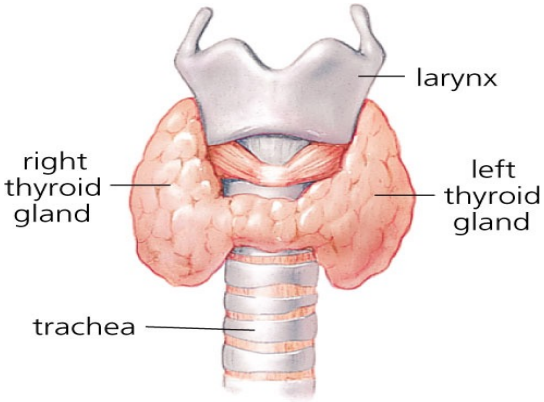
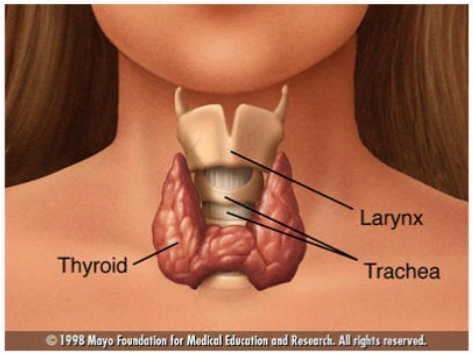
The Thyroid Gland

- Located at the upper portion of the trachea.
- Composed of two lobes
- Found in the neck;
- Responsible for the concentration of iodine & biosynthesis of thyroid hormones from Tyrosine
- Weighs 10-20g in adults
- Larger in women
- Plays a major role in the regulation of metabolism



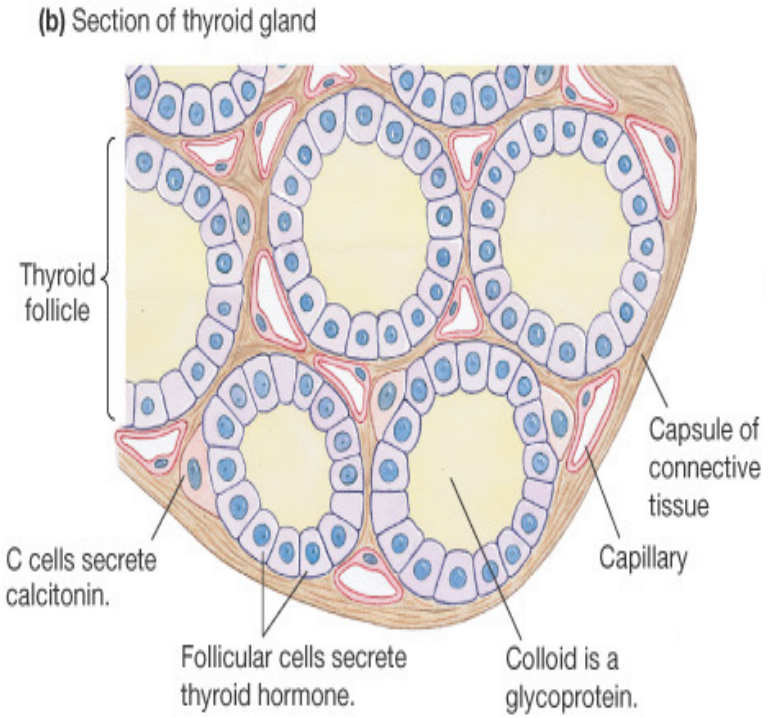


The thyroid gland is located at the base of your neck, just below your Adam's apple.

Thyroid Gland: Hormones and Iodine Metabolism

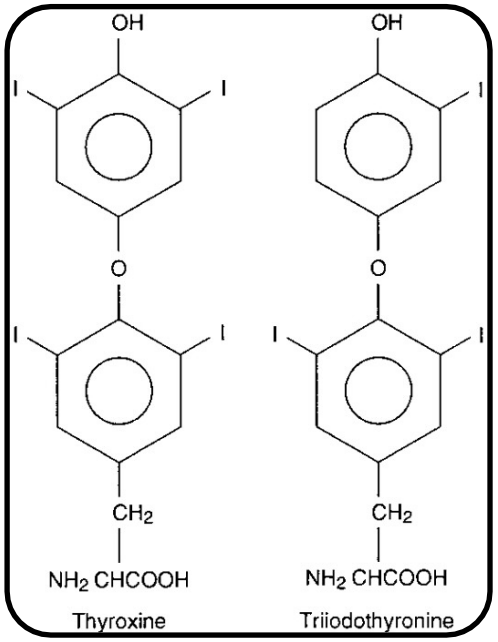
Hormones of the Thyroid gland:

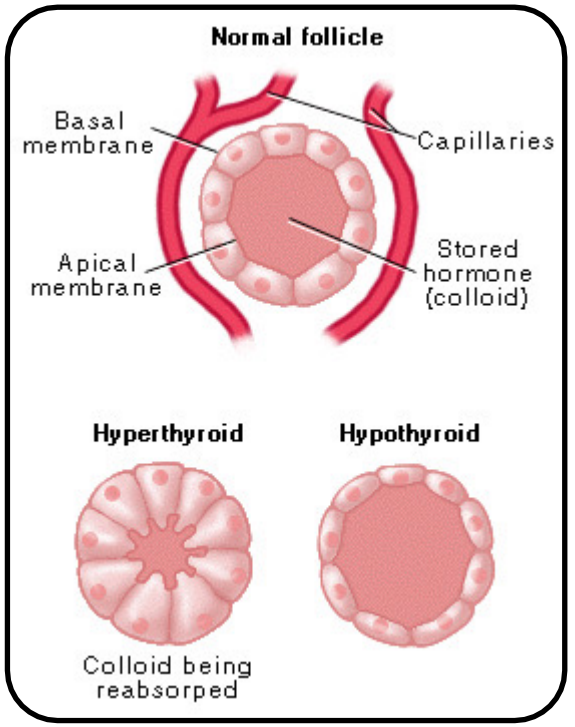
- Parafollicular C-cells secrets calcitonin (CT)
- Follicule cells secret;
  - Amine hormones:
  - Thyroxine (tetraiodothyronine) T4 & triiodothyronine T_3
    - ↑ growth
    - ↑ metabolism
    - Thermogenic



Thyroid Hormones

- Triiodothyronine (T_3) and Tetraiodothyronine (T_4)/Thyroxine
- Major secretory product is T_4
- 15% of T_3 is secreted by thyroid, the rest is produced in the peripheral tissues by the de-iodination of T_4
- Follicle consists of single layer of epithelial cells surrounding a sphere of colloid which contains the protein "Thyroglobulin"





- Recommended intake of iodine is 150µg/day to maintain hormone synthesis
- Dietary source of iodine is mainly fish
- Iodide should be added to foods (salt)

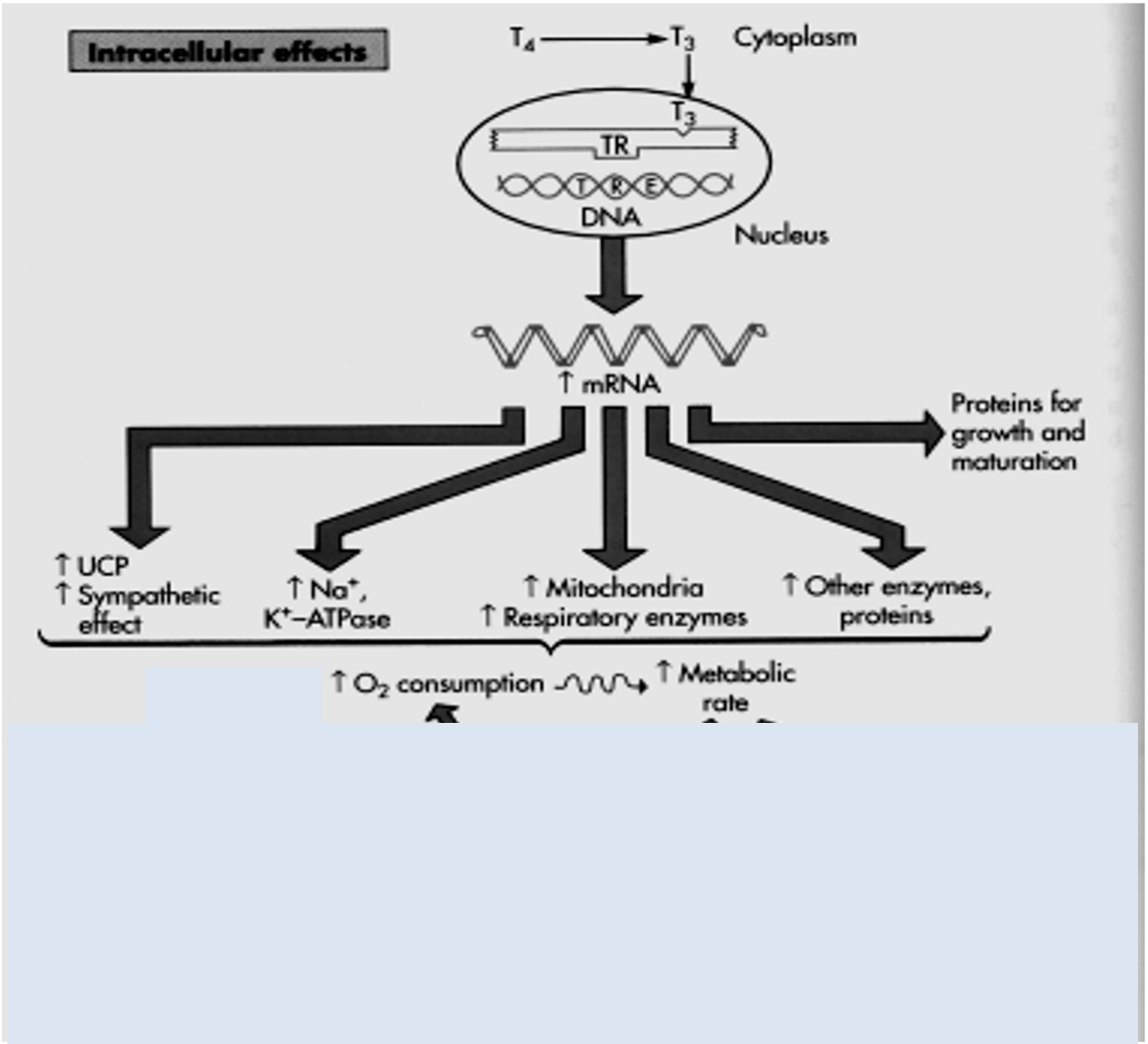
Thyroid Hormone: Transport

- T3 & T4 leave the thyroid gland by diffusion
- Both are transported in blood by three transport proteins, **Thyroxine binding globulin (TBG), transthyretin and albumin**
- A majority (70%) of T4 & T3 is bound to **TBG**
- Both enter their target cells by diffusion.
- Half life: 6- 7 days

Thyroxine and its precursors: Activity

- T4 mainly functions as a prohormone.
- T3 is the main active thyroid hormone and has the highest binding affinity for thyroid hormone receptor (TR).

Thyroxine and its precursors: Activity



TR: thyroid receptor.

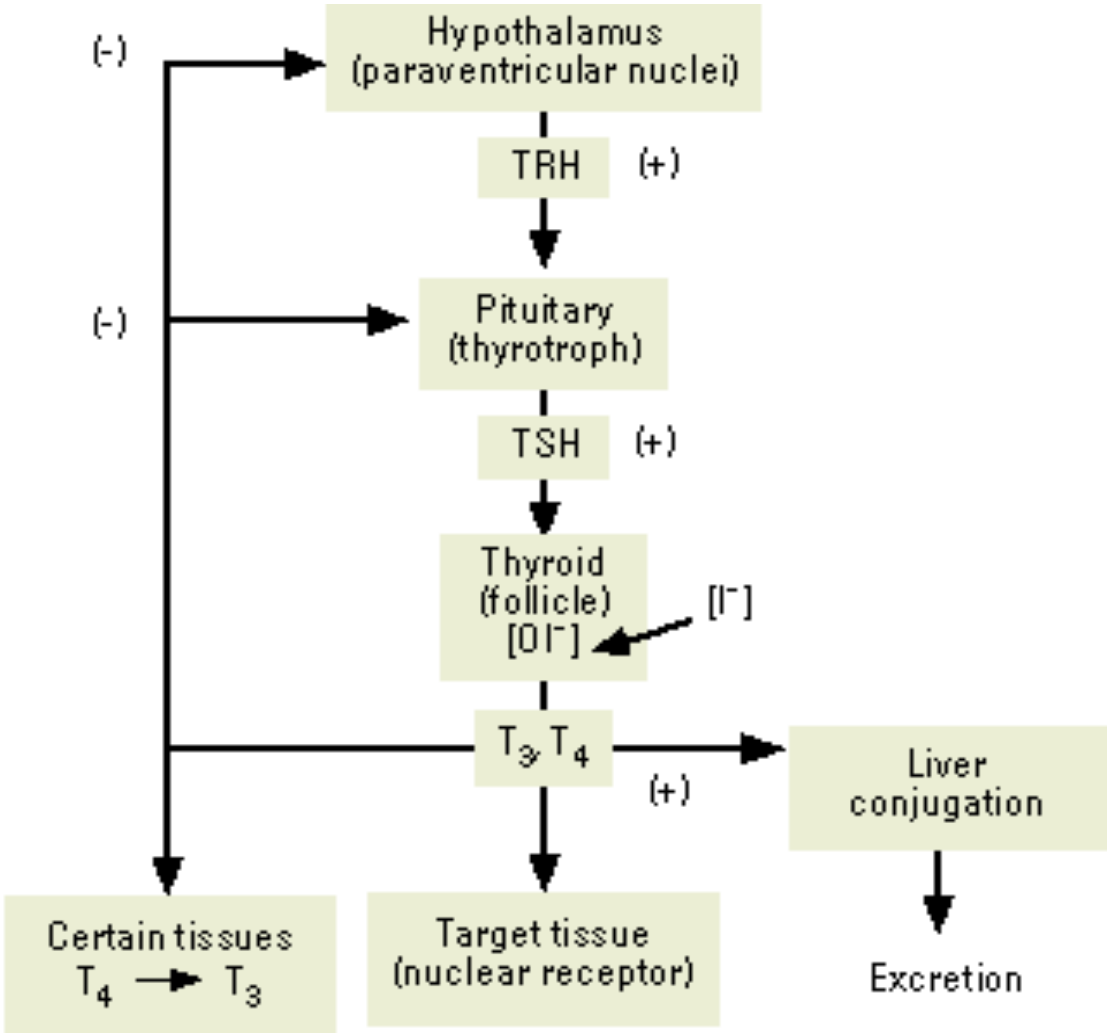
TRE: thyroid response element.

Actions of the Thyroid Hormones:

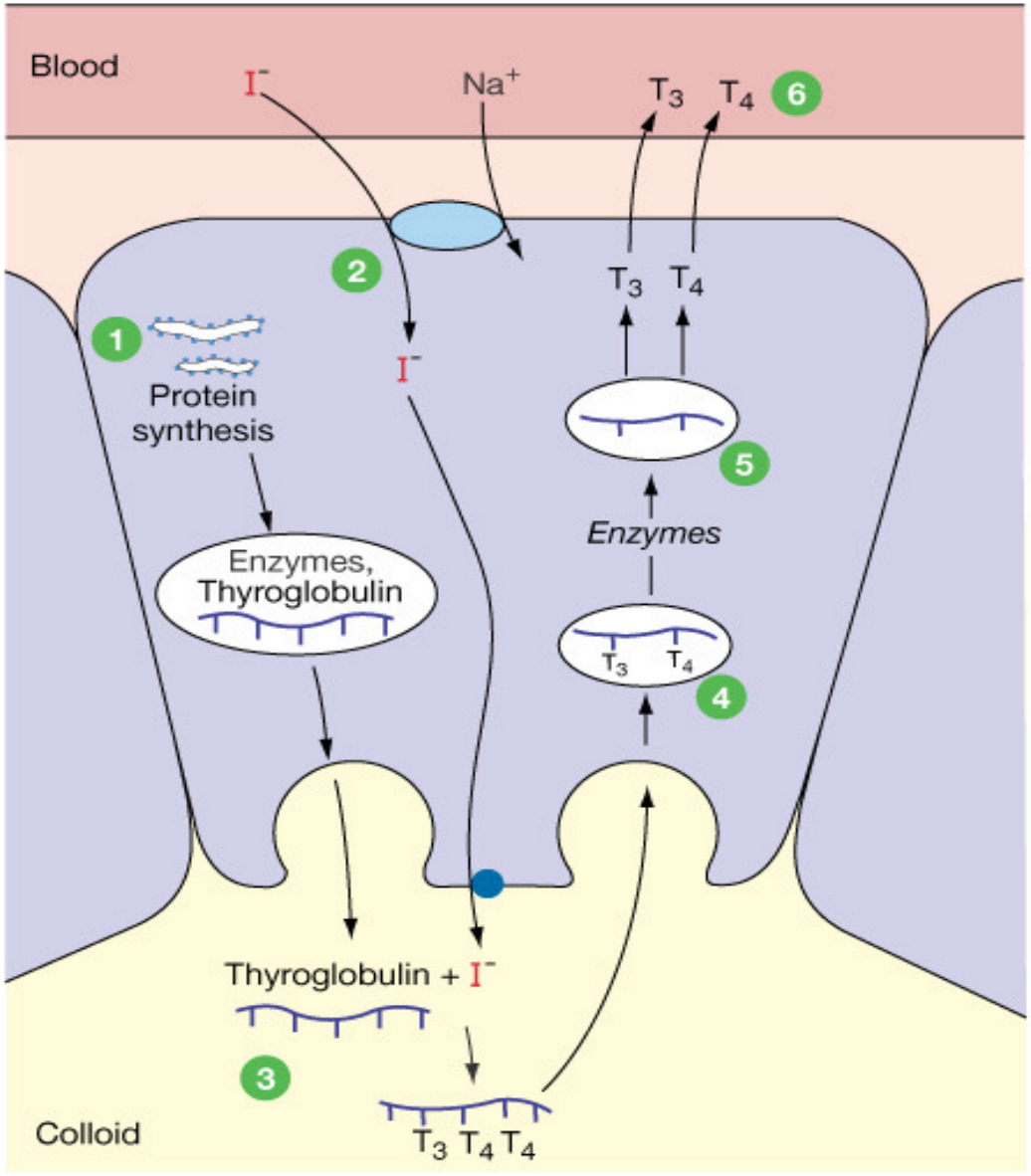
- Enhance growth and protein synthesis.
- Essential for the development of the nervous system.
- Increase oxygen consumption and basal metabolic rate.
- Increase body temperature “Calorigenic effect”.
- Cardiovascular effect:
    - Increase heart rate.
    - Increase force of contraction.

Regulation of thyroid Gland Activity

- Thyroid hormone feedback regulation of gland activity via suppression of TRH and TSH secretion.



Thyroxine and its precursors: Structure & Synthesis



1. Follicular cell synthesizes enzymes and thyroglobulin for colloid.
2. I^- is co-transported into the cell with Na^+ and transported into colloid.
3. Enzymes add iodine to thyroglobulin to make T_3 and T_4.
4. Thyroglobulin is taken back into the cell.
5. Intracellular enzymes separate T_3 and T_4 from the protein.
6. Free T_3 and T_4 enter the circulation.

Figure : Thyroid hormone synthesis

Biosynthesis

- Iodine **actively transported** to the thyroid gland under the influence of **TSH**. This is an energy-dependent process and is linked to **the Na+-K+ ATPase.**
- **Thyroid Peroxidase** Enzyme (**TPO**) convert Iodine to to a higher valence state, **iodide** (I+) using **hydrogen peroxide** as an oxidizing agent.
- **TPO** catalyze **coupling of Iodide with tyrosine residues of thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT)**.
- The **coupling** of two DIT molecules to form T4—or of an MIT and DIT to form T3—occurs within the thyroglobulin molecule.

DIT + DIT → T4

DIT + MIT → T3

- Thyroxine **stored as Thyroglobulin.**
- **TSH** enhances lysosomes to release Thyroxine from Thyroglobulin.
- **5′-Deiodinase** convert Thyroxine (T4) to Triiodothyronine (T3) mainly in the peripheral tissues (80%).

Thyroxine and its precursors: Structure & Synthesis

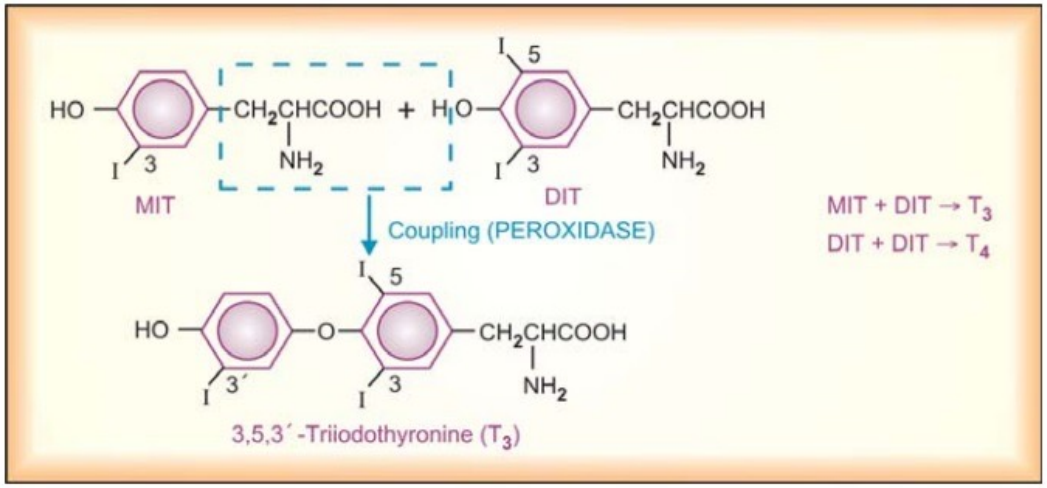


Fig. 18.2: Coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT) to produce triiodothyronine (T_3)

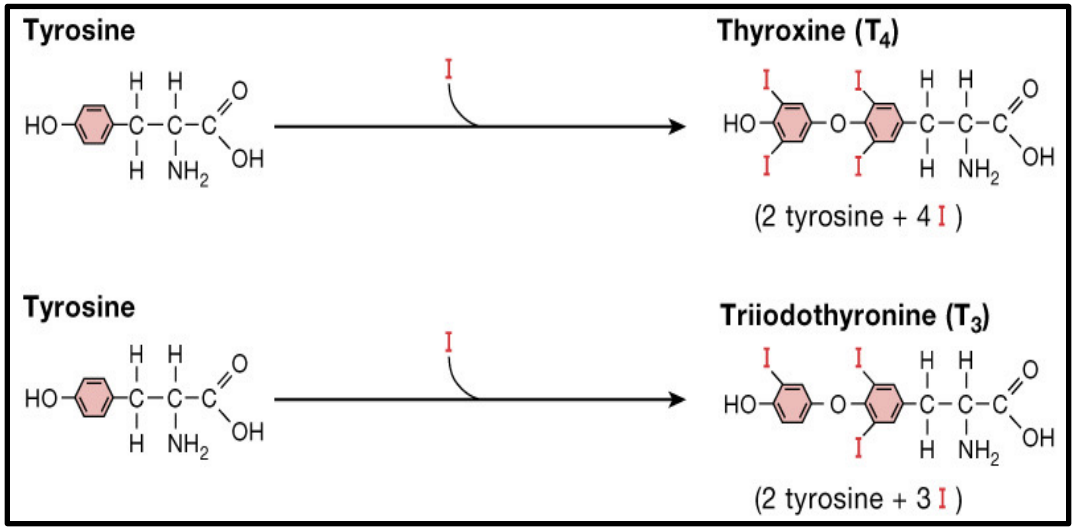


Figure : Thyroid hormones are made from tyrosine and iodine

- The thyroid hormones T3 and T4 are unique in that **iodine** (as iodide) is an **essential** component of both and require iodine for their **bioactivity.**
- These hormones; they are synthesized as part of thyroglobulin; they are **stored** in an intracellular reservoir (**colloid**)

- **Thyroglobulin is the precursor of T4 and T3.**

- It contains **115 tyrosine residues**, each of which is a potential site of iodination.

- About **70%** of the iodide in thyroglobulin exists in the inactive precursors,**monoiodotyrosine (MIT) and diiodotyrosine (DIT),** while **30% is in the iodothyronyl residues, T4 and T3.**

IN SUMMMARY…….

STAGES OF SYNTHESIS OF THYROID HORMONES

•Synthesis of thyroid hormones occurs in five stages:

1.Thyroglobulin synthesis

2.Iodide trapping

3.Oxidation of iodide

4.Transport of iodine into follicular cavity

5.Iodination of tyrosine

6.Coupling reactions.

1.Thyroglobulin Synthesis

•Endoplasmic reticulum and Golgi apparatus in the follicular cells of thyroid gland synthesize and secrete thyroglobulin continuously.
•Thyroglobulin molecule is a large glycoprotein containing 140 molecules of amino acid tyrosine.
•After synthesis, thyroglobulin is stored in the follicle.

2. AND 3 Iodide Trapping

•Iodide is actively transported from blood into follicular cell, against electrochemical gradient.
•This process is called iodide trapping.
•Iodide is transported into the follicular cell along with sodium by sodium-iodide symport pump, which is also called iodide pump.
•Normally, iodide is 30 times more concentrated in the thyroid gland than in the blood.
•However, during hyperactivity of the thyroid gland, the concentration of iodide increases 200 times more.

6. Transport of Iodine into Follicular Cavity

•From the follicular cells, iodine is transported into the follicular cavity by an **iodide-chloride pump called pendrin.**

5.Iodination of Tyrosine

•Combination of iodine with tyrosine is known as iodination.
•It takes place in thyroglobulin.
•First, iodine is transported from follicular cells into the follicular cavity, where it binds with thyroglobulin.
•This process is called **organification of thyroglobulin**.
•Then, iodine (I) combines with tyrosine, which is already present in thyroglobulin.
•Iodination process is accelerated by the enzyme iodinase, which is secreted by follicular cells.
•Iodination of tyrosine occurs in several stages.
•Tyrosine is iodized first into **monoiodotyrosine (MIT)** and later into **di-iodotyrosine (DIT)**.
•MIT and DIT are called the iodotyrosine residues

6.Coupling Reactions

•Iodotyrosine residues get coupled with one another.

•The coupling occurs in different configurations, to give rise to different thyroid hormones.

•Coupling reactions are:

1.One molecule of DIT and one molecule of MIT combine to form tri-iodothyronine (T3).

2.Sometimes one molecule of MIT and one molecule of DIT combine to produce another form of T3 called reverse T3 or rT3. Reverse T3 is only 1% of thyroid output.

iii.Two molecules of DIT combine to form tetraiodothyronine (T4), which is thyroxine.

Tyrosine + I = Monoiodotyrosine (MIT)

MIT + I = Di-iodotyrosine (DIT)

DIT + MIT = Tri-iodothyronine (T3)

MIT + DIT = Reverse T3

DIT + DIT = Tetraiodothyronine or Thyroxine (T4)

Structure Activity Relation Ship:

- Angle between the two aromatic rings must be 120^0.

- Triiodothyronine is 4 times more active than Thyroxine.

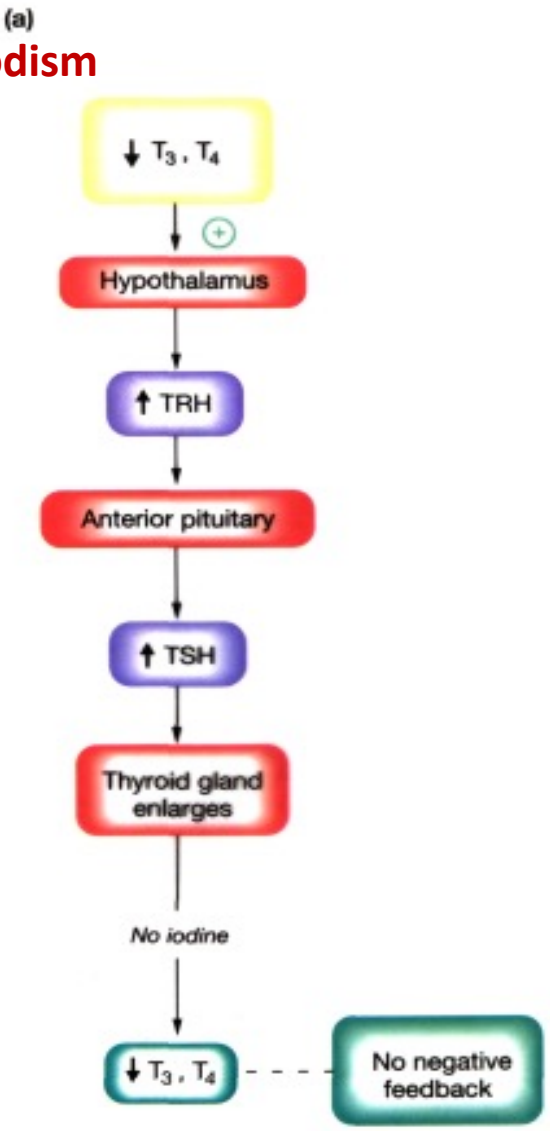
Disease Due to Hypothyroidism:

- **Hypothyroidism** – lack of thyroid hormone in tissues; can **be primary** (failure of thyroid), **secondary** (failure of pituitary) or **tertiary** (disorder of hypothalamus)
- **Goiter**: – enlargement of the gland because of increased stimulation of TSH

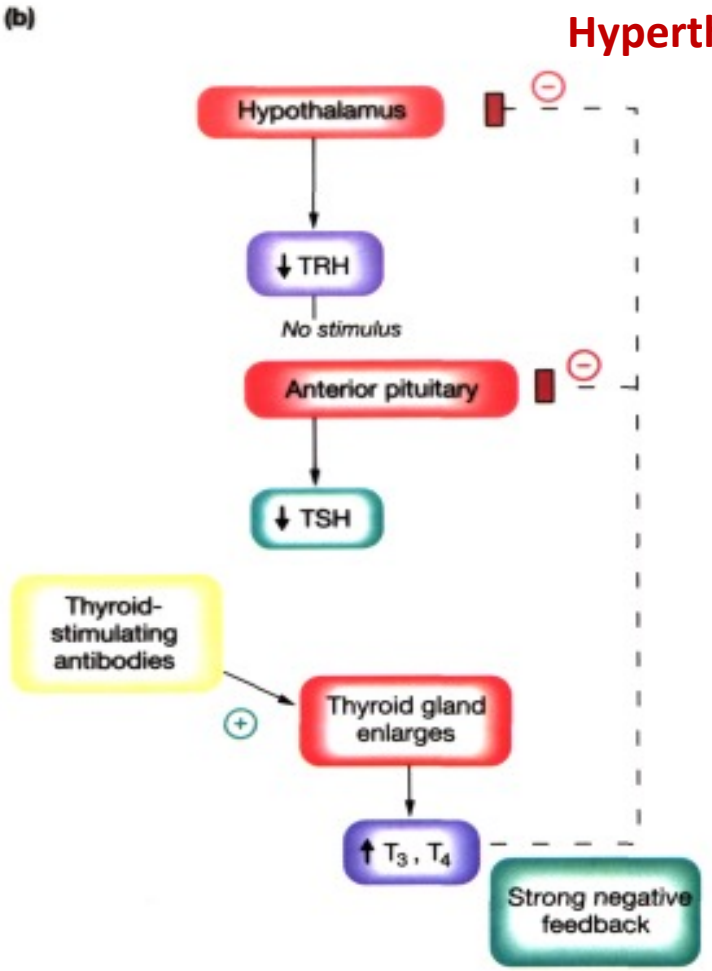
  - Causes: Lack of iodine in diet.
  - Symptoms:
    - » Enlargement in the thyroid gland (Thyroid Hypertrophy).
    - » Low level of thyroxine.
    - » High level of TSH.
  - Treatment: Iodine.
- **Cretinism**:
  - Irreversible condition due to deficiency of thyroxine soon after birth.
  - Retardation in Physical and Mental development.

T3 & T4 Control Pathways & Diseases from Malfunction

a-Goiter
Hypothyrodism



b-Graves' disease
Hyperthyrodism



- **Myxedema**:
  - Deficiency **of thyroxine in adults** due to:
    - » Removal of thyroid gland by surgery.
    - » Destruction of the gland by Radioactive Iodine.
    - » Atrophy of the thyroid gland.
  - Symptoms:
    - » Muscle weakness.
    - » Poor appetite.
    - » Slow heart rate
    - » Dry cold skin
  - Treatment:
    - » Thyroxine for life.

Disease Due to Hyperthyroidism:

- **Thyrotoxicosis:**

excess action of the thyroid hormones (hyperactivity, nervousness, fatigue, palpitations, sweating…)

- **Graves' disease (Diffuse Toxic Goiter):**

  - Causes: Autoimmune disease resulted in Enlargement and excessive secretion of the thyroid gland and the most common cause of hyperthyroidism (**increaseT3 & T4 hormones levels , decrease TSH and TRH)**
  - Symptoms:
    - » Enlargement in the thyroid gland (Thyroid Hypertrophy).
    - » Protrusion of the eye balls.
    - » High body temperature and flushes.

- Thyroid cancer:
- Treatment: Antithyroid drugs.