DRUGS USED IN HYPOTHYROIDISM

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Slides were adapted from prof. AlMotrfi and prof. Bassiouni

Learning objectives

By the end of this lecture, students should be able to:

- Describe different classes of drugs used in hypothyroidism and their mechanism of action

- Understand their pharmacological effects, clinical uses and adverse effects.

- Recognize treatment of special cases of hypothyroidism such as myxedema coma

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

Primary hypothyroidism

Inadequate function of the gland itself - causes

- Iodine deficiency is the most common cause of primary hypothyroidism and endemic goiter worldwide
- Autoimmune: Hashimoto’s thyroiditis
- Radioactive iodine treatment of hyperthyroidism
- Post thyroidectomy
- Anti-thyroid drugs (CMZ , PTU)
- Other drugs (lithium, amiodarone)
- Sub-acute thyroiditis
- Thyroid carcinoma

Secondary hypothyroidism-causes

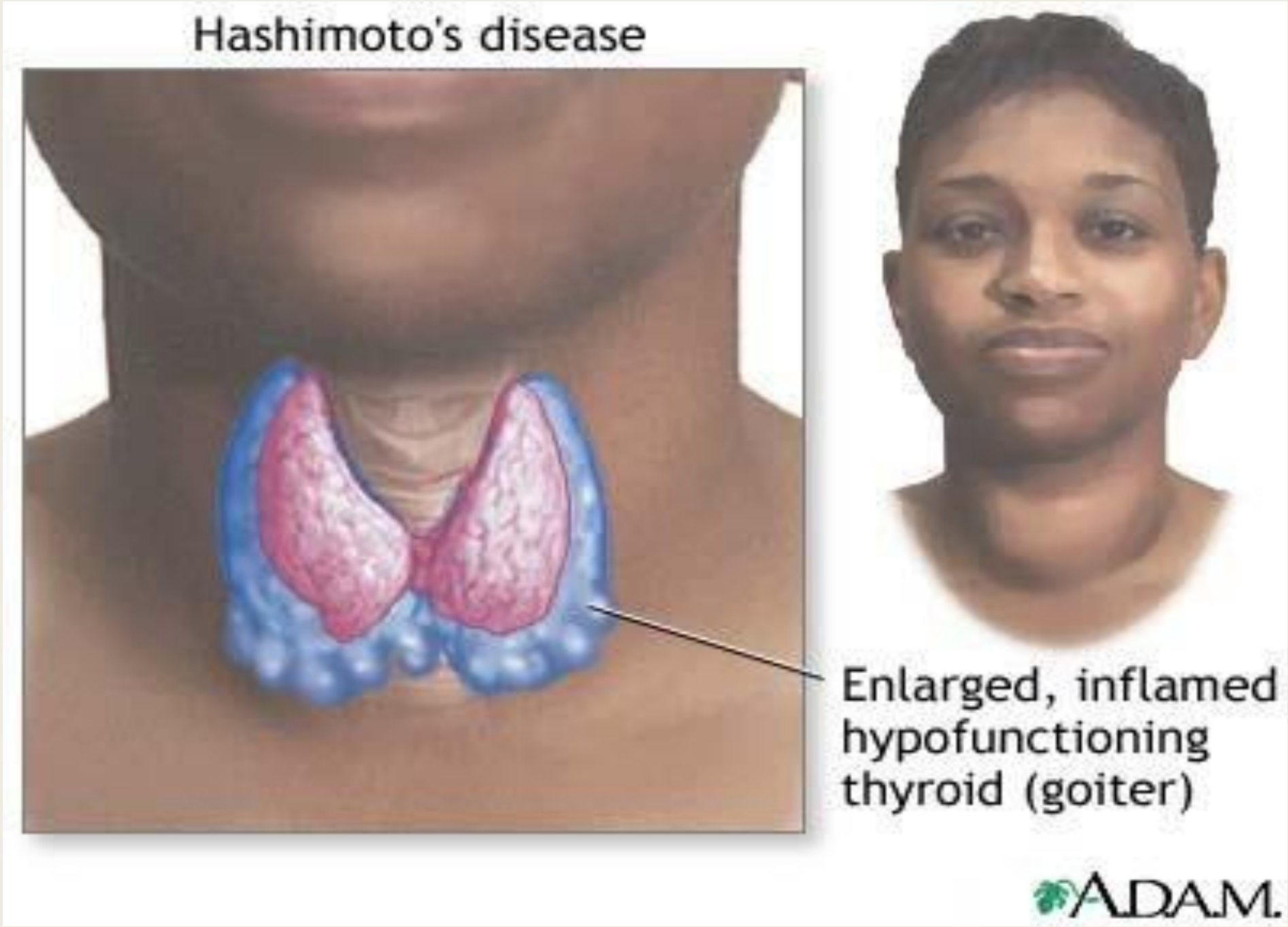
- Hypothalamic disease
- Pituitary disease

Early Manifestations of Hypothyroidism

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

Late Manifestations of Hypothyroidism

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


Hashimoto's disease
Enlarged, inflamed hypofunctioning thyroid (goiter)
A.D.A.M.

Treatment of Hypothyroidism

- **Replacement therapy with synthetic thyroid hormone preparations :**
- **LEVOTHYROXINE (T_4)**
- **LIOTHYRONINE (T_3)**
- **LIOTRIX**

Thyroid preparations

- **LEVOTHYROXINE: (T_4)**
- A synthetic form of the thyroxine (T_4) , is the drug of choice for replacement therapy
- Stable and has a long half life (7 days)
- Administered once daily.
- Restore normal thyroid levels within 2-3 weeks
- Absorption is increased when hormone is given on empty stomach

Thyroid preparations

- **LEVOTHYROXINE: (T_4)**
- Oral preparations available from 0.025 to 0.3 mg tablets
- Parenteral preparation 200-500µg
- In old patients and in patients with cardiac problems , treatment is started with reduced dosage.
- Levothyroxine is given in a dose of 12.5 – 25 µg/day for two weeks and then increased every two weeks.

Clinical uses

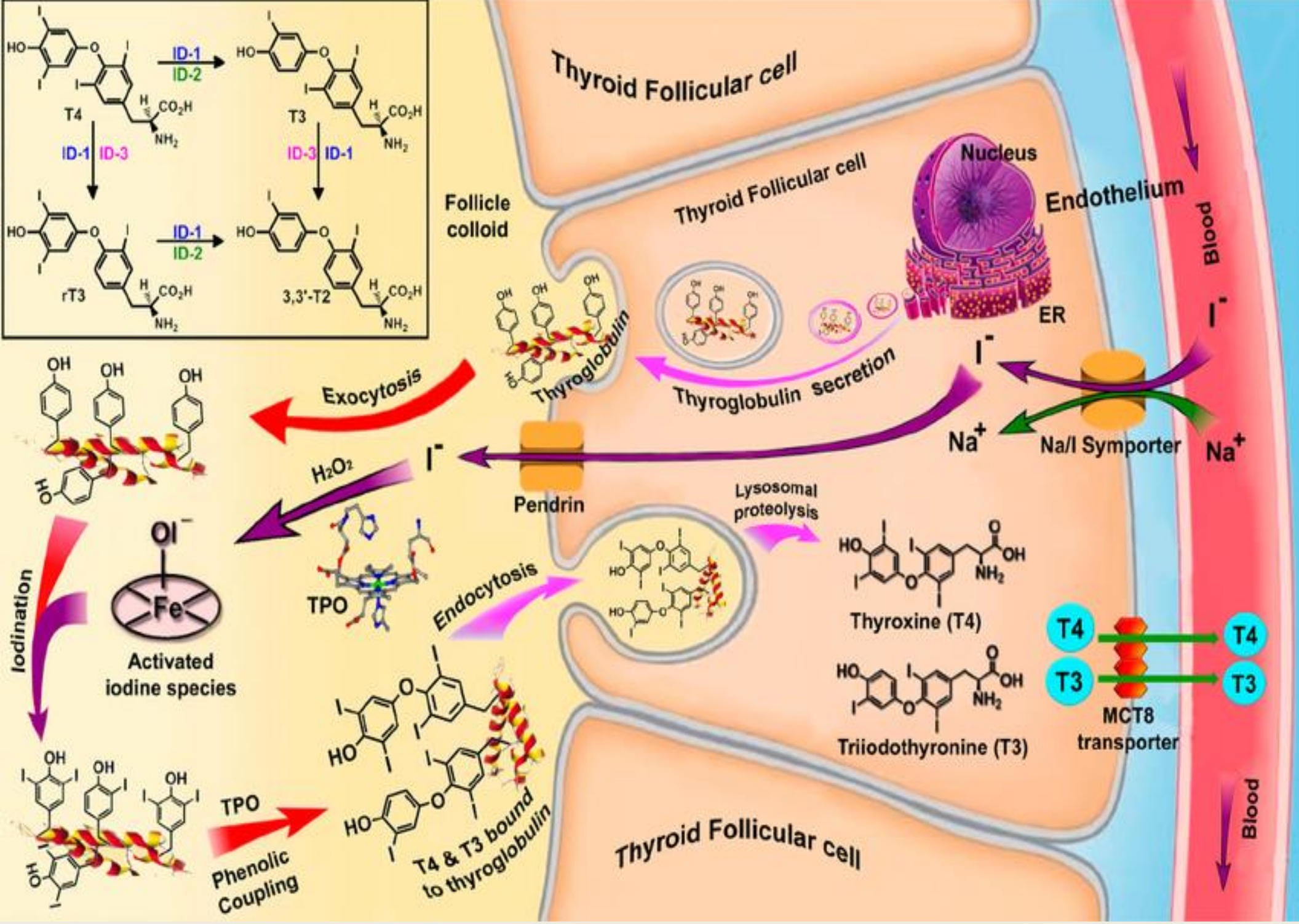
- Hypothyroidism, regardless of etiology

including :

- ❖ Congenital
- ❖ Hashimoto thyroiditis
- ❖ Pregnancy

Metabolism of thyroid hormones

- **Major pathway of thyroid hormone metabolism is through sequential deiodination**
- **80% of circulating T_3 is derived from peripheral T_4 by monodeiodination**
- **The liver is the major site of degradation for both T_4 and T_3**
- **80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and rT_3 (reverse T_3 ,which is inactive)**


T4
T3
rT3
3,3'-T2
ID-1
ID-2
ID-3
Thyroid Follicular cell
Follicle colloid
Nucleus
Endothelium
Blood
ER
Thyroglobulin
Thyroglobulin secretion
Exocytosis
I^-
Na^+
Na/I Symporter
H_2O_2
Pendrin
Lysosomal proteolysis
OI^-
Fe
Activated iodine species
TPO
Endocytosis
Iodination
Thyroxine (T4)
Triiodothyronine (T3)
MCT8 transporter
Phenolic Coupling
T4 & T3 bound to thyroglobulin

ADVERSE EFFECTS OF OVER DOSE

- **CHILDREN :**
- Restlessness, insomnia
- Accelerated bone maturation

- **ADULTS :**

- Cardiac arrhythmias (Tachycardia, atrial fibrillation)
- Tremor, restlessness, headache
- Heat intolerance
- Muscle pain
- Change in appetite, weight loss

Thyroid preparations

- **LIOTHYRONINE (T_3) :**

- More potent (3-4 times) and rapid onset of action than levothyroxine

- Has a short half life - not recommended for routine replacement therapy (requires multiple daily doses)

- Should be avoided in cardiac patients

- Oral preparation available are 5-50µg tablets

- Parenteral use 10µg/ml

Pharmacokinetic of Thyroid Hormones

Hormone	Biologic Potency	$t_{1/2}$(days)	Protein Binding (%)
Levothyroxine (T_4)	1	6-7	99.96
Liothyronine (T_3)	4	≤ 2	99.5

Thyroid preparations

- **LIOTRIX :**

- Combination of synthetic T4 & T3 in a ratio 4:1 that attempt to mimic the natural hormonal secretion

- The major limitations to this product are high cost and lack of therapeutic rationale because 35% of T4 is peripherally converted to T3

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 for rapid response but it may provoke cardiotoxicity
- I.V. hydrocortisone may be used in case of adrenal and pituitary insufficiency.

HYPOTHROIDSM AND PREGNANCY

- 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

Good luck