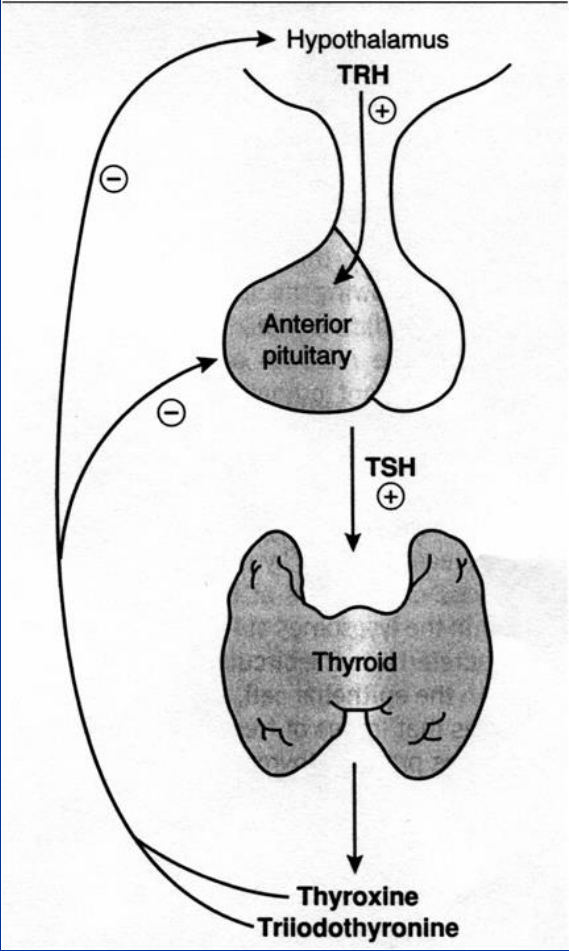
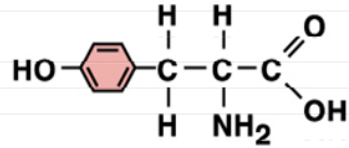


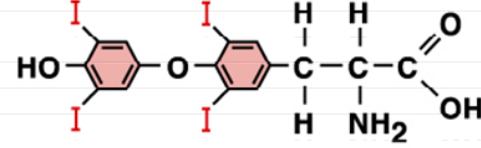
Thyroid Gland Hormones



Tyrosine

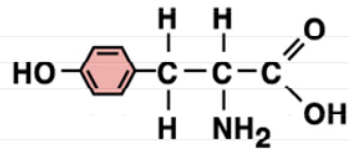


Thyroxine (T₄)

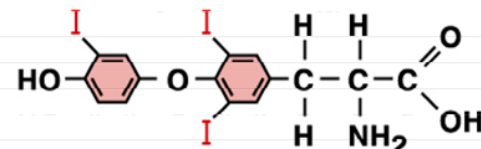


(2 tyrosine + 4 I)

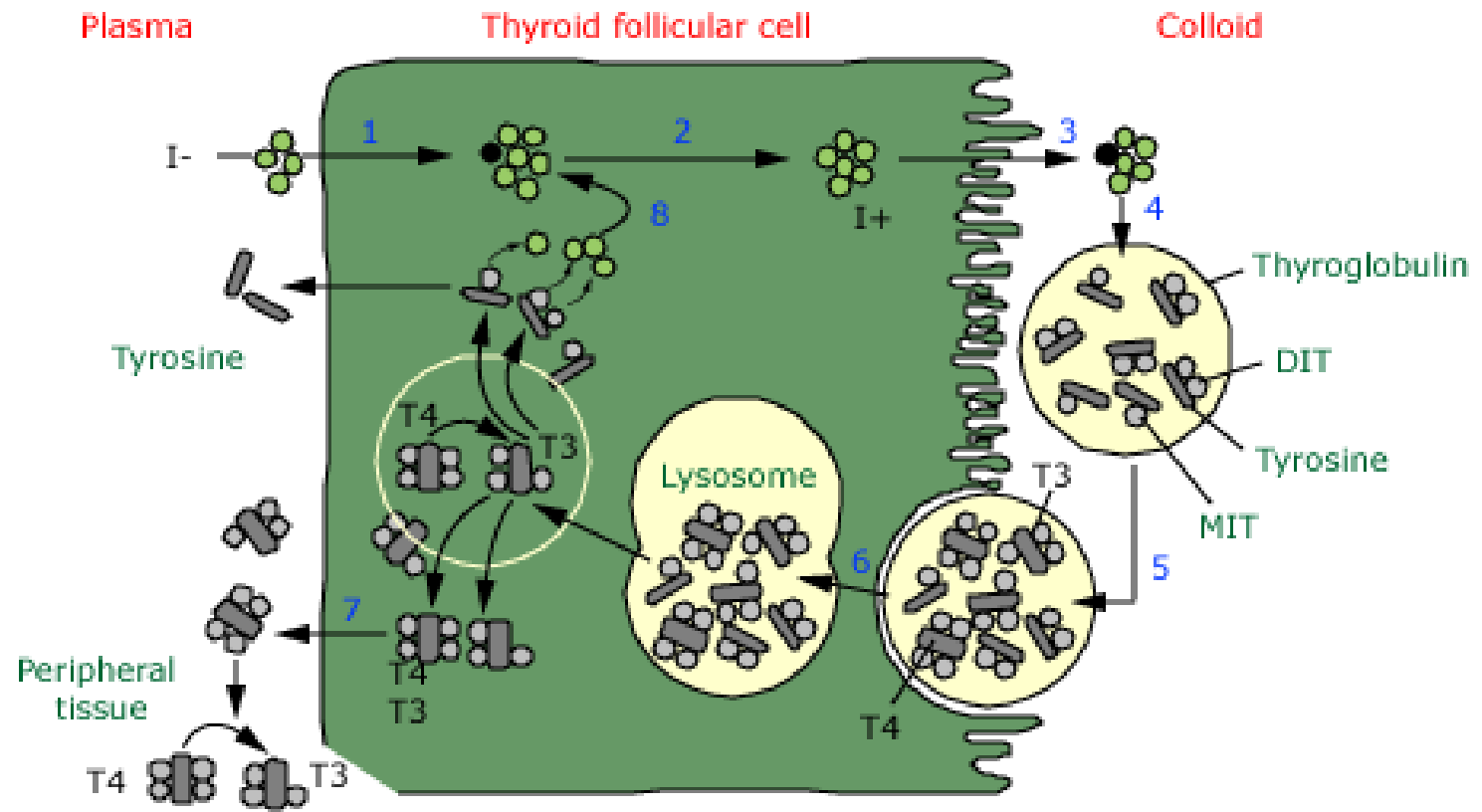
Tyrosine



Triiodothyronine (T₃)



(2 tyrosine + 3 I)



■ 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 T_4 is converted in periphery to T_3 by deiodinase enzyme

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

- **Thyroid content:**

T_4 (Thyroxine) > T_3 (4:1)

- **Source:**

T_4 = thyroid gland; T_3 = deiodination of T_4 (80% of T_3 is formed by deiodination of T_4 in peripheral tissues)

- **Potency:**

T_3 > T_4 (Free T_3 is 3-5 times more active than free T_4)

- **Protein binding:**

T_4 > T_3 (T_4 99.97% bound; T_3 99.5% bound)

- **Half-life:**

T_4 = 1 wk; T_3 = 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 T_4 is converted to T_3 in target cells
- Only the T_3 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

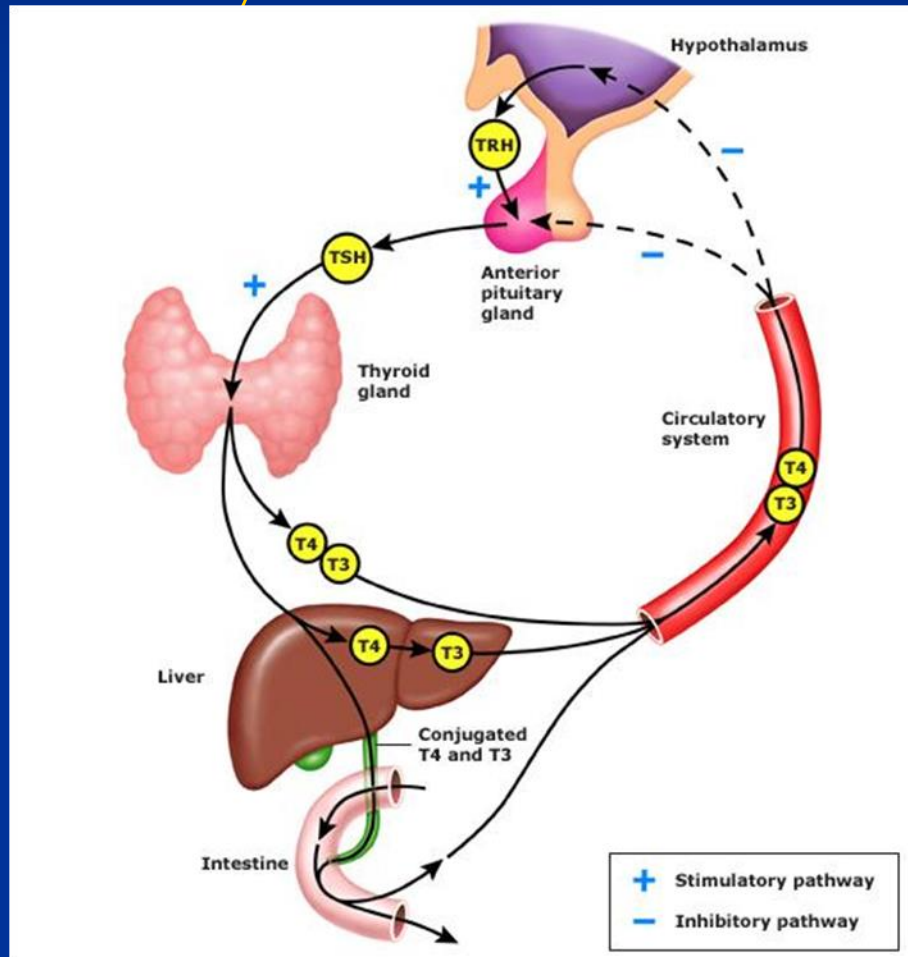
- ↑ lipolysis; ↑ lipid breakdown

- ↓ Cholesterol blood level

- ↑ β-adrenergic receptors in most tissues

- ↑ GIT motility...

■ 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...

■ 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

■ R_x: HRT

■ 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

■ Clinical uses to thyroid hormones:

- Hypothyroidism

- Thyroid cancer

- 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 $\frac{1}{4}$ the potency with respect to other effects (e.g. growth and development, calorogenic effect...etc)

■ Side effects to thyroid hormones:

- Hyperthyroidism
- Allergic reactions

■ Hyperthyroidism

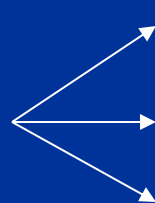
Thyrotoxicosis

Grave's disease

Hyperthyroidism

Hyperplasia of thyroid

Exophthalmos



■ **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)

■ R_x of hyperthyroidism:

- Propranolol
- Antithyroid drugs
- Surgery

Propranolol controls the manifestations of thyrotoxicosis

It has no antithyroid activity

- **Antithyroid drugs:**

- ** **Thiourea derivatives (Thionamides)**

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); propylthiouracil is not

■ Disadvantages:

- Delayed onset of action (12-18 hrs)
- Prolong R_x (12-18 months)
- Side effects
- High relapse rate

**** Iodide (K^+ or Na^+):**

Solution and oral tab.

■ MOA:

↓ oxidation ↓ release of T_4 , T_3 (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)
- R_x of hyperthyroidism and Grave's disease (intermediate dose)
- R_x 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 ^{131}I
- Disadvantage: hypothyroidism - is dose dependent
- Contraindications: pregnancy (absolute), 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 T_4 to T_3

Inhibit release of T_4 & T_3

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