



# Endocrine



## Title: Sheet 4 – Thyroid & Antithyroid Drugs

Writer: Sama Otoum

Science: Ameen Alsaras

Grammar: Ibrahim N. Dbaybo

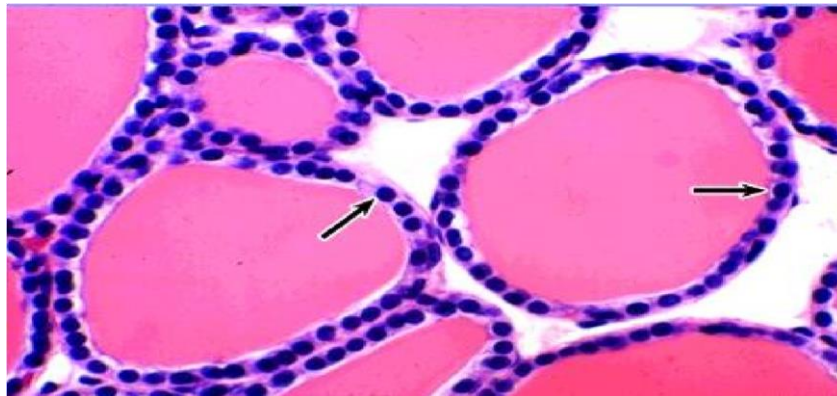
Doctor: Dr. Manar Zraikat

## Thyroid & Antithyroid Drugs

- ✓ There are three hormones which are secreted by the thyroid gland:
  1. **Thyroxine** (T4 or 3,5,3,5-tetraiodothyronine)
  2. **Triiodothyronine** (T3 or 3,5,3-triiodothyronine)
  3. **Calcitonin**
- ✓ Every part of our body is affected by the hormones released from the thyroid gland in one way or another, and it seems that almost every cell needs to acquire a **constant amount** of those hormone, depending on the situation.

### Thyroid Gland Structure

If you take a close look at the following picture, you will notice that the **structure of the thyroid gland** is mainly composed of **thyroidal follicles**:



1. Each one of these follicles is **lined** by **simple cuboidal epithelium** -blue color- (epithelial colloidal cells).
    - From what we've covered in other lectures, please recall that those cells are also called **follicular cells**.
    - Regarding their main functions:
      - i. Hormones release.
      - ii. Iodine uptake
      - iii. Thyroglobulin synthesis; both the iodine and the thyroglobulin are used in the production of the thyroid hormones.
  2. Inside them we have **colloid** (pinkish color) in which the hormones are synthesized.
- ✓ Important points that **weren't mentioned by the doctor** but you need to know them:

1. In the thyroid gland we have other cells which are called **parafollicular cells** or **C cells** and they are the ones responsible for secretion of **calcitonin**. Meaning that the parafollicular cells secrete calcitonin while the follicular cells (Epithelial cells) secrete T4 and T3. –not found in the slides-
2. Thyroglobulin (Tg) is a 660 kDa, **dimeric** protein produced by the **follicular cells** of the thyroid and **used entirely within the thyroid gland**. Thyroglobulin protein accounts for approximately **half** of the protein content of the thyroid gland. – slide 3-

## Thyroid Hormones Synthesis (2:39)

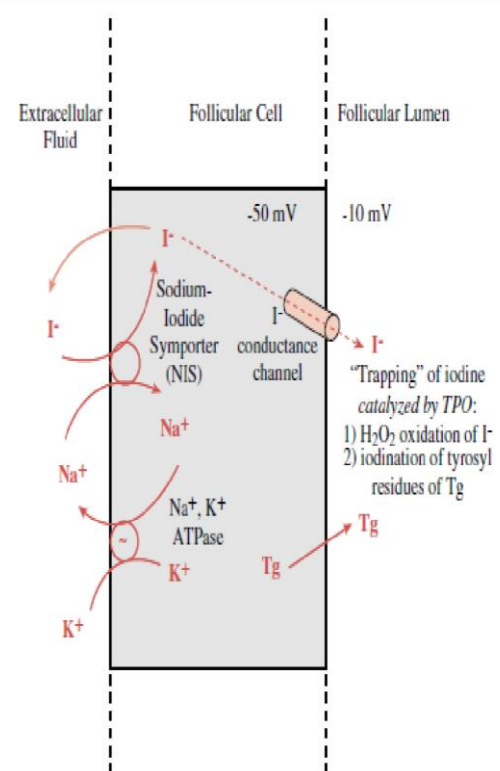
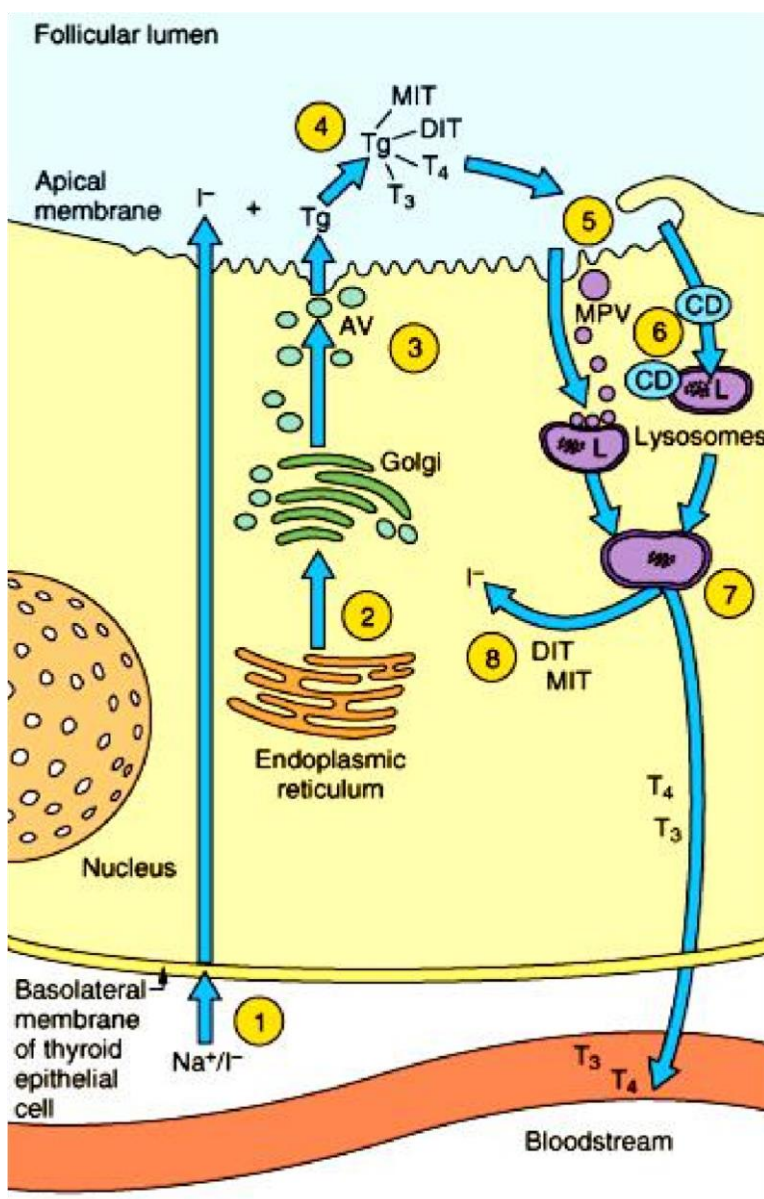
- ✓ When we say “Thyroid Hormones”, we mean T3 and T4.
- ✓ Thyroid hormones are composed of **iodine** (its uptake occurs by the epithelial cells) and **tyrosine**.
- ✓ Steps of the synthesis process:
 

In the file of this lecture, there are two slides which clarify the synthesis of thyroid hormones; a superficial one and a detailed one. The doctor explained both, but I combined all the points mentioned in both slides and tried to make it as simple as possible, so please refer to slide 6 and 7.

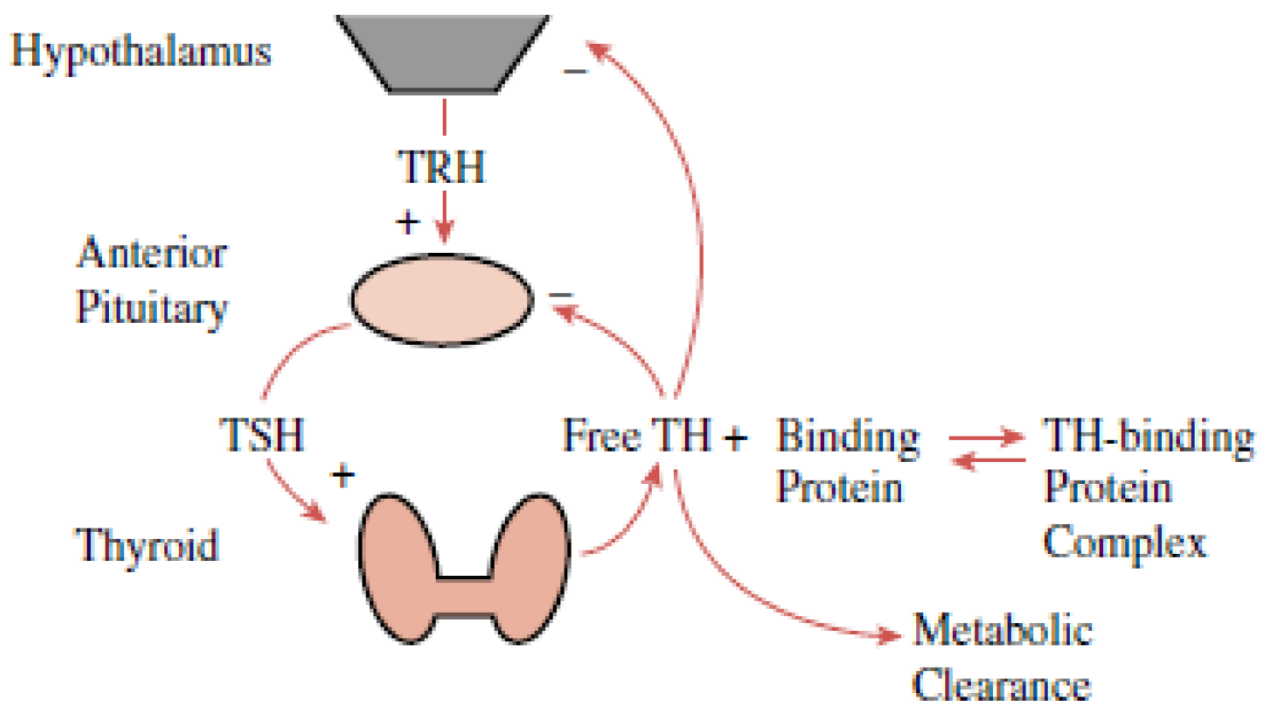
  1. The synthesis starts by the uptake of iodide ( $I^-$ ) by a channel found in the basolateral membrane of epithelial colloidal cells called **sodium iodide symporter** and then it is transported to the apical membrane (by pendrin-extra information-).
  2. **Iodide (inactive)** is **oxidized** to **iodine  $I_2$  (active)** by the thyroidal peroxidases in the follicular lumen and **NOT** the epithelial colloidal cells.
  3. Polypeptides of thyroglobulin (Tg) are synthesized in the RER.
  4. Posttranslational modifications of thyroglobulin occur in Golgi apparatus.
  5. Once Tg is in the follicular lumen, the iodine is **activated** and the following happens:
    - i. **Thyroglobulin** contains tyrosine residues, these residues are **iodinated** producing **MIT** (monoiodotyrosine) and **DIT** (diiodotyrosine).
    - ii. Then **condensation** of DITs and MITs takes place producing **T3** and **T4**:
 
$$DIT + DIT \longrightarrow T4$$

$$MIT + DIT \longrightarrow T3$$
    - iii. The previous steps which together are known as **iodination/coupling process** or **organification/coupling process** produce a **fully** iodinated thyroglobulin containing MIT, DIT, T4 (mainly) and small amounts of T3.

- In physiology Dr.Saleem mentioned that not all the tyrosine residues can be iodinated, but here it is mentioned that the thyroglobulin is fully iodinated.
- iv. The thyroglobulin with its contents is stored in a structure called **colloid**.
  6. Once we have **TSH stimulations**, the villi at the apical membrane engulf the colloid and **endocytose** the iodinated Tg either as colloid droplets (**CD**) or small vesicles (**MSD**).
  7. **Lysosomal proteolysis** of Tg and its contents are released:
    - i. T<sub>3</sub> and T<sub>4</sub> are released into the circulation.
    - ii. DIT and MIT are de-iodinated and then the tyrosine and **iodide** are recycled.



## Regulation of thyroid hormones



- ✓ Regarding this picture, the doctor only mentioned that the hypothalamus secretes TRH, which stimulates the anterior pituitary to release TSH. In the end, the thyroid hormones are released by the thyroid gland, affecting their targets.

## Physiological Actions of Thyroid Hormones (8:30)

- ✓ We mentioned earlier that the thyroid hormones affect almost every cell in our body.
- ✓ Their functions are:
  1. Normalizing the growth and development
  2. Regulating the body temperature and energy levels
  3. Enhancing and regulating **CNS** excitability
- ✓ **T3** is 3 to 4 times **more potent** than T4 in **heat production**. **T4, in colloid**, is about 4 times more **numerous** than T3. – not discussed by the doctor-



- ✓ **Insufficiency** of thyroid hormones results in **primary hypothyroidism**, which means that the thyroid gland itself is unable to produce sufficient amounts of T3 and T4.
- ✓ The **pathological conditions** associated with hypothyroidism are:
  1. **Cretinism:**
    - A condition of **impeded mental and physical growth** found amongst **children and infants** due to **congenital deficiency** of thyroid hormones.
    - It should be treated through **thyroid hormone supplements** in order to restore the balance.
  2. **Myxedema:**
    - It is associated with **severe** deficiency of thyroid hormones in adults
    - It also accompanied by **some dermatological** changes due to the **hypothyroidism**.
    - Some of those dermatological changes can happen in some cases of hyperthyroidism. – not mentioned by the doctor-
    - Its treatment is associated with **regulating the concentration** the hormones through supplements.

### **Thyroid Hormone's Mechanisms of Action (11:26)**

- ✓ There are two mechanisms of action by which the thyroid hormones accomplish their effects:
  1. **Genomic (nuclear) action:** It is when T3 binds to its receptor, forming a hormone-receptor complex, which binds to an appropriate hormone response element on DNA, altering the transcription of some **genes**.
  2. **Non-genomic action:**
    - It is associated with the **rapid response** that happens when a person is given a specific dose of thyroid hormones, due to their **physiological effect**.
    - Non-genomic actions respond to a range of thyroid hormone metabolites (T4, T3, rT3, T2). – not mentioned by the doctor-
    - The magnitude of non-genomic actions is usually only a few fold in contrast to the multifold genomic actions. The effects of **non-genomic** actions are **limited** in comparison to the many effects of the genomic actions.

## Hypothyroidism Treatment

- ✓ Basically, the treatment of the hypothyroidism is dependent on thyroid hormones or thyroid hormones like structures.
- ✓ The italicized names of drugs haven't been mentioned by the doctor.

### 1. Lyothyronine sodium (*Cymol*);

- It is the sodium salt of naturally occurring **T3**.
- It **isn't** used as a **maintenance replacement treatment** because of its short half-life, but it is used as a **therapy** of hypothyroidism **ONLY** in a few cases, such as an **initial therapy** for myxedema or myxedema coma. Also, it can be used for **short-term suppression of TSH** in patients undergoing surgery for thyroid cancer. (Remember that thyroid hormones have a negative feedback effect on the anterior pituitary gland, inhibiting the secretion of TSH)

### 2. Levothyroxine sodium:

- It is the sodium salt of naturally occurring **T4**.
- It is used a replacement therapy in cases of hypothyroidism.
- Commonly used

### 3. Liotrix (*Thyrolar*):

- Combination of T4 (levothyroxine sodium) and T3 (Lyothyronine sodium) with the ratio of 4:1 to mimic the normal ratio secreted by the thyroid gland (state of euthyroid).

## Hyperthyroidism Treatment (16:00)

- ✓ The idea behind the treatment of hyperthyroidism is related to **reducing the excess amount of thyroid hormone** by thinking about something that will antagonize the function of those excessive hormones (**antithyroid drugs**)

### 1. Thionamides:

- Combination of propylthiouracil (*methimazole*) and methylthiouracil (*Tapazole*) used to **decrease the synthesis** of thyroid hormones.
- Most commonly used in U.S
- They **don't have** an effect on the **pre-existing** thyroid hormones.
- The effect of the drug will start to appear when the **pre-existing intrathyroidal storage of the hormones is depleted** and now no new hormones will be synthesized.

- ✓ The antithyroid drugs aren't only used for the treatment of **Hyperthyroidism**, but also in **the preparation of patients for surgical subtotal thyroidectomy**, as we need those drugs in order to suppress the thyroid hormones.
- ✓ The majority of the adverse effects of antithyroid drugs are associated with **long-term use** and when the recommended dose is **exceeded**. The adverse effects are:
  - i. **Agranulocytosis**: a severe and dangerous leukopenia (lowered white blood cell count) causing a neutropenia in the circulating blood
  - ii. **Rash**
  - iii. **Cholestatic jaundice**
  - iv. **Drug fever**
  - v. **Psychosis** (is an abnormal condition of the mind that results in difficulties determining what is real and what is not)

## 2. Iodides (NaI, KI):

- They **inhibit the secretion** of T3 & T4 and further **synthesis**. (negative feedback)
- They decrease the size & vascularity of the hyperplastic gland. – not mentioned by the doctor-
- Uses:
  - i. **Thyroid crisis** (thyroid storm), where the situation is life threatening because of hyper-secretion of thyroid hormones and hypermetabolic state (**thyrotoxicosis**).
  - ii. **Operation preparation**, especially if we want to remove a part of the thyroid gland; as we need to suppress its function and its hormones.
- **Adverse effects**:
  - i. **Rash**
  - ii. **Swollen salivary glands and mucous membrane ulcerations**

## 3. Radioactive iodine:

- The concept is the same in iodine or reactive iodine; as they both **inhibit** the secretion and production of thyroid hormones.
- $I^{131}$  is the only isotope used in treatment of **thyrotoxicosis**.
- Therapeutic effect is dependent on
  - i. Penetration of the thyroid gland (.4-2 mm) and emission of beta rays.
  - ii. Long half-life (5days)
- Forbidden in pregnancy.



#### 4. $\beta$ -adrenoceptor blockers ( $\beta$ blockers):

- They block receptors in sympathetic nervous system, preventing the overstimulation of those receptors and thus, reducing the secretion of thyroid hormones.
- Effective treatment of **thyrotoxicosis**.
- Such as propranolol