بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Pharmacology | FINAL 2

Pharmacology Of the Thyroid gland

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Thyroid hormones and anti-thyroid drugs

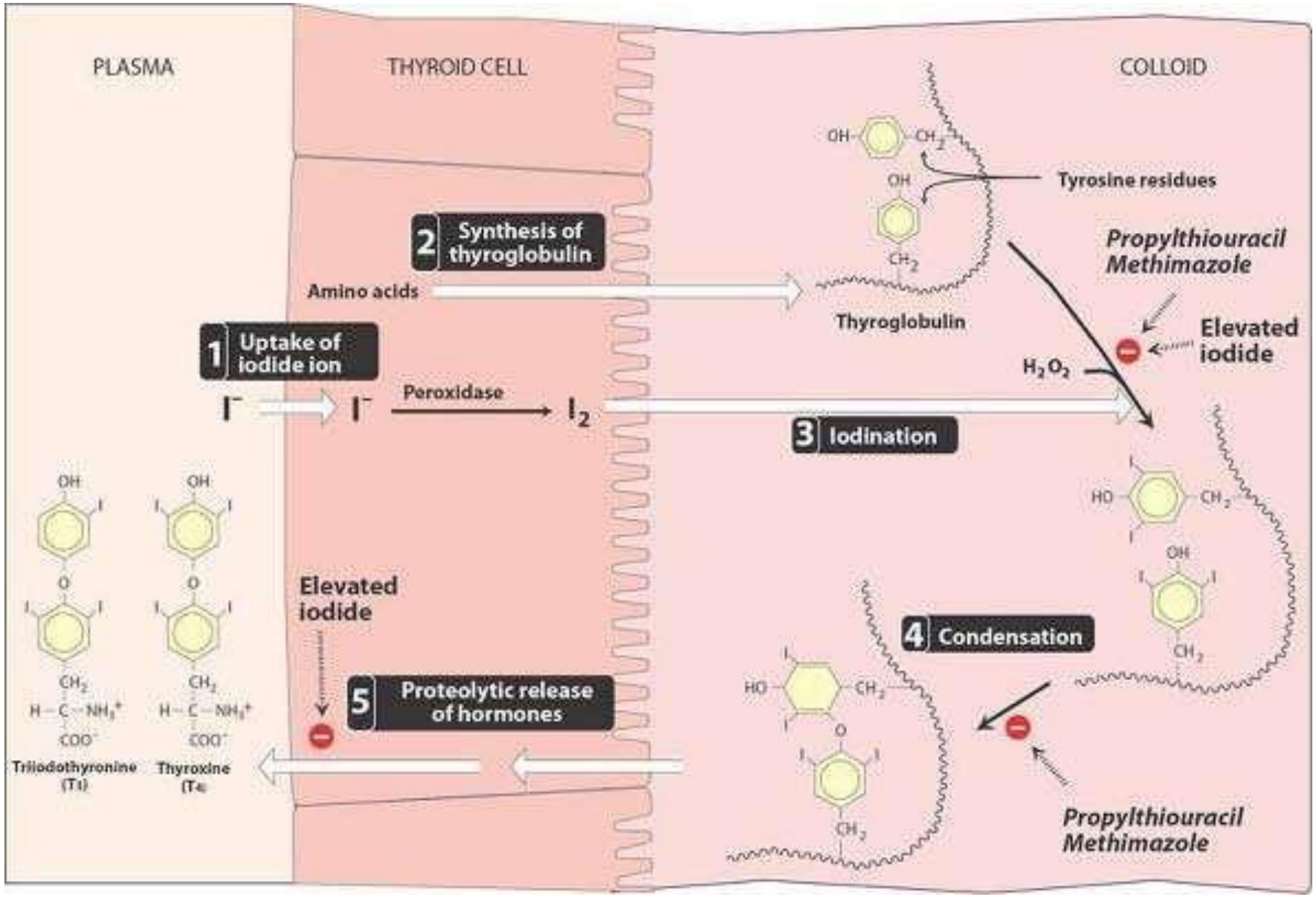
"اللهم لا سهل إلا ما جعلته سهلًا، وأنت تجعل الحزن إذا شئت سهلًا"

✓ Thyroid hormones

- The **thyroid gland** is regulated by the **anterior pituitary gland**, which secretes **thyroid-stimulating hormone (TSH)**. TSH binds to **TSH receptors** on the thyroid gland, stimulating it to **synthesize** thyroid hormones and then **release** them into the bloodstream.
- **In pharmacology**, we do not focus on the detailed steps of thyroid hormone synthesis that are covered in physiology. Instead, the important concept is that before thyroid hormones enter the blood, there are **two main processes**:

1. **Synthesis** of thyroid hormones within the thyroid gland.
2. **Release** of the synthesized hormones into the blood circulation.

Synthesis of T3 and T4



✓ Thyroid hormone synthesis (Briefly):

The synthesis of thyroid hormones occurs in the **thyroid follicles**.

1. Iodide uptake:
Iodide (I^-) enters the follicular cells through the **Sodium-Iodide transporter** , a cotransporter that transports sodium and iodide into the cell.

2. Oxidation:
Inside the thyroid gland, iodide is **oxidized to iodine (I_2)** by the enzyme **thyroid peroxidase**.

3. Iodination:
The iodine is then attached to **tyrosine residues** on the protein **thyroglobulin**, forming:
MIT (Monoiodotyrosine) – one iodine atom.
DIT (Diiodotyrosine) – two iodine atoms.

4. Condensation:
The iodinated tyrosines combine to form thyroid hormones:
MIT + DIT –> T3 (Triiodothyronine)
DIT + DIT –> T4 (Thyroxine)

✓ Thyroid hormone synthesis (Briefly):

5. Storage:

Once T3 and T4 are synthesized, they are **not released immediately**. Instead, they are **stored inside the follicular lumen (colloid)** while still **bound to protein (thyroglobulin)**

Note: It was mentioned in the lecture that the thyroid hormones are bound to the border of the follicles, but actually they are stored in the follicular lumen (colloid) and bound to thyroglobulin.

6. Release:

When the thyroid gland is stimulated by **TSH**, the colloid is taken back into the follicular cells. **Proteolytic enzymes (proteases)** digest thyroglobulin, releasing **T3 and T4**, which are then secreted into the bloodstream.

✓Transport in Blood:

Since **T3 and T4 are lipophilic** , they can't circulate freely in the blood. Therefore, they are transported mainly bound to plasma proteins like **Albumin.**

✓ Action at the target cell:

- Because thyroid hormones are **lipophilic**, they diffuse across the cell membrane without the need for membrane transporters.
- Inside the cell, **T4** (which is the **less active form**) , is converted into **T3** (the **more biologically active form**), by the enzyme **deiodinase** through **deiodination** (removal of one iodine atom).

IMPORTANT NOTES:

- Almost all cells in the body require thyroid hormones for normal growth, metabolism, and function.
- **T3 is more potent than T4.** What does this mean?
- It means that T3 produces its biological effect at a much lower concentration than T4. In other words, one molecule of T3 has approximately the same biological activity as about 10–15 molecules of T4. Therefore, T3 is considered more potent than T4.
- **Potency is different from efficacy**. Potency refers to the amount of drug or hormone needed to produce a given effect, whereas efficacy refers to the maximum effect that can be produced. Thus, T3 and T4 may have similar efficacy, but T3 has greater potency.

- Finally, **T3 binds to intracellular receptors** to produce its physiological effects.

✓ Action at the target cell:

- **Ligands** including drugs, which bind to **intracellular receptors** usually have **more biological responses** than drugs which bind to and activate **extracellular receptors**. Why?

  Ans : Because when intracellular receptors are activated by drugs, including **thyroid hormones**, they move to the nucleus and bind to DNA. There, they control **gene transcription and protein synthesis (translation)**, resulting in **many biological responses**.

- The major functional role of **thyroid hormones** in our body is to **maintain metabolism**.
- They also **sensitize epinephrine and norepinephrine (adrenaline & noradrenaline) to their receptors**, especially **β-adrenergic receptors**. This means that epinephrine and norepinephrine bind more effectively to **β-adrenergic receptors**, resulting in an **increased sympathetic response**.

- As we discussed in the previous lecture, when a patient comes with a **hormonal imbalance**, there are two possibilities: either there is a **deficiency** of the hormone or **overstimulation** of the hormone.

✓ *Hypothyroidism:*

- For example, if a patient has a **deficiency of thyroid hormones, T3 or T4**, this condition is called **hypothyroidism**.
- Hypothyroidism can cause different clinical conditions, such as **goiter and myxedema**, depending on the cause and severity.
- How can I know that the patient has hypothyroidism from the **clinical features**?

  Ans: The patient may have **weight gain, fatigue, cold intolerance, and dry skin**. But these clinical features can be similar to other diseases, so we can't depend only on the clinical features. Therefore, we request a **laboratory test to confirm the diagnosis** , especially **TSH**.

- TSH has an **inverse relationship with T3 and T4** because T3 & T4 exert **negative feedback inhibition** on TSH secretion. So, when the level of thyroid hormones increases, they inhibit the secretion of TSH. Therefore, in **primary hypothyroidism**, where there is a deficiency of T3 and T4 , the **TSH level will be high**.

✓ Treatment of hypothyroidism:

- Since hypothyroidism means there is a deficiency of thyroid hormones, we need to compensate for this deficiency by giving **replacement therapy**.
- Although both **T3 and T4** can be used as thyroid hormone replacement, **T4 is the preferred and more commonly prescribed option**. The drug used is **levothyroxine**, a synthetic form of T4.
- **Why do we prefer T4 over T3?**

Although **T3 is more potent than T4**, we usually prefer T4 for the treatment of hypothyroidism for several reasons.
First, **T4 has a longer half-life and longer duration of action**, whereas T3 has a shorter half-life and duration of action.
Keep in mind that **hypothyroidism is a chronic condition**, so the patient may need treatment for **months or years**. In chronic conditions, it is preferable to use a drug with a **longer duration of action**, because it requires a **lower frequency of administration**. This usually improves **patient compliance**.
The second reason is that **T3 is more potent and acts more rapidly**. If the patient receives excessive T3, it can produce **more rapid cardiovascular effects**, such as **increased heart rate**.

- **When do we use T3?**

  T3 is generally **not the routine first-line treatment** . It may be used in **severe hypothyroidism**, particularly **in an emergency** such as myxedema coma, where the patient has severe metabolic slowing, profound fatigue, altered mental status, and potentially loss of consciousness.
  In this situation, we need a **rapid-acting and more potent thyroid hormone**, so **T3** may be used because it acts more rapidly than T4.

KEEP IN MIND:

Hypothyroidism → ↓ T3/T4 → ↑ TSH in primary hypothyroidism → replacement therapy → T4 (levothyroxine) is preferred.

T4: longer half-life & duration of action + fewer cardiovascular effects → preferred for chronic treatment (usual treatment)

T3: more potent + faster acting → generally not first-line → may be used in severe cases such as **myxedema coma**.

Before we get into drug-food interactions, let's start with a little story...

It Wasn't the Drug... It Was the Cheese!

قصة أُم بشار و الجبنة البيضاء

أم بشار كانت مريضة hypothyroidism وكانت تأخذ levothyroxine وكل ستة أشهر كانت تيجي تفحص الـTSH
لكن الغريب إنه كل مرة كان الـ TSH يطلع مرتفع.
فكانت الفكرة المتخذة إنها ممكن تكون من المرضى القلة اللي عندهم مشكلة في ال deoionization
وفي أحد الأيام، وأثناء حديثها مع أحد المرضى المراجعين عن طريقة أخذها للدواء، حكت إنها كانت تستيقظ الصبح، تأكل جبنة بيضاء، وبعد نصف ساعة تأخذ حبة الـlevothyroxine.
وهنا جاءت لحظة الإدراك عند الطبيب!!!
قال لها: "عفواً!!! عيدي!!!"
فأعادت له كيف كانت تأخذ الدواء، ثم تنهد الطبيب و قال " رح أجيبلك معي المرة الجاي جبنة بيضاء بس اقطعي الجبنة البيضاء مع الدواء "

Um Bashar had hypothyroidism and was taking levothyroxine. Every six months, she would come for a TSH test, but her TSH was always high.
The initial thought was that she might be one of the few patients who had a problem with deionization.
One day, while talking to one of the patients about how she was taking her medication, she mentioned that every morning she would wake up, eat some white cheese, and then, after half an hour, take her levothyroxine tablet.
And here came the doctor's Aha! moment!
The doctor said:"Excuse me!!! Say that again!!!"
She repeated how she was taking the medication, and suddenly, the doctor realized what was happening.
He told her:"Next time, I'll bring you some white cheese, but you have to separate the white cheese from the medication!" Keep going through the next slides to find out!

✓ *Levothyroxine and Food-Drug Interactions:*

- When a patient comes with **hypothyroidism**, we prescribe **levothyroxine**. But you don't just prescribe levothyroxine and that's it. There is some **critical information that you should be aware of, and you should also make the patient aware of**.
- First, there is an important **food-drug interaction** between levothyroxine and foods or supplements containing high amounts of **calcium and iron**, especially dairy products and iron supplements.
- This interaction **decreases the absorption of levothyroxine**. And without proper absorption, the drug cannot reach the bloodstream and then reach the cells to exert its effect.

- ***How do we advise the patient?***

  We tell the patient to take levothyroxine on an empty stomach, preferably in the morning, about 1-2 hours before breakfast.
  Also, if the patient is taking calcium or iron supplements, they should be separated from levothyroxine by at least 4 hours.
  This does not mean that the patient has to fast for a very long time. The important thing is simply to leave an appropriate interval between the drug and food, especially foods or supplements containing calcium or iron.

- For example, don't take your levothyroxine and then immediately eat **kunafa** or another dairy product :)

- ***<u>And why do we prefer giving it in the morning</u>?***

  There are several reasons. Levothyroxine increases metabolic activity and can **enhance the body's responsiveness to the sympathetic nervous system**, so taking it close to bedtime may cause problems with sleep or **insomnia** in some patients. Also, in the morning, the stomach is usually empty, so it is easier to maintain proper absorption.

✓ *Misuse of Levothyroxine for Weight Loss:*

- Another important point is that **levothyroxine should never be misused for weight loss**. Because thyroid hormones increase the metabolic rate, some people may think, "Okay, if it increases metabolism, then I can take it to lose weight." But this is a misuse of the drug and can be dangerous.
- Sometimes there are weight-loss products marketed as **"100% natural"**, but in reality, some may be adulterated with thyroid hormones such as levothyroxine.

- ***Why does levothyroxine promote fat breakdown?***

  Thyroid hormones increase metabolic activity and can enhance the effects of the **sympathetic nervous system**. In adipose tissue, adrenergic stimulation of **β2 and β3 receptors** promotes **lipolysis**, meaning the breakdown of stored fat.

- ***You may ask: Why don't we use levothyroxine for weight loss?***

  Because its effects are **not limited to adipose tissue**. Excess thyroid hormone also affects the cardiovascular system. Misuse can cause **tachycardia, arrhythmias, and increased cardiac workload**, and in severe cases, it can lead to **cardiac arrest and sudden death**.

- So, levothyroxine is a treatment for **hypothyroidism**, not a weight-loss drug, and it should be used only at the appropriate dose and under medical supervision.

Thyroid hormones

Mechanism of action of T3 and T4

- In the cell, T4 is enzymatically deiodinated to T3, which enters the nucleus and attaches to specific receptors.

- T4 is converted to T3 by deiodinases.
- Both T4 and T3 **<u>are absorbed after oral administration,</u>** as they are not proteins and stable at low pH. In contrast, protein hormones may be degraded in the stomach, leading to **denaturation** and loss of their structure and function.

Food, calcium preparations, and aluminum-containing antacids can decrease the absorption of T4 but not of T3.

How does calcium decrease levothyroxine absorption?
Calcium decreases levothyroxine absorption through **chelation**. Calcium binds to levothyroxine in the gastrointestinal tract and forms an **insoluble or poorly absorbable complex**, thereby decreasing the intestinal absorption of levothyroxine.

Thyroid hormones

- The hormones are metabolized through the microsomal P450 system
  >>> Drugs that induce the P450 enzymes, such as phenytoin, rifampin, and phenobarbital, accelerate metabolism of the thyroid hormones.

- levothyroxine (T4) is used to treat hypothyroidism.

- Toxicity manifests itself as nervousness, heart palpitations and tachycardia, intolerance to heat, and weight loss.(sympathetic sympotms)
  >>> beta- blockers are used to reduce the sympathetic ativation.

- **Why is levothyroxine the treatment of choice?**
- **Why should levothyroxine be taken on an empty stomach?**
- **Which laboratory test is most commonly used to monitor the adequacy of levothyroxine therapy?**
- **What are major side effects of levothyroxine?**

The opposite situation is **hyperthyroidism**. Regardless of the underlying cause, such as **Graves' disease, viral infection causing damage to the cells and release of stored hormones, or toxic nodular disease**, hyperthyroidism is clinically manifested by:

·**Low TSH**
·**High T3 and T4**

We mainly depend on the **TSH test**, as it is more accurate. **TSH < 0.5** indicates hyperthyroidism.

The symptoms include:

-**Palpitations** -**Weight loss**
-**Protruding eyes** -**Heat intolerance**

Heat intolerance occurs because of **vasodilation of the blood vessels supplying the external organs**, associated with activation of the sympathetic system.
The main concern is the effect on the **heart**, particularly palpitations. Therefore, we need a medication with a **negative inotropic effect** to reduce cardiac contractility.
Two groups of drugs are mentioned:

·**Beta blockers**
·**Calcium-channel blockers**

Before choosing the drug, we determine the cause of the palpitations. **Adrenaline binds to β1 receptors**, producing the cardiac effect. Therefore, based on this mechanism, **beta blockers are selected rather than calcium-channel blockers.**

Since the palpitations result from adrenaline binding to β1 receptors in the heart, we want to administer a drug that blocks this interaction. Propranolol can be used for this purpose. It is a **non-selective β-blocker** that blocks β1 and β2 receptors. By blocking β1 receptors, propranolol prevents the cardiac effects of adrenergic stimulation.

Anti-thyroid drugs

Beta blockers

do not treat the underlying cause; they treat the symptoms of hyperthyroidism, particularly **palpitations**.

- β-Blockers that **lack sympathomimetic activity (Pindolol and acebutolol)**, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism.
- Intravenous administration is effective in treating thyroid storm.
- An alternative in patients suffering from severe heart failure or asthma is the calcium channel blocker, diltiazem.

Other agents used in the treatment of thyroid storm include :

1. PTU (WHY?!) because it inhibits the peripheral conversion of T4 to T3 but methimazole does not)
2. Iodides
3. Glucocorticoids (to protect against shock).

Therefore, in addition to treating the symptoms, the **underlying cause should also be treated** using drugs that inhibit thyroid hormone **synthesis or release**.

- Anti-thyroid drugs such as:
- **Thionamides / thiouracils**
- Examples: **PTU and methimazole**.

Anti-thyroid drugs

propylthiouracil (PTU) and methimazole

- Are concentrated in the thyroid.

MOA:

1. Inhibit the oxidative processes required for iodination of tyrosyl groups
2. Inhibit the coupling of iodotyrosines to form T3 and T4.
3. **PTU** can also block the conversion of T4 to T3.

- These drugs have no effect on the thyroglobulin already stored in the gland >>>> **observation of any clinical effects of these drugs may be delayed until thyroglobulin stores are depleted.** مهم

لما الحياة تكشرلك عارف تعمل ايه ؟

PTU & Methimazole – explanation

These drugs **go to the thyroid gland and inhibit thyroid hormone synthesis.**
They inhibit:
Oxidative processes → iodination → coupling/conversion.
However, they **do not inhibit proteolytic activity**, meaning that they do not prevent the **release of previously stored T3 and T4.**
Therefore, after starting treatment, **T3 and T4 can still be detected in the patient's blood** because the thyroid gland already contains stored thyroid hormones.
Think of the thyroid as a **factory with stored products:**
The drug stops the factory from **synthesizing new products**, but the **old products already in storage are still available and can be released.**
Consequently, **T3 and T4 may remain elevated in the blood for weeks to months until the pre-existing stores are depleted.**
In summary, these drugs **prevent the synthesis of new thyroid hormones but do not prevent the release of previously stored hormones.**
Therefore, their **onset of action is slow.**
The patient takes the treatment for approximately **3-6 months**, after which the test is repeated to evaluate the response.

PTU – Special Effect Compared with Methimazole

·**PTU (propylthiouracil)** has an additional effect compared with methimazole: it inhibits the **deiodinase enzyme**, thereby preventing the conversion of **T4 to T3**.
·This property is clinically useful in a **thyroid storm (thyroid attack)**.
·In thyroid storm, a **beta blocker** is given to protect the heart from the excessive thyroid-related cardiac effects.
·**PTU is also administered to inhibit the conversion of T4 → T3.** Therefore, T4 remains as T4 rather than being converted into the more active T3.
·This does **not directly reduce the amount of existing T4 and T3**; rather, it prevents further conversion of **T4 into T3**.
·Since the activity of **T4 is lower than that of T3**, preventing this conversion decreases the thyroid hormone response/activity.
Question: Why is PTU administered in an emergency rather than methimazole?
Because PTU has the additional ability to inhibit deiodinase and therefore prevent the conversion of T4 to T3.

A thyroid storm is a rare, severe, and life-threatening medical emergency where an overactive thyroid gland suddenly releases a massive amount of thyroid hormones into the body. This causes a dangerous spike in heart rate, blood pressure, and body temperature, requiring immediate hospital care

Anti-thyroid drugs

propylthiouracil (PTU) and methimazole

- Are well absorbed from the gastrointestinal tract >>>> Taking orally.

- **Adverse effects include:**

Agranulocytosis rare but very serious, a **sharp decline in white blood cells**, resulting in a marked reduction in the patient's immune defense, can be **fatal.**

(is the most serious adverse effect. Patients should immediately report fever, sore throat, or signs of infection, and the drug should be stopped while obtaining a complete blood count.)

1. Rash
2. Edema.

- Why is propylthiouracil preferred over methimazole during the first trimester of pregnancy and in the treatment of thyroid storm?

Anti-thyroid drugs

Radioactive iodine

- Destruction of the gland by beta particles emitted by radioactive iodine ($_{131}I$), which is selectively taken up by the thyroid follicular cells.
- Normal thyroid follicular cells and most differentiated thyroid cancer cells express the sodium-iodide symporter on their cell membrane.

- **Side effect:** hypothyroid as a result of this drug >>> require treatment with levothyroxine.

- Is used for the treatment of thyroid cancer, **Not all types of thyroid cancer respond to radioactive iodine.**

·**Radioactive iodine** enters the bloodstream and, after distribution, is **selectively taken up by the thyroid gland**.
·This selective uptake occurs because thyroid cells contain the **sodium-iodide symporter (NIS)**, which transports iodide, including radioactive iodide, into the thyroid cells.
·Radioactive iodine then becomes **concentrated within the thyroid gland**.
·It emits **beta (β) radiation**, which causes destruction of nearby thyroid cells. The effect on more distant cells is progressively lower.
·Because of its radioactive effects, **radioactive iodine is contraindicated during pregnancy**.
·Exposure to other individuals should be minimized after radioactive iodine administration. 0.5 m **distance from other people** because of radiation exposure.

The tumor is examined by a **pathologist** to determine the type of thyroid carcinoma.
If the cancer cells express the **sodium-iodide symporter**, they can take up radioactive iodine and therefore can respond to radioactive iodine treatment.

- **Which thyroid cancers respond?**

Papillary and follicular carcinoma responses well because cancer cells retain iodine uptake, while anaplastic carcinoma does NOT response; poorly differentiated, usually lacks sodium-iodide symporter expression.

·Therefore, the response of a thyroid cancer to radioactive iodine depends on whether the cancer cells **retain the ability to take up iodine through the sodium-iodide symporter**.

Does medullary carcinoma response to radioactive iodine? Why?

Hypothyroidism After Radioactive Iodine Treatment

·After treatment with **radioactive iodine, hypothyroidism may develop**.
·This occurs because radioactive iodine **destroys thyroid tissue**, reducing its ability to produce thyroid hormones.
·If hypothyroidism develops, we return to the management of **hypothyroidism and treat it accordingly**.
·The main idea is that **developing treatable hypothyroidism is preferable to leaving the thyroid cancer untreated**.

The **benefit-risk balance** is very important. Physicians always have to weigh the **benefits against the risks** before choosing a treatment. This is why treatment should be **personalized**, because the benefit-risk balance may differ from one patient to another.
For example, in one patient the **benefits of a treatment may outweigh its risks**, while in another patient a different option, such as **surgery**, may be considered depending on the benefit-risk balance.

Anti-thyroid drugs

Iodide

- Inhibits the iodination of tyrosines (so-called acute **Wolff-Chaikoff effect**).
- This effect lasts only a few days.
- Iodide inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood.
- Today, iodide is rarely used as the sole therapy.
- However, it is employed to treat potentially fatal thyrotoxic crisis (thyroid storm) or prior to surgery, **because it decreases the vascularity of the thyroid gland.**

Iodide is included among the **anti-thyroid drugs** because a **highly concentrated iodide solution** can temporarily inhibit thyroid hormone release.
This is known as the **Wolff-Chaikoff effect**. It acts like a temporary "shock" to the thyroid gland; the effect is **not permanent**.
When a patient receives a solution containing a **very high concentration of iodide**, it reaches the thyroid gland and inhibits the **release of T3 and T4**. According to the notes, this occurs through inhibition of the **proteolytic enzyme/activity** responsible for hormone release.
Therefore, concentrated iodide solution can be used when a **rapid effect is required**, such as in an emergency, because it rapidly decreases the release of T3 and T4.
The notes also state that iodide causes a **decline in TSH**, which results in:

↓ thyroid gland size

↓ thyroid vascularization

For this reason, another use of concentrated iodide solution is **before thyroid surgery**. It is given before the surgical procedure to decrease the **size and vascularity of the thyroid gland**, making surgical removal easier.
Important: the effect is temporary
The thyroid gland is initially "shocked" by the high concentration of iodide and stops releasing thyroid hormones. However, this response lasts only for a **short period**.
After approximately **10-14 days**, the thyroid gland adapts and can begin using iodide again for the production of **T3 and T4**. Therefore, concentrated iodide solution should **not be used for prolonged treatment**.
So, its two main uses are:

- **Emergency treatment** → rapidly inhibit the release of T3 and T4.
- **Before thyroid surgery** → decrease thyroid size and vascularization.

- **What are the main clinical indications for iodide in patients with hyperthyroidism?**

1) Before thyroid surgery to reduce thyroid vascularity and intraoperative bleeding.
2) Thyroid storm.
3) After administration of thionamides (e.g., PTU or methimazole) to rapidly inhibit thyroid hormone release.

Anti-thyroid drugs

Iodide

- Iodide is not useful for long-term therapy, (why?!) because the thyroid ceases to respond to the drug after a few weeks.

Adverse effects are relatively <u>minor</u> and include:

1. Sore mouth and throat
2. Swelling of the tongue or larynx
3. Rashes (Iodide can trigger hypersensitivity reactions in the skin.)
4. Ulcerations of mucous membranes
5. Metallic taste in the mouth.

Iodide is concentrated in the salivary glands and secreted into saliva. This causes local irritation and inflammation of the oral and pharyngeal mucosa, leading to soreness.

رسالة من الفريق العلمي:

ما بين الفتور و العودة...

في خِضَمّ الانشغال بالدراسة، و تفاصيل الحياة اليومية، قد نغفل أحيانًا عن أمرٍ لا يقل أهمية عن كل ما نسعى إليه؛ **وهو الإنسان الذي نصبح عليه خلال هذه الرحلة.**

فالقيمة الحقيقية للإنسان لا تُقاس بما يحققه فحسب، وإنما بما يحافظ عليه من مبادئ، وما يتركه من أثر، وبالطريقة التي يعامل بها من حوله.

قد تتغير اهتماماتنا، ويقل حضورنا، وتمرّ بنا فترات من الفتور والتراجع، وهذا جزء من طبيعة الإنسان. لكن تبقى هناك أشياء يجدر بنا ألا نسمح للظروف أن تغيّرها فينا؛ **علاقتنا بالله، أخلاقنا، تواضعنا، وحسن تعاملنا مع الآخرين.**

ومن الجميل أن يراجع الإنسان نفسه من حين إلى آخر، لا ليحاسبها على كل تقصير، وإنما ليتأكد أنه لا يبتعد تدريجيًا عن القيم التي كان يؤمن بها، ولا يصبح شخصًا مختلفًا عما كان يتمنى أن يكونه ، فالعودة إلى الطريق الصحيح ليست تراجعًا، ومراجعة النفس ليست ضعفًا، والاعتراف بالتغيّر ليس عيبًا.

ولعل أجمل ما يمكن أن يفعله الإنسان أحيانًا، ليس أن يبدأ من جديد، **بل أن يعود إلى ما كان عليه قبل أن تأخذه الحياة بعيدًا عن نفسه.**

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			