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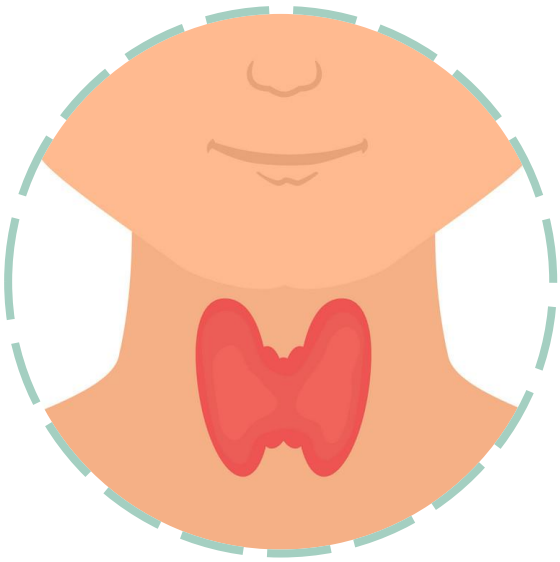
Mnemonic File



Endocrine Block

Pharmacology team 438

Hyper and Hypothyroidism

Objectives:

By the end of the lecture , you should know:

- Describe different classes of drugs used in hyperthyroidism and hypothyroidism and their mechanism of action
- Understand their pharmacological effects, clinical uses and adverse effects
- Recognize treatment of special cases such as hyperthyroidism during pregnancy, Graves' disease and Thyroid Storm and special cases of hypothyroidism such as myxedema coma

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Hyperthyroidism

Thyroid Function

- Normal amount of thyroid hormones are essential for normal growth and development by maintaining the level of energy metabolism in the tissue.
- Either too little or too much thyroid hormones will bring disorders to the body.

Important Functions

Growth & development, especially in the embryo & brain

Thermoregulation increase basal metabolic rate (BMR)

Helps **maintain metabolic energy** balance

CVS: increase heart rate & cardiac output which increase oxygen demand

Iodine Importance

- Thyroid hormones are unique biological molecules in that **they incorporate iodine**[1] in their structure
- Adequate iodine intake (diet, water) is required for normal thyroid hormone production
- Major sources of iodine are: iodized salt, iodated bread, dairy products, shellfish
- Minimum requirement: 75 micrograms/day

Iodine Metabolism

1. Dietary iodine is absorbed in the GI tract, then taken up by the thyroid gland (or removed from the body by the kidneys)

2. Iodide taken up by the thyroid gland is **oxidized by peroxidase** in the lumen of the follicle:

$$I^- \xrightarrow{\text{Peroxidase}} I_2$$

Iodide → Iodine

3. Oxidized iodine can then be used in production of thyroid hormones

Thyroid Hormones[2]

Tetraiodothyronine (T_4\ thyroxine)

Triiodothyronine (T_3)

Synthesis

Iodine trapping: uptake of iodine by the thyroid gland

Oxidation of iodine: (to its active form) **thyroid peroxidase** (key enzyme of the synthesis)

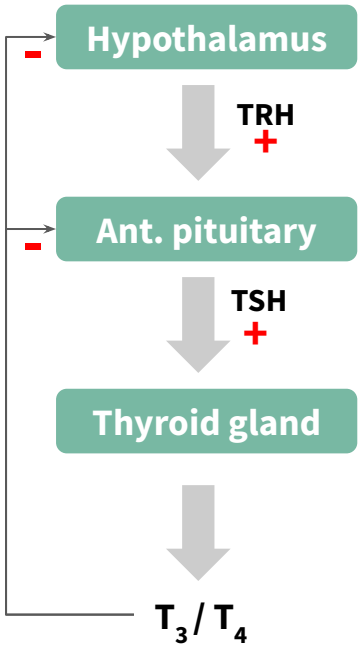
Iodine organification: The iodination of tyrosyl groups of thyroglobulin into MIT and DIT

Formation of T_4 and T_3 from MIT and DIT: Thyroid peroxidase

1: Cannot be synthesized by the body, has to be supplied by diet.
2: once produced, they can control their own levels by feedback mechanisms

Thyroid Regulation

1. Hypothalamus secretes **Thyrotropin-Releasing Hormone** (TRH) which stimulates synthesis and release of thyrotropin (**Thyroid Stimulating Hormone** or TSH) by the anterior pituitary.
2. TSH then stimulates the thyroid gland to uptake iodine, synthesize and release T4&T3.
3. T4 & T3 levels feedback to both hypothalamus and pituitary affecting the release of TRH & TSH.
4. **Thyroid hormones** exert negative feedback on TSH release at the level of the anterior pituitary:
   a. Inhibition of **TSH synthesis.**
   b. Decrease in **pituitary receptor for TRH.**
5. **TSH** release is influenced by hypothalamic **(TRH)**, and by thyroid hormones themselves



Thyroid Hormone Disorders

Hypothyroidism: Refers to disorders in which the thyroid gland secretes decreased amounts of hormones

Thyroid neoplasia: Benign enlargement or malignancies of the gland

Thyrotoxicosis: Is a term for all disorders with increased levels of circulating thyroid hormones[1]

Hyperthyroidism: Refers to disorders in which the thyroid gland secretes increased amounts of hormones

Also defined as: Hypermetabolic state cause by thyroid hormone excess at the tissue level	**Also defined as:** Increased thyroid hormone synthesis and secretion
Not all patients with thyrotoxicosis have hyperthyroidism	All patients with hyperthyroidism have thyrotoxicosis

Causes of Thyrotoxicosis[2]

With High RAIU

- Graves' disease (60-80%)
- Multinodular goitre (14%)
- Adenomas/ Carcinomas

With low RAIU

- Thyroiditis
- Iodine-induced thyrotoxicosis:
  - Drugs (e.g. amiodarone[3])
  - Radiografic contrast media

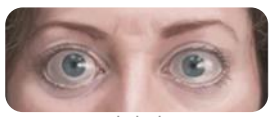
1: Regardless of the cause. Therefor we can consider hyperthyroidism is a type of thyrotoxicosis but not vise versa.
2: Tested by hyperactive iodine uptake.
3: a powerful anti arrhythmic drug that contains iodine.

Features of Diseases

Features of Graves' Disease (diffuse toxic goiter)

- Cause by thyroid stimulating **immunoglobulins** that stimulate TSH receptor, resulting in sustained thyroid over activity.
- Mainly in young adults **aged 20-25**
- 5 times more frequent in **women**
- Swelling and soft tissues of hands and feet
- Clubbing of fingers and toes


pretibial myxedema


Exophthalmos

- Half of cases have **Exophthalmos** (not seen with other causes of hyperthyroidism)
- 5% have **pretibial myxedemia** (thyroid dermopathy)

Features of Toxic Multinodular Goiter

- Second most common cause of hyperthyroidism
- Most cases in women in **5th to 7th decades**
- Often have **long-standing goiter** (chronic)
- Symptoms usually develop slowly

Thyrotoxicosis

Symptoms:

- Irritability
- Dysphoria
- **Heat intolerance and sweating**[1]
- **Palpitations**
- Fatigue & weakness
- **Weight loss**[2]
- Diarrhea

Signs:

- Arrhythmia
- Thyroid enlargement
- **Warm, moist skin**
- **Exophthalmos**
- **Pretibial myxedema**

Treatment of Hyperthyroidism

01 **Thioamides (Antithyroids)**

02 **Iodides\ Iodine**

03 **Radioactive Iodine**

04 **β-blockers**

05 **Surgery**

1: Very typical presentation, characteristic for graves.
2:Despite increased food uptake

1) Thioamides

Drugs	Propylthiouracil (PTU)	Methimazole\Carbimazole **Carbimazole:** prodrug converted to the active metabolite methimazole
MOA	• **Both PTU and Methimazole:** Inhibits synthesis of thyroid hormones **by inhibiting the peroxidase enzyme** that catalyzes the iodination of tyrosine residues. ★ **Additional Mechanism for PTU ONLY**: blocks the conversion of T_4 to T_3 in peripheral tissues	
P.K	• Rapidly absorbed ★ **Protein binding: 80-90%** • Accumulation: in thyroid • Excreted by kidneys as inactive metabolite within 24 hours • Half-life: 1.5 hours (short) • Administered every 6-8 hours	• Rapidly absorbed ★ **Protein binding: most of the drug is free**[1] • Accumulation: in thyroid • Excretion is slow, 60-70% of drug is recovered in urine in 48 hours[2] • Half-life: 6 hours (long)[2] • Administered every 8 hours
Pregnancy	• Crosses placenta **less readily** as it is highly protein bound ★ **Recommended in pregnancy**	• Concentrated in thyroid & **crosses placenta** ★ **Not recommended in pregnancy**
Breast feeding	• Less secreted in breast milk ★ **Recommended**	• Secreted ★ **Not recommended**
ADRs	• Skin reactions (frequency: 4-6%): Urticarial or macular reaction[3] • Arthralgia (1-5%) • GIT effects (1-5%): Gastric distress and nausea • Polyarthritis (1-2%): So-called anti-thyroid arthritis[4] ★ **Agranulocytosis** (0.1-0.5%): **Seen in patients with Graves' disease**; occurs within 90 days of treatment	
	★ **Immunoallergic hepatitis**(0.1-0.5%) • ANCA-positive vasculitis (Anti-neutrophil cytoplasmic antibodies[5]) (rare)	• Abnormal sense of taste or smell (rare)

2) Iodine\ Iodide

Drug	1- Organic iodides: iopanoic acid or ipodate 2- Potassium iodide or lugol's solution
MOA	• Inhibit thyroid hormone synthesis and release ★ **Block the peripheral conversion of T_4 to T_3** ★ The effect is **not sustained**[6] (produce a **temporary remission** of symptoms)
Uses	★ **Prior to thyroid surgery to decrease vascularity & the size of gland** • Following radioactive iodine therapy • Thyrotoxicosis
C.I	★ **Should not be used as single therapy** ★ **Should not be used in pregnancy**[7]
ADR	• May produce iodism[8] (rare, as iodine isn't much used now), Iodism symptoms: skin rash, hypersalivation, oral ulcers, metallic taste, bad breath

1: More free drug = more drug available to induce its action
2: Long duration of action = less frequent administration.
3: most common side effect.
4: that is why when a patient comes complaining of arthritis always ask about medications.
5: test for ANCA levels when treating with PTU.
6: should not be given alone unless used for a short period of time.
7: cross the placenta
8: only if given in large amounts

3) Radioactive Iodine (RAI)

Drug	Radioactive Iodine (RAI)
MOA	• 131 I isotope (**therapeutic effect due to emission of β rays**[1]) ★ Accumulates in the thyroid gland and **destroys parenchymal cells**, producing a long-term decrease in thyroid hormone levels.
P.K	• Clinical improvement may take 2-3 months • Half-life 5 days ★ **Cross placenta & excreted in breast milk** = C.I in pregnancy and breastfeeding • Available as a solution or in capsules • **Advantages:** ○ Easy to administer, effective, painless and less expensive ○ safe if given within therapeutic dose, and less toxic than other drugs • **Disadvantages:** ○ High incidence of delayed hypothyroidism[2] ★ **Large doses have cytotoxic actions** (necrosis[3] of follicular cells followed by fibrosis) ○ May cause genetic damage ○ May cause leukemia & neoplasia induced by the genetic damage
Uses[4]	• Hyperthyroidism mainly **in old patients (above 40)** • Graves' disease • Patients with toxic nodular goiter[5] • Can be used as a diagnostic method

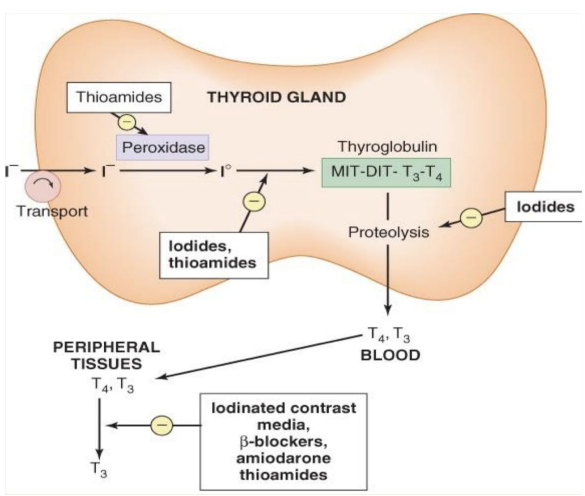
4) β-blockers[6]

Drug	Propranolol\ Atenolol\ Metoprolol
Uses	★ Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism such as tremors, palpitation, heat intolerance and nervousness
C.I	• Propranolol[7] is contraindicated in **asthmatic patients**

5) Thyroidectomy

Sub-total thyroidectomy is the treatment of choice in very large gland or multinodular goiter

Summary for the MOAs



1: leading to disruption of the hyperactive follicles.
2: due to disruption of more follicles than intended = production of less hormones than normal.
3: as necrosis is irreversible, if patient reaches to this stages, he/she will need life-long supplementation of thyroid hormones
4: RAI can be used for both diagnostic and therapeutic measures. 5: to decrease functional cells
6: symptomatic treatment only (treats the symptoms of sympathetic activation induced by excess thyroid hormones)
7: non-selective, possibly leading to bronchospasm

Special Conditions of Hyperthyroidism and their Management

Thyrotoxicosis during pregnancy

- Better to start therapy **before** pregnancy with ^{131}I or subtotal thyroidectomy to avoid acute exacerbation during pregnancy
- During pregnancy:
  - Radioiodine is contraindicated
  - **Propylthiouracil is the drug of choice during pregnancy**

Thyroid Storm

- It is a medical emergency of a **sudden acute exacerbation of all the symptoms of thyrotoxicosis**, presenting as a life-threatening syndrome.
- There is hypermetabolism, and excessive adrenergic activity, **death may occur due to heart failure and shock.**

Management of Thyroid Storm:

1. It should be treated in an ICU for close monitoring of vital signs and for access to invasive monitoring and inotropic support
2. Correct electrolyte abnormalities, **treat cardiac arrhythmia** (if present) & aggressively control hyperthermia by applying ice packs
3. **Promptly administer antiadrenergic drugs (e.g. propranolol) to minimize sympathomimetic symptoms (Life saving treatment)**
4. High-dose propylthiouracil (PTU) is preferred because of its early onset of action, but it has a risk of severe liver injury and acute liver failure.
5. Administer iodine compounds (Lugol's iodine or potassium iodide) orally or via a nasogastric tube.
6. **Hydrocortisone** 50 mg IV every 6 hours **to prevent shock.**
7. Rarely, plasmapheresis has been used to treat Thyroid Storm.

Management of Graves' Disease

Mild/Moderate Hyperthyroidism

[small or moderately enlarged thyroid; children or pregnant or lactating women]

1. Primary **antithyroid** drug therapy should be considered
2. **Start methimazole**, 5-30 mg/day, (**PTU preferred in pregnant women**)
3. Monitor thyroid function every 4-6 weeks until **euthyroid state** achieved
4. Discontinue drug therapy after 12-18
5. Monitor thyroid function every 2 months for 6 months, then less frequently, **if:**
   - **Relapse:** Definitive radioiodine therapy in adults (second course of antithyroid drug therapy in children)
   - **Remission:** Monitor thyroid function every 12 months indefinitely

Severe Hyperthyroidism:

[markedly elevated serum T4 or T3 and very large goitre, >4 times normal]

1. Definitive therapy with **radioiodine** preferred in **adults**
2. Normalization of thyroid function with antithyroid drugs before surgery in elderly patients and those with heart disease

Hypothyroidism

Hypothyroidism

- Thyroid gland does not produce enough hormones
- May be congenital, primary or secondary
- Congenital: in children, hypothyroidism leads to delay in growth (**dwarfism**) **and intellectual development (cretinism)**
- People who are most at risk include those over age 50 & mainly in females
- Prevalence is 14/1000 females and 1/1000 males .
- Diagnosed by low plasma levels of T3 & T4 and TSH

Types of Hypothyroidism

- **Primary:** Inadequate function of the gland itself.
  - **Iodine deficiency: most common cause of primary hypothyroidism & endemic goiter** worldwide
  - Autoimmune: Hashimoto's thyroiditis
  - **Radioactive iodine treatment of hyperthyroidism**
  - **Post-thyroidectomy**
  - Antithyroid drugs (CMZ , PTU)
  - Other drugs (lithium, amiodarone[1])
  - Subacute thyroiditis
  - Thyroid carcinoma
- **Secondary:**
  - Hypothalamic disease
  - Pituitary disease

Manifestations of Hypothyroidism

Early

- Fatigue and lack of energy
- Cold intolerance
- Constipation
- Weakness
- Muscle or joint pain
- Paleness
- Thin, brittle hair and fingernails

VS

Late

- Decreased sense of taste and smell
- Dry flaky skin
- Hoarseness
- Menstrual disorders, infertility
- Puffy face, hands and feet
- Thinning of eyebrows

Treatment of Hypothyroidism

Replacement therapy with synthetic thyroid hormone preparations[2]:

01 **Levothyroxine (T4)**

02 **Liothyronine (T3)**

03 **Liotrix** [3]

1: Amiodarone is a powerful antiarrhythmic that's rich in iodine and can lead to both hypothyroidism and hyperthyroidism. The most likely mechanisms of AIH are an enhanced susceptibility to the inhibitory effect of iodine on thyroid hormone synthesis and the inability of the thyroid gland to escape from the Wolff-Chaikoff effect after an iodine load in patients with preexisting Hashimoto thyroiditis. In addition, iodine-induced damage to the thyroid follicles may accelerate the natural trend of Hashimoto thyroiditis toward hypothyroidism. Patients without underlying thyroid abnormalities are postulated to have subtle defects in iodine organification that lead to decreased thyroid hormone synthesis, peripheral down regulation of thyroid hormone receptors, and subsequent hypothyroidism.

2: Treat the underlying cause first and then give replacement therapy . 3: A mixture of both T4 and T3.

Drug	Levothyroxine (T4)

P.K	• A synthetic form of thyroxine (T4) **is the drug of choice for replacement therapy**[1]
	  ○ **Stable, long half life (7days)**
	  ○ Administered once daily
	  ○ Restore normal thyroid levels within 2-3 weeks
	• Absorption is increased when hormone is given on **empty stomach**
	• Metabolism:
	  ○ Major pathway of thyroid hormone metabolism is through sequential deiodination
	  ○ 80% of circulating T3 is derived from peripheral T4 by monodeiodination
	  ○ The liver is the major site of degradation for both T4 & T3
	  ○ 80% daily dose of T4 is deiodinated to yield equal amount of T3 and rT3 (reverse T3, which is inactive)

Uses	• Hypothyroidism regardless of etiology:
	  ○ Congenital
	  ○ Pregnancy
	  ○ Hashimoto thyroiditis

Dose	• Oral preparations are available form 0.0025-0.3mg tablets • Parenteral preparations[2] 200-500µg • Given in a dose of 12.5-25µg/d for 2 weeks then increased every 2 weeks

ADR	**ADRs of <u>overdose</u> (shows the symptoms of hyperthyroidism)**
	• **In children:**
	  ○ restlessness , insomnia
	  ○ accelerated bone maturation
	• **In adult:**
	  ○ **cardiac arrhythmia (tachycardia , atrial fibrillation)**
	  ○ tremor, restlessness, headache,
	  ○ change in appetite, weight loss,
	  ○ heat intolerance
	  ○ muscle pain

Caution	★ **In old patients and in patients with cardiac problems** treatment is started with reduced dosage.

Drug	Liothyronine (T3)

P.K	★ **Advantages:**
	  ○ More potent (3-4 times)
	  ○ rapid onset of action than levothyroxine
	★ **Disadvantages:**
	  ○ It has short half life, so not recommended for routine replacement therapy (requires multiple daily doses)
	  ○ should be avoided in cardiac patients[3]

Dose	• Oral preparation available are 5-50µg tablets • Parenteral use 10µg/ml

1. Levothyroxine is the drug of choice and used for **routine** replacement therapy because its half life is long and less administrations are required.
2. For emergencies
3. Liothyronine has more cardiac side effects than Levothyroxine.

Comparison in P.K of the drugs

	Potencity	T1\2 (days)	Protein binding
Levothyroxine (T4)	1 (low)	**6-7 (longer)**	99.96
Liothyronine (T3)	**4 (more potent)**	⩽2 (short)	99.5

Drug	Liotrix
MOA	• Combination of synthetic T4 & T3 in a ratio 4:1 that attempt to **mimic the natural hormonal secretion**
Disadvantages	• The major limitations to this product are: ○ High cost ○ **Lack of therapeutic rationale because 35% of T4 is peripherally converted to T3**

Special Conditions of Hypothyroidism and their Management

Myxedema Coma

- Life –threatening hypothyroidism
- ★ **The treatment of choice is loading dose of levothyroxine intravenously** 300-400µg initially followed by 50µg daily
- **I.V. liothyronine can be used for rapid response but it may provoke cardiotoxicity**[1]
- I.V. hydrocortisone may be used in case of adrenal and pituitary insufficiency.

Hypothyroidism in Pregnancy[2]

★ In pregnant hypothyroid patient **20-30% increase in thyroxine is required** because of :
- ○ elevated maternal thyroxine binding globulin (TBG) induced by estrogen
- ○ early development of fetal brain which depends on maternal thyroxine

1. Used for healthy adults with no history of cardiac problems
2. In either hypo or hyper, it's recommended to treat the condition before pregnancy.

Quiz

MCQ

Q1- Which of the following is the treatment of choice for hypothyroidism ?

A- Iodide B- Levothyroxine C- Liotrix D- Propylthiouracil

Q2- A 42-year-old man was undergoing surgery in order to remove a very large nontoxic goiter, apparently due to iodide deficiency. A short course of potassium iodide was administered before surgery. Which of the following statements best explains why this drug was given to the patient?

A-To overcome iodine deficiency after surgery
B- To reduce the size and vascularity of the thyroid gland
C- To decrease the risk of hypothyroidism after surgery
D- To inhibit the excessive secretion of TSH from the pituitary

Q3- A 41-year-old man complained to his physician of increased appetite, palpitation and diarrhea. Lab results confirmed the diagnosis of mild hyperthyroidism and a treatment with methimazole was started. Which of the following actions most likely mediated the therapeutic effectiveness of the drug in this patient?

A- Inhibition of iodine absorption from the gut B- Stimulation of thyroid peroxidase
C- Blockade of iodine uptake by the thyroid gland D- Inhibition of tyrosine iodination

Q4- A 47-year-old woman complained to her physician of painless enlargement of thyroid gland and fullness in her throat. Lab results revealed high titers of thyroid peroxidase antibodies. A diagnosis of Hashimoto's thyroiditis was made and an appropriate treatment was started. Which of the following drugs was most likely prescribed?

A- Propranolol B- Potassium iodide C- Levothyroxine D- Methimazole

SAQ

Q1-A 30-years-old pregnant patient was diagnosed with mild hyperthyroidism, what is the drug of choice in this case ?

2-3)40-years-old patient came with signs of hyperthyroidism, after investigations it turns out that he has severe hyperthyroidism and need a thyroidectomy.

Q2-Which drug can be used in this case before the surgery?
Q3-What is the M.O.A of that drug?

Q4-A 56-years-old cardiac patient diagnosed recently with hypothyroidism, what is the drug that should be avoid in this case?

Q5-A patient with Myxedema Coma was diagnosed to have adrenal and pituitary insufficiency, what is the drug of choice in this case ?

Answers:

MCQ

Q1	B
Q2	B
Q3	D
Q4	C

SAQ

Q1	Propylthiouracil
Q2	Iodides
Q3	Inhibit thyroid hormone synthesis and release, Block the conversion of T4 to T3.
Q4	Liothyronine
Q5	I.V. hydrocortisone

pharmacology

Team 438

Thank you for all your love and support.

Good luck future doctors!

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