENTIAL T4, T3 INTERACTIONS

1- **Drugs reducing thyroid hormone production:**
   - ❖ **Lithium, Iodine-containing medications, Amiodarone.**
2- **Drugs reducing thyroid hormone absorption:**
   - ❖ **Sucralfate, Ferrous sulfate, Cholestyramine, Colestipol, Aluminum-containing antacids, Calcium products.**
3- **Drugs increasing metabolism of thyroxine:**
   - ❖ **Rifampin, Phenobarbital, Carbamazepine, Warfarin, Oral hypoglycemic agents.**
4- **Drugs displacing thyroid hormones from protein binding:**
   - ❖ **Salicylates (Aspirin), Furosemide, Mefenamic acid.**