



ENDOCRINE

PHARMACOLOGY

Modified 3 



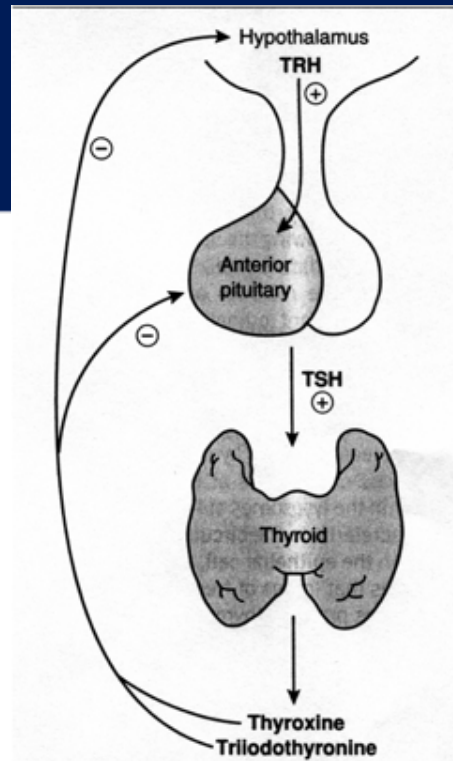
WRITER: Lujain Slaihat

CORRECTOR: Lujain Slaihat

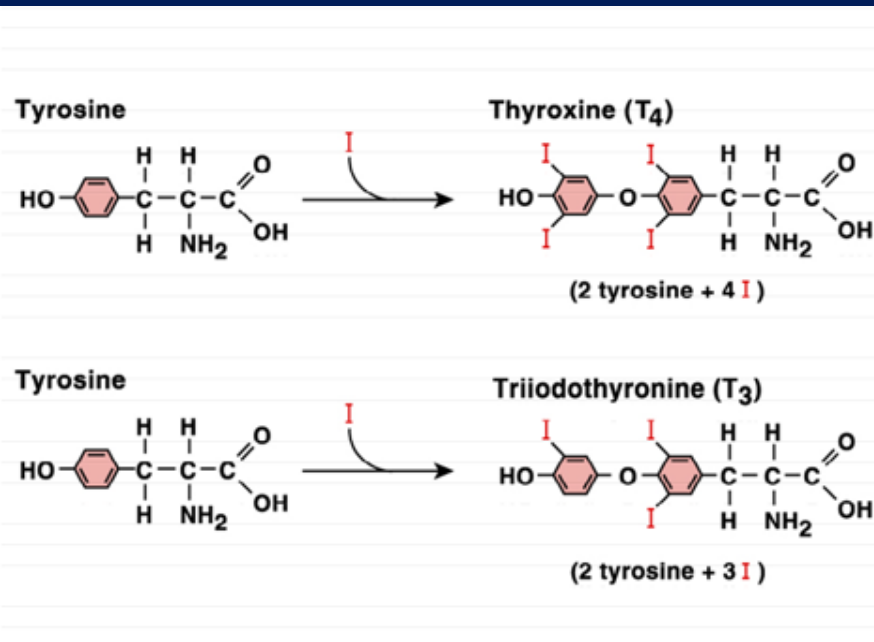
DOCTOR: Suhil Zmeili

Thyroid Gland Hormones

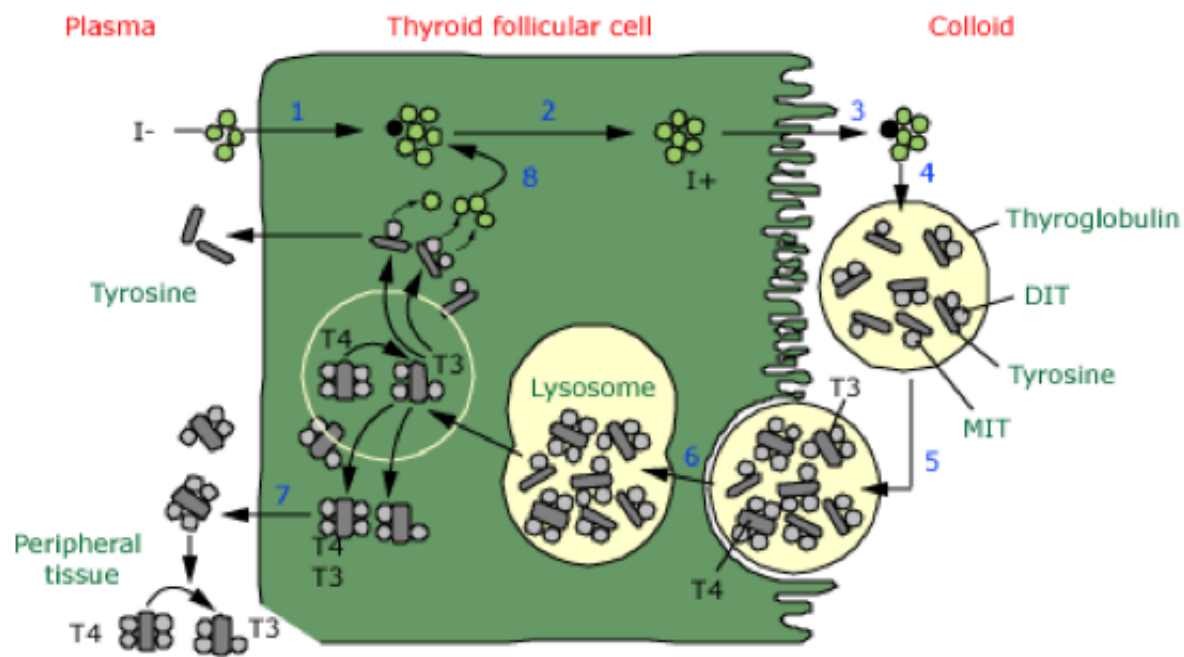




Hypothalamus release TRH → Anterior pituitary release TSH → thyroid (follicular cell release T3 & T4 that negatively feedback at the level of pituitary (mainly) & little pit on the hypothalamus
 + parafollicular cell release calcitonin involved in regulation of calcium metabolism .



T3 & T4 : amino acid derivatives
(iodinated tyrosine)



T4 produce little effect. The main action of T4 is transport to peripheral tissue then converted to T3

The machinery of formation start by

1. uptake of iodide by thyroid follicle from the blood
2. Enter the thyroid follicle
3. Oxidation iodide to iodine
4. Iodination (addition iodine to tyrosine residues on thyroglobulin)
5. Coupling reaction
6. Endocytosis & cleavage by lysosomal enzymes to produce T3 & T4 that stored in special pool
7. Release to blood

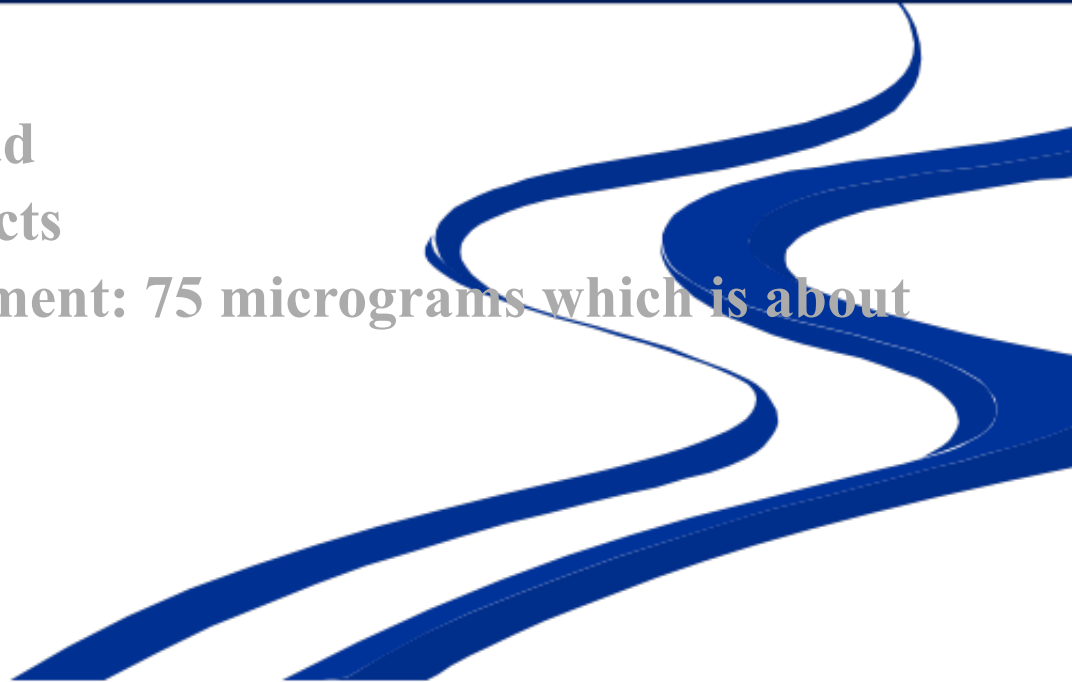
- **Iodide**

Needed for synthesis of thyroid hormones

Sources:

- Iodized salt
- Iodated bread
- 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

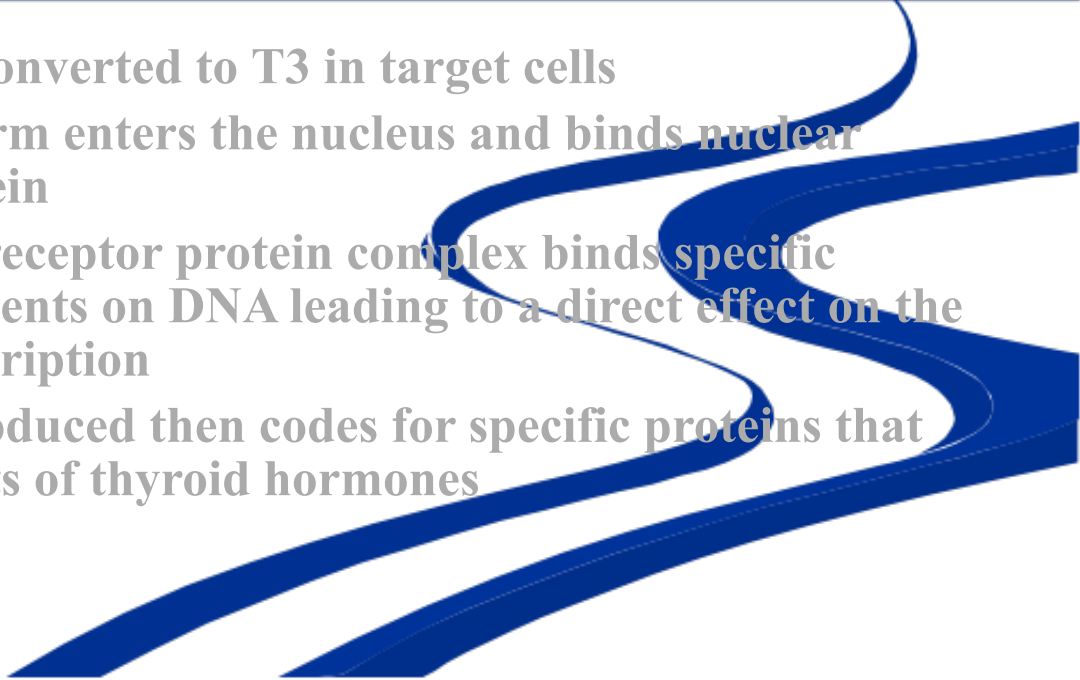
Thyroid hormones travel in blood bound to a specific thyroxine binding globulin (TBG)

- **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 by 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
- 
- A decorative graphic consisting of several thick, wavy blue lines that flow from the right side of the text area towards the bottom left of the slide.

- **General effects of thyroid hormones:**

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

- Calorigenic effect:

- ↑ BMR; ↑ O₂ consumption; ↑ general metabolism; ↑ CHO metabolism

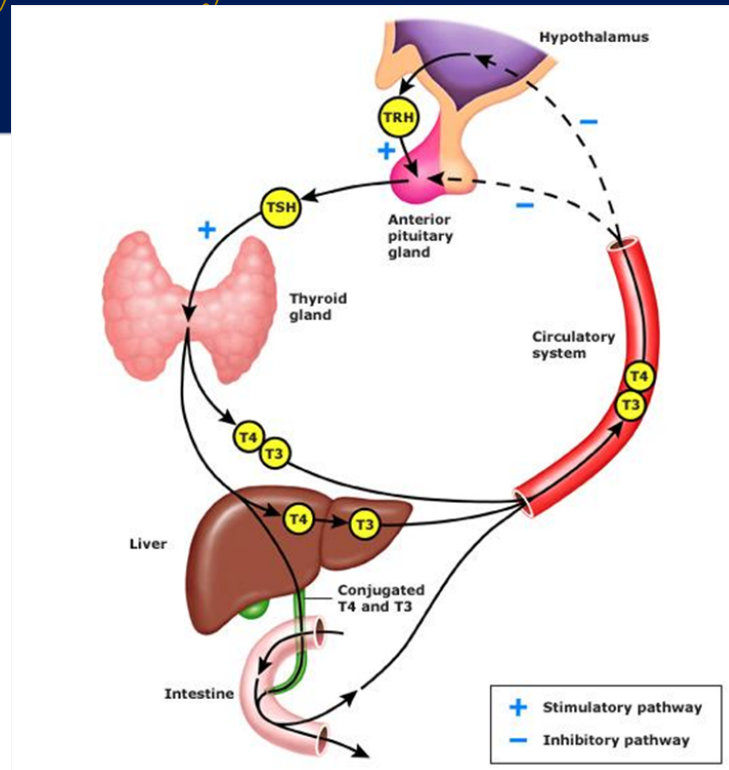
- ↑ lipolysis; ↑ lipid breakdown

- ↓ Cholesterol blood level

- ↑ β-adrenergic receptors in most tissues

- ↑ GIT motility... [Let to diarrhea](#)

- Pathways of thyroid hormone metabolism



- **Disorders affecting the thyroid gland:**

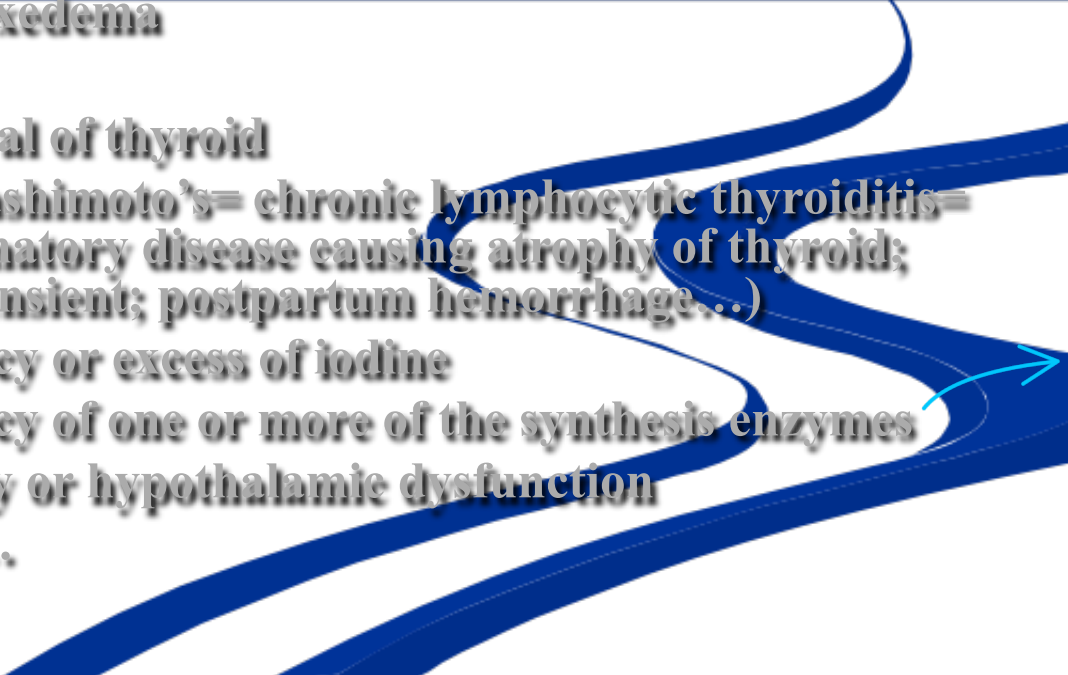
Hypothyroidism

In Children → Cretinism

In adults → Myxedema

- **Causes:**

- **Surgical removal of thyroid**
- **Thyroiditis (Hashimoto's= chronic lymphocytic thyroiditis= an AI inflammatory disease causing atrophy of thyroid; infectious; transient; postpartum hemorrhage...)**
- **Severe deficiency or excess of iodine**
- **Severe deficiency of one or more of the synthesis enzymes**
- **Severe pituitary or hypothalamic dysfunction**
- **Drug induced...**



Involved in synthesis of thyroid hormones

- **Hypothyroidism-symptoms**

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

Stroke volume and heart rate decreased; non pitting edema

- **Rx : HRT** (Hormone replacement therapy)

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.

- **Thyroid hormones preparations:**

- **Thyroid USP (bovine, ovine, porcine) oral**

- **Thyroid extract (Thyroglobulin) oral**

- ***l*- thyroxine sodium; synthetic T4, oral**

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

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

All have $t_{1/2}$ of 1 wk except liothyronine

Allergies more with animal preparations

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

Iodine in salts rarely causes allergies.

The most widely used in management of hypothyroidism is synthetic T4.

- **Clinical uses to thyroid hormones:**

- **Hypothyroidism**

- **Thyroid cancer** (TSH- dependent)

- **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:**

- **Hyperthyroidism**

- **Allergic reactions**

- **Hyperthyroidism**

Thyrotoxicosis →

Grave's disease

Hyperthyroidism

Hyperplasia of thyroid

Exophthalmos

To call hyperthyroidism as
Grave's disease you should see
these three signs



- **Hyperthyroidism-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**

- **Surgery**

Propranolol controls the manifestations of thyrotoxicosis

It has no antithyroid activity

Anti thyroid drug : is drug hits any step in synthetic machinery of thyroid hormone

- **Antithyroid drugs:**

- ** **Thiourea derivatives (Thionamides)** They have no effect on release of thyroid hormone

Methimazole, Carbimazole, Propylthiouracil

Carbimazole (pro-drug) is converted to Methimazole

- **Potency:**

Methi. > Carbi. > Propyl. All effective orally

- **MOA:**

Inhibitors to thyroid peroxidase enzyme

Interfere with oxidation, iodination, and coupling reactions. Propyl. + ↓ peripheral deiodination of T₄

- **Side effects to thionamides:**

- Allergy

- Hepatic dysfunction

- Agranulocytosis (also an absolute contraindication to their use)

- Methimazole is teratogenic (aplasia cutis congenita); → (Congenital defect of skin)
propylthiouracil is not

- **Disadvantages:**

- Delayed onset of action (12-18 hrs)

- Prolong Rx (12-18 months)

- Side effects

- High relapse rate

When you stop taking that drug, the condition reoccur

Because it doesn't work on release mechanism.
To affect the synthetic way, it takes time

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

**** 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

**** Radioactive iodine=RAI (^{131}I):**

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 in the near future. 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 it's teratogenic activity ophthalmopathy (relative-RAI therapy may cause or worsen this condition)**
- **Side effects:**
 - **Pulmonary fibrosis**
 - **Teratogenicity and carcinogenicity**

**** Lithium carbonate:**

Oral and S.R tab.

Has similar MOA to iodide

Has 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

**** Iodinated contrast media:**

e.g. Iodate

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

- **Drugs reducing thyroid hormone production**

Lithium, Iodine-containing medications, Amiodarone

- **Drugs reducing thyroid hormone absorption**

Sucralfate, Ferrous sulfate, Cholestyramine, Colestipol,
Aluminum-containing antacids, Calcium products

- **Drugs increasing metabolism of thyroxine**

Rifampin, Phenobarbital, Carbamazepine, Warfarin, Oral
hypoglycemic agents

- **Drugs displacing thyroid hormones from protein binding**

Salicylates (Aspirin), Furosemide, Mefenamic acid

Exam Q : most dangerous side effect of insulin : hypoglycemia