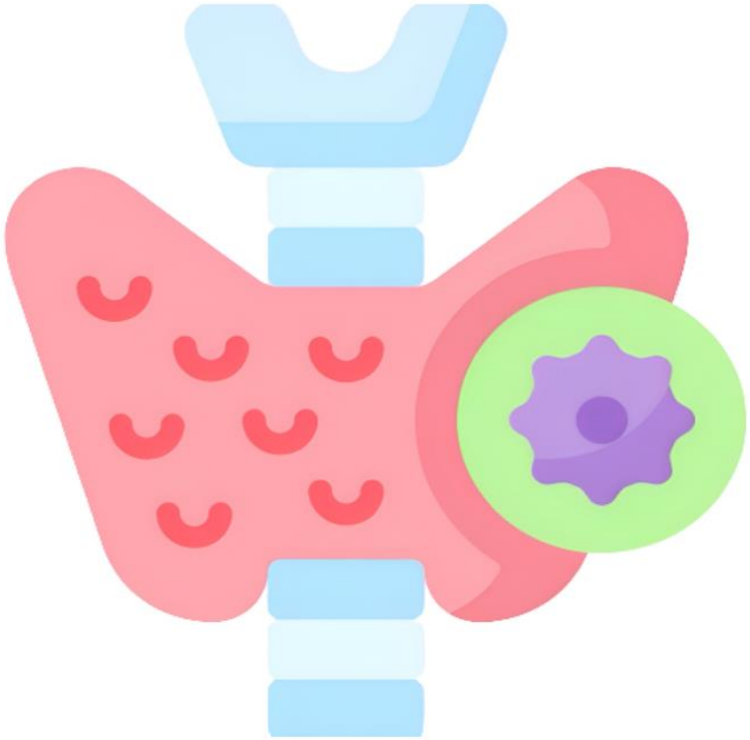
Endocrine system 5

physiology



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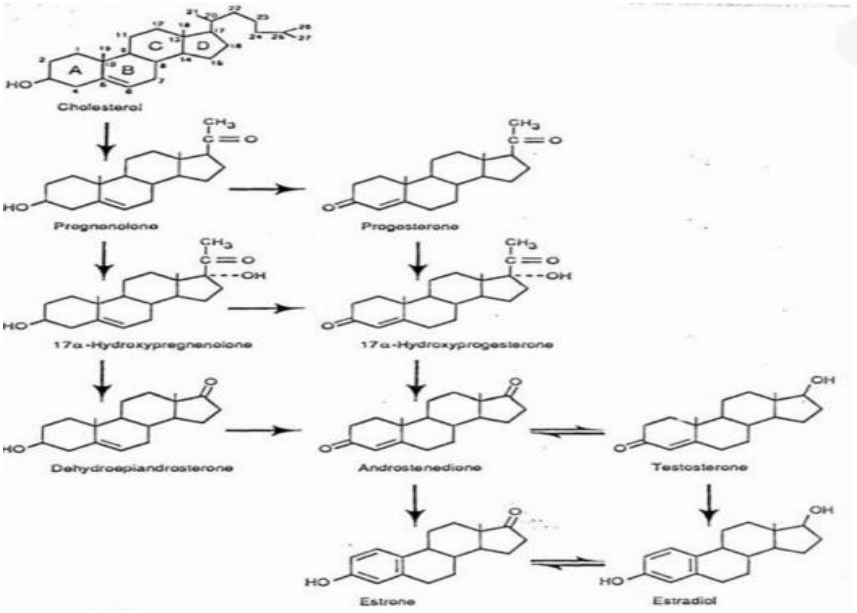
Androgens & Estrogens

They are secreted **mainly** by the zona reticularis of adrenal cortex, and **minorly** by zona fasciculata .

- Two weak androgens are produced from the reticularis: Dehydroepiandrosterone (DHEA) and Androstenedione. These two hormones produce **Testosterone** which is <u>the most potent</u> androgen.
- Testosterone produces **estradiol** while androstenedione produces **estrone**.
- Estrogens are three hormones: **estradiol**, **estrone** and **estriol**. Estrone and estradiol are produced directly from the adrenal cortex as well as ovaries, while estriol is produced from estrone or estradiol.



- Adrenal androgens are more important in females (especially after menopause, when the ovaries stop functioning).
- In males, androgens are also secreted by testes so they're **not normally** important in all stages of male's life.
- Androgens function :
  - **In females** : pubic and axillary hair & libido.
  - **In males** : spermatogenesis; male secondary sex characteristics.

- If the synthesis of cortisol is blocked, the level of corticosterone increases **as well as** the level of androgens.

Thyroid Gland

It lies in front of the trachea, composed of right and left lobes joined by isthmus, It has rich blood supply and weighs 25 gram in adults.

By 12 weeks of gestation, thyroid gland of the fetus begins to produce hormones (T3, T4) under the effect of pituitary gland of the fetus.
Production of these hormones is **essential for normal development of the skeletal and nervous system** during the fetal life, deficiency in these hormones during embryogenesis will cause many diseases like **cretinism** because maternal thyroid hormones **can't cross the placenta**.

Thyroid gland is composed of follicles which are encircled by **follicular epithelial cells** that synthesize the hormones and store it in the **lumen of the follicle** which is called **colloid**. The colloid (which is a fluid that contain proteins, enzymes and minerals) stores the thyroid hormones for the time they are needed. In between these follicles there are parafollicular cells that produce unrelated hormone which is **calcitonin** which decreases Ca++ serum level. (Unrelated to the function of thyroid gland).

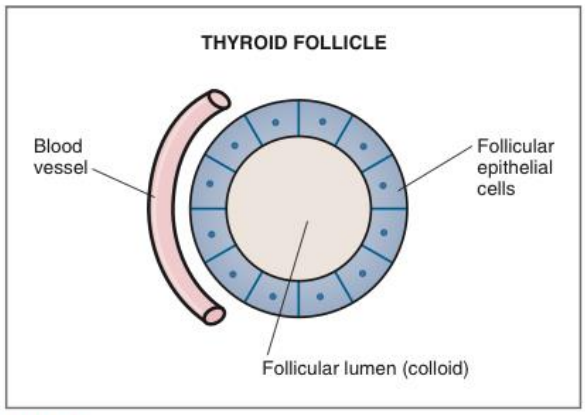
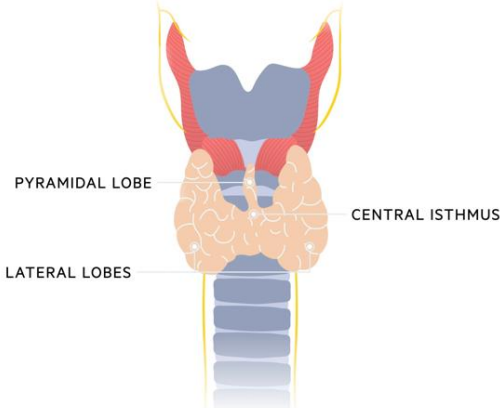
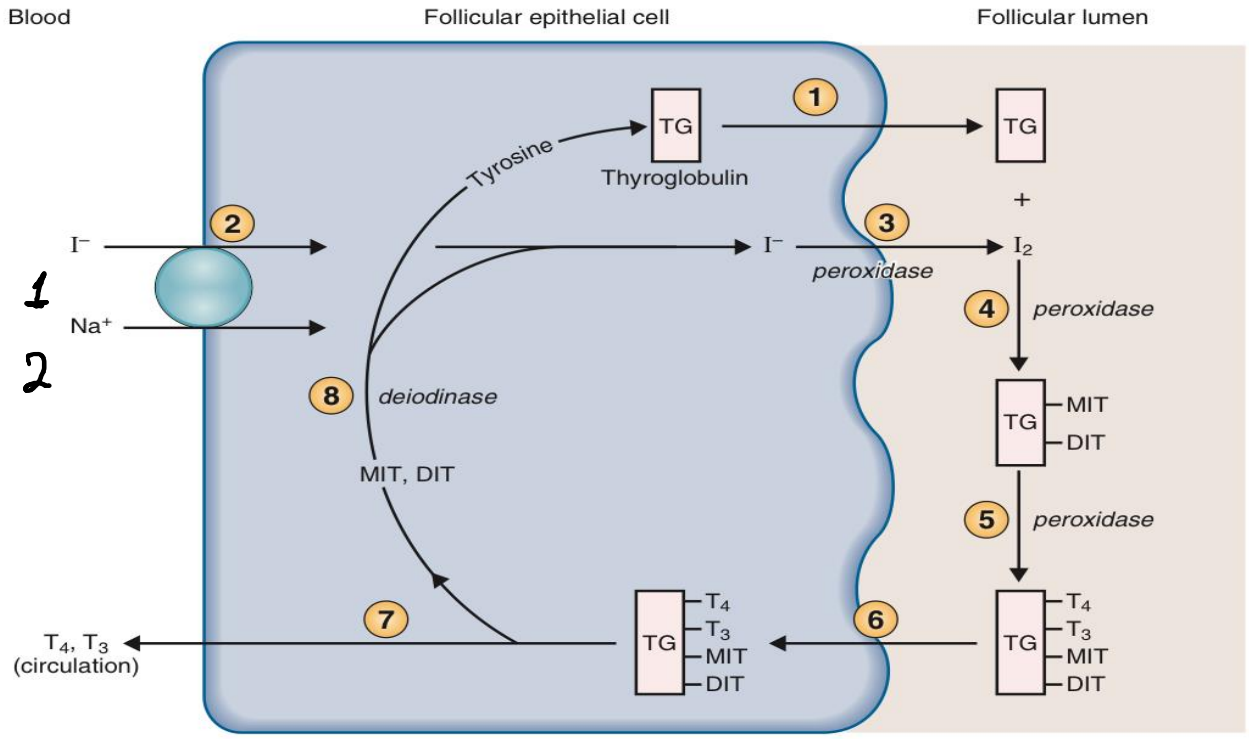


Fig. 9.17 Schematic drawing of a thyroid follicle. Colloid is present in the follicular lumen.



A. Synthesis of thyroid hormones :



** Each step in synthesis is **stimulated by TSH.**

1. **Thyroglobulin** is synthesized from (100-130) tyrosine amino acids in the follicular cells then extruded into the colloid, not all the tyrosine residues can participate in the production of thyroid hormones, only 4-8% can be iodinated.
2. **The iodide pump (Na^+\I^- cotransporter)** is present in the thyroid follicular cells, actively transport I^- into the follicular cells **(Iodine trapping).**
3. **Oxidation of I^- to I_2** is catalyzed by a peroxidase enzyme. **I_2** is the reactive form that will be organified by combination with tyrosine on thyroglobulin.

4. **Organification OR Iodination:** Tyrosine residues of thyroglobulin react with I_2 to form **mono-iodotyrosine** (MIT) and **di-iodotyrosine** (DIT). (free tyrosine residues can't participate in the iodination step)

5. **Coupling of MIT and DIT :**

While MIT and DIT are attached to thyroglobulin, two coupling reactions occur (step5):

- ✓ When two molecules of DIT combine, **thyroxine (T4)** is formed.
- ✓ When one molecule of DIT combines with one molecule of MIT, **triiodothyronine (T3)** is formed.
- ✓ Iodinated thyroglobulin is stored in the follicular lumen (colloid) until the thyroid gland is stimulated to secrete thyroid hormones

Note: Thyroid gland is a unique gland, it is considered the only gland that produces hormones and stores them for 2-3 months (6 months for iodine). Also, it is the only gland that incorporate inorganic material (iodine) with organic material (tyrosine).

6. When thyroid cells are stimulated, iodinated thyroglobulin is taken back into the follicular cells by **pinocytosis**.
7. In the circulation, most of T3 and T4 is bound to **thyroxine-binding globulin (TBG).**

Note: thyroid gland produces three hormones: T3,T4, and reverse T3 (rT3) rT3 and T3 only differs in the location of the iodine on the compound, while T3 and T4 differs in the number of the iodine elements.

8. **Conversion of T4 to T3 and reverse T3 (rT3) :**

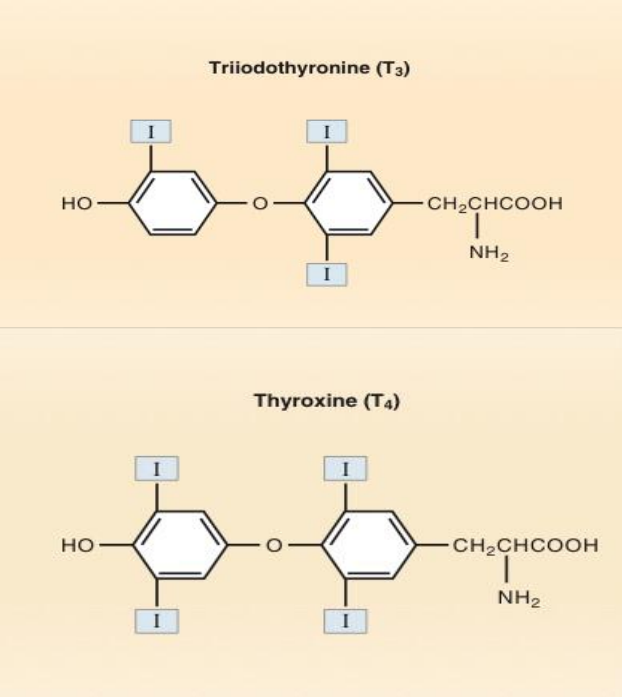
- ✓ In the peripheral tissue, T4 is converted to T3 or rT3.
- ✓ **T3 is more active than T4.**
- ✓ rT3 is totally inactive hormone.

- ✓ T4 is the main one, has low activity or sometimes no activity, but it's a **prohormone** (produces the other hormones T3 and rT3, and other products).
- ✓ 75% of T3 is synthesized from T4, 25% is synthesized directly from thyroid.
- ✓ 95% of rT3 is synthesized from T4, 5% is synthesized directly from thyroid.
- ✓ 99.98% of T4 is bound, 99.5% of T3 is bound (T3 and T4 are very dangerous hormones if they were free in excess concentrations; they burn everything in the body, catabolize the proteins so they must be bound to proteins, therefore, the free percentage should be very low; T3 just 0.5% is free while T4 just 0.02% is free and this binding will also increase the half-life of the hormones).

Some notes about the synthesis :

- Most iodides are excreted by the kidneys.
- Iodide is transported out of the thyroid cells across the apical membrane (The cells have a basal membrane facing the blood and an apical membrane facing the follicular lumen. The material in the lumen of the follicles is **colloid**, which is composed of newly synthesized thyroid hormones attached to thyroglobulin) by chloride-iodine ion counter-transport molecule called **pendrin.**
- **Thyroglobulins** are the major substrates that combine with iodine to form thyroid hormones in which they remain part of them during synthesis and storage.
- Only 4-8% of the amino acids are used to produce thyroid hormones.
- Peroxidase is located at the apical membrane where iodination of tyrosine occurs.

- Thyroid hormones become free from thyroglobulin by the action of proteases.



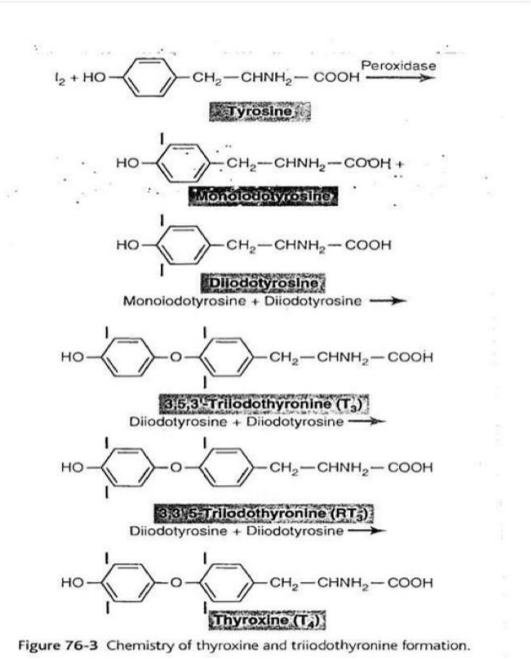


Figure 76-3 Chemistry of thyroxine and triiodothyronine formation.

B. Regulation of thyroid hormones secretion:

Thyroid gland is stimulated by **TSH** (glycoprotein) and inhibited by cortisol, growth hormone dopamine and somatostatin. First, **TRH (secreted by the hypothalamus)** binds to its receptors in the pituitary gland cell membrane and activates phospholipase C to cleave PIP2 into IP3 and DAG, which eventually leads to TSH release.

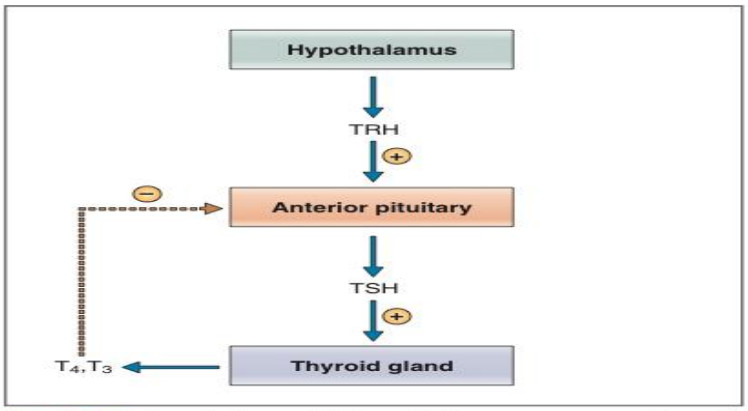


Fig. 9.19 Regulation of thyroid hormone secretion. T_3, Triiodothyronine; T_4, thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone.

Then, **TSH** binds to its receptor on the basal membrane of the follicular cells which will activate **adenylyl cyclase** to increase the formation of **cAMP** to stimulate hormones secretion.

Two second messengers are stimulated **(DAG & IP3)** for the growth of cells of the thyroid gland .

- **TSH** is a protein hormone that is composed of 2 subunits: **α subunit** (nonspecific or nonfunctional) and **β subunit** (specific and functional), in order to β subunit to function it should be bound to the α subunit.

- **Feedback effect of thyroid hormone:** increased thyroid hormones in the body fluids decreases the secretion of thyroid hormones themselves, TSH directly from the anterior pituitary and TRH from the hypothalamus.

- **Factors affecting thyroid hormone secretion:**

Stimulatory Factors	Inhibitory Factors
TSH Thyroid-stimulating immunoglobulins Increased TBG levels (e.g., pregnancy)	I^- deficiency Deiodinase deficiency Excessive I^- intake (Wolff-Chaikoff effect) Perchlorate, thiocyanate (inhibit Na^+-I^- cotransport) Propylthiouracil (inhibits peroxidase enzyme) Decreased TBG levels (e.g., liver disease)

Extra: **Thyroid-stimulating immunoglobulins** are components of the IgG fraction of plasma proteins and are **antibodies to TSH receptors** on the thyroid gland, stimulate the release of T3 and T4. Also, they circulate in high concentration in patients with Graves' disease.

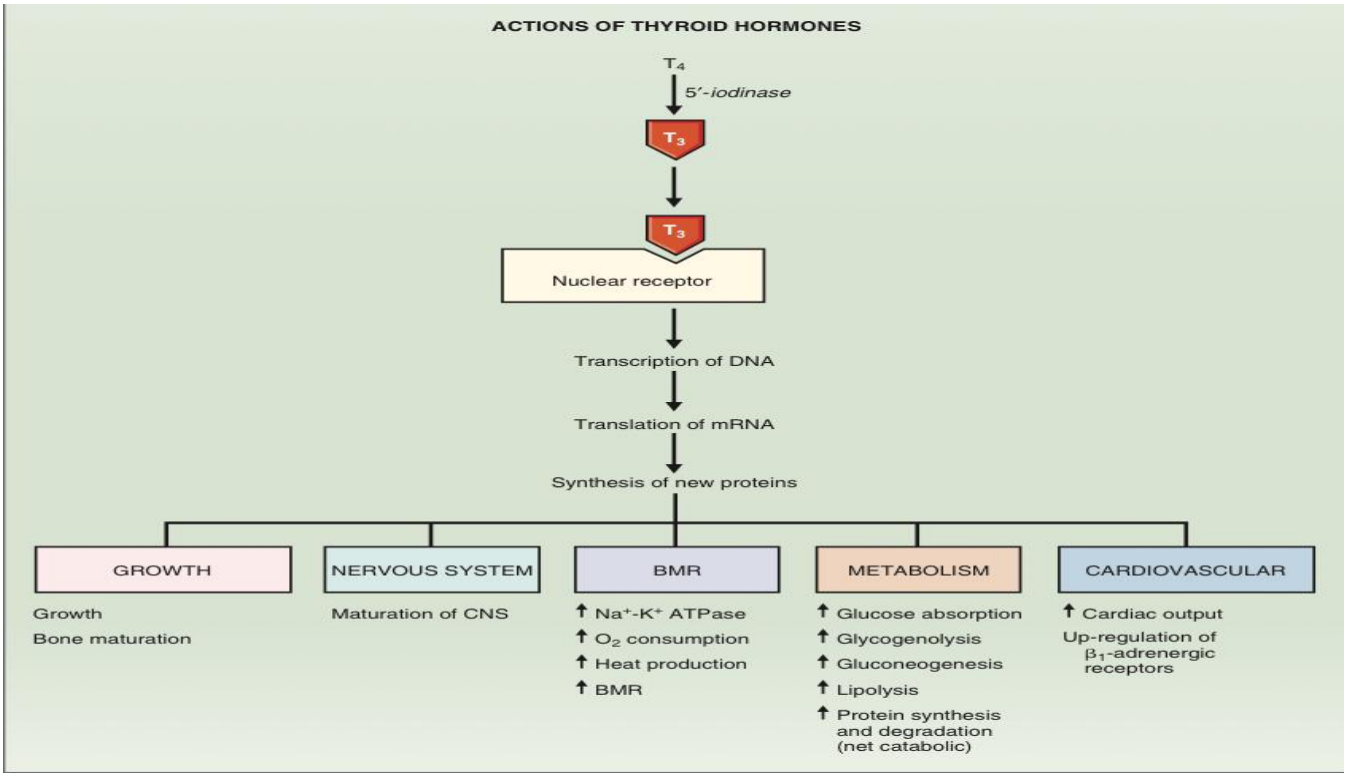
❖ **Thyroxine transport :**

Thyroid hormones (T3&T4) circulate in the bloodstream either bound to plasma proteins or free. Most of them circulates bound to **thyroxine-binding globulin (TBG)**. Smaller amounts circulate bound to T4-binding prealbumin and albumin.

Binding of these hormones to proteins has advantages such as: prolong the half-life, prevent their filtration by kidneys and maintain the normal level of these hormones in plasma.

T3 and T4 are very dangerous hormones if they were free in excess concentrations; they burn everything in the body, catabolize the proteins and so on. Therefore, the free percentage should be very low (T3 just 0.5% is free while T4 just 0.02% is free).

C. **Actions of thyroid hormone:** (from the picture)



D. Notes :

- **Hormones that function on the growth :** GH, IGF-1 , insulin, thyroid hormones, glucocorticoids, androgens and estrogens.
- **Excess release of thyroid hormones doesn't produce overgrowth as GH but causes loss of weight.**
- Thyroxine at normal concentrations has a permissive effect on the action of GH on protein synthesis; in its absence, amino acid uptake, and protein synthesis are not much stimulated.
- Reduced thyroid activity in childhood produces dwarfs who are mentally retarded, whereas reduced GH in childhood produces dwarfs with normal intelligence.