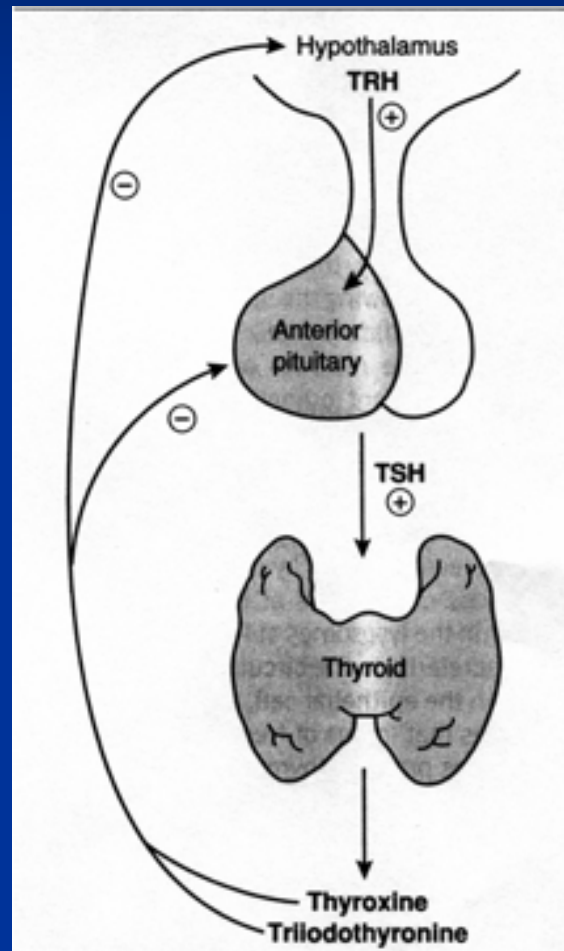
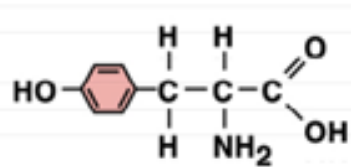


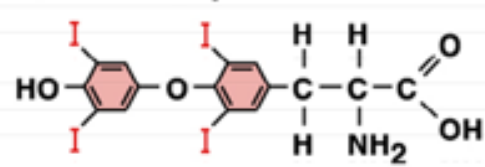
# Thyroid Gland Hormones



**Tyrosine**

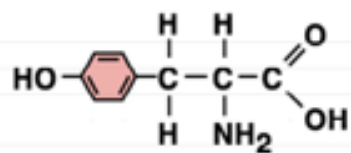


**Thyroxine (T<sub>4</sub>)**

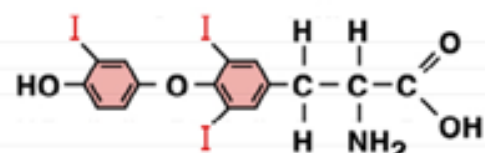


(2 tyrosine + 4 I)

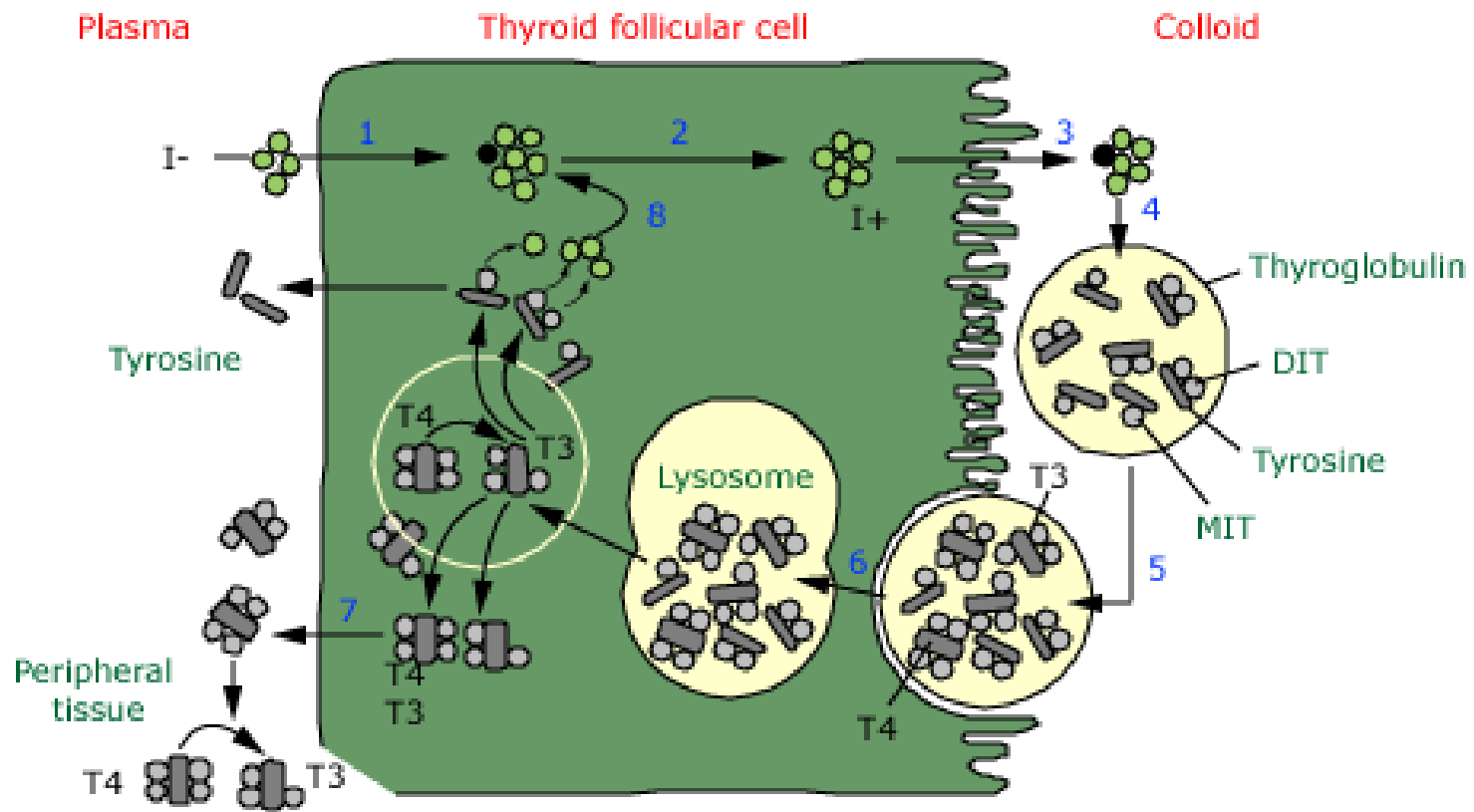
**Tyrosine**



**Triiodothyronine (T<sub>3</sub>)**



(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; ↑ O<sub>2</sub> consumption; ↑ general metabolism; ↑ CHO metabolism

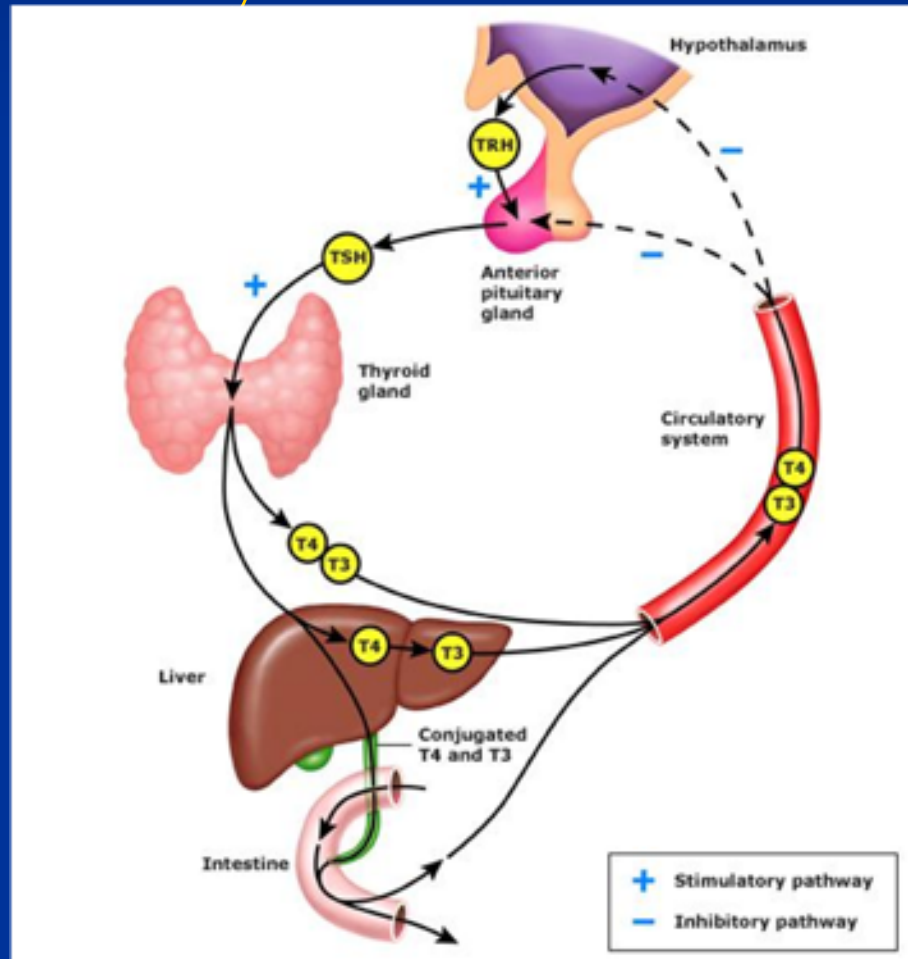
- ↑ lipolysis; ↑ lipid breakdown

- ↓ Cholesterol blood level

- ↑  $\beta$ -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<sub>x</sub>: HRT

## ■ Thyroid hormones preparations:

- Thyroid USP (bovine, ovine, porcine) oral
- Thyroid extract (Thyroglobulin) oral
- $\ell$ - 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  $\frac{1}{4}$  the potency with respect to other effects (e.g. growth and development, calorigenic effect...etc)

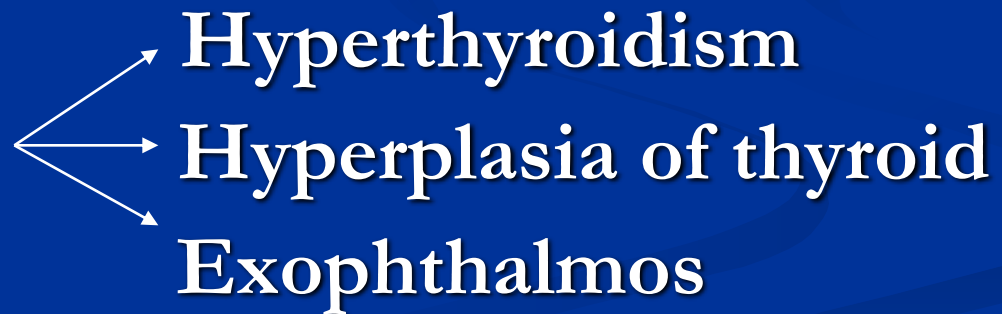
## ■ Side effects to thyroid hormones:

- Hyperthyroidism
- Allergic reactions

## ■ Hyperthyroidism

Thyrotoxicosis

Grave's disease



## ■ Hyperthyroidism-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<sub>x</sub> 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 T<sub>4</sub>

## ■ 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<sub>x</sub> (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 ( $^{131}\text{I}$ ):**

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  $^{131}\text{I}$
- 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