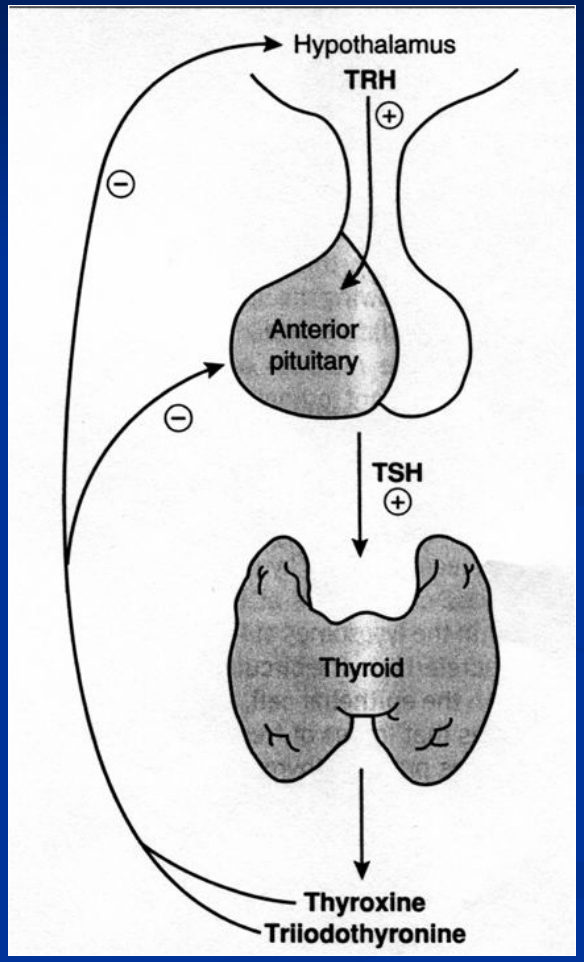
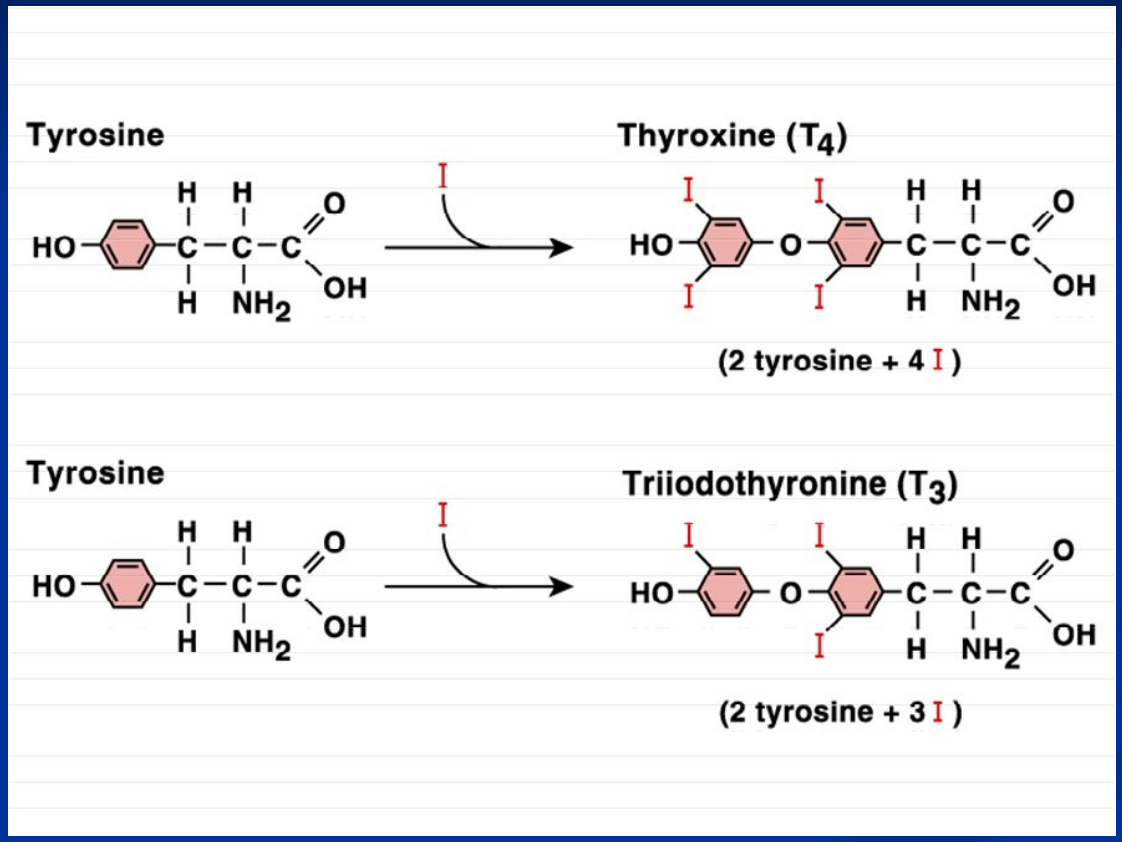
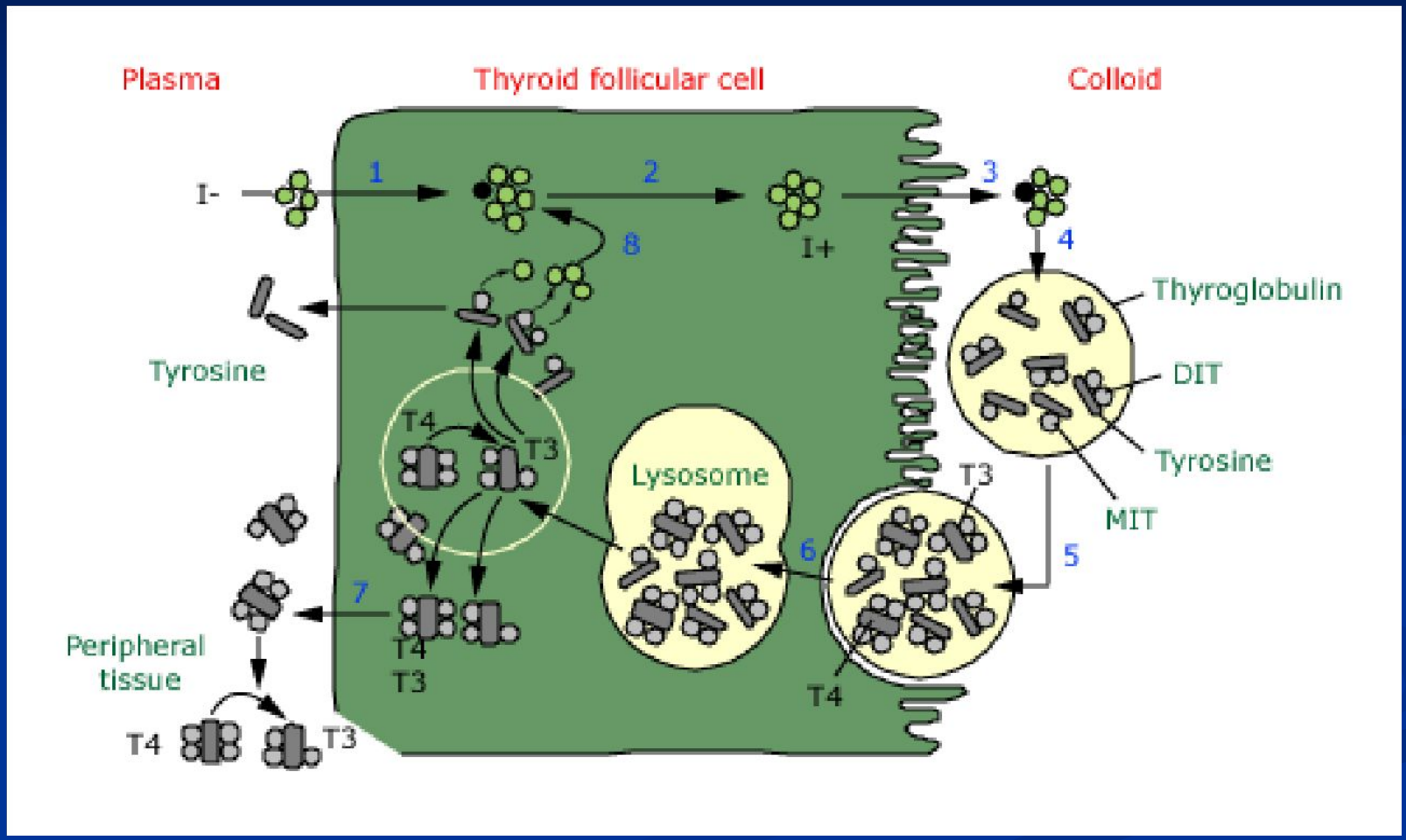
Thyroid Gland Hormones


Hypothalamus
TRH
+
−
Anterior pituitary
−
TSH
+
Thyroid
Thyroxine
Triiodothyronine


Tyrosine
Thyroxine (T_4)
I
HO
C
H
O
OH
NH_2
(2 tyrosine + 4 I)
Tyrosine
Triiodothyronine (T_3)
(2 tyrosine + 3 I)


Plasma
Thyroid follicular cell
Colloid
I-
1
2
I+
3
4
8
Thyroglobulin
DIT
Tyrosine
MIT
Tyrosine
T4
T3
Lysosome
T3
6
5
7
T4
T3
Peripheral tissue
T4
T3
T4

- **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 T3 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

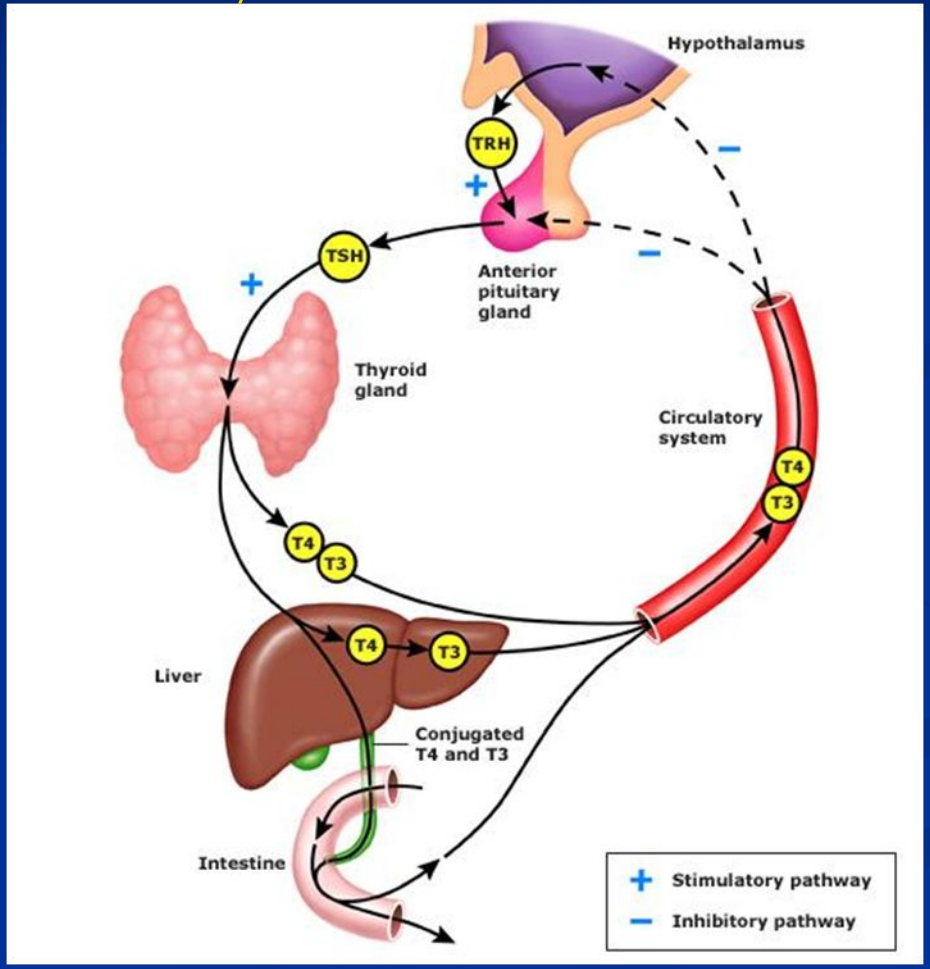
- **General effects of thyroid hormones:**

- Promote growth & development (essential for growth in childhood)
- Calorigenic effect:

↑ BMR; ↑ O_2 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 T_4, oral
- Liothyronine sodium, synthetic T_3, oral & I.V
- Liotrix, synthetic T_4 & T_3 (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 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

- **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 perioxidase enzyme

Interfere with oxidation, iodination, and coupling reactions. Propyl. + ↓ peripheral deiodination of T_4

- **Side effects to thionamides:**

- Allergy
- Hepatic dysfunction
- Agranulocytosis (also an absolute contraindication to their use)
- Methimazole is teratogenic (aplasia cutis congenita); propyltiouracil 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. Ipodate

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 T_4, T_3 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