Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

THYROID HORMONES AND THERMOGENESIS

* Please check out this link to know if there are any changes or additions.

We advice to study **"thyroid + hypo and hyper thyroidism"** physiology lectures before you start studying this lecture.

Revised by
هشام الغفيلي & خولة العماري

Color index: **Important** | Doctors notes | Further explanation.

OBJECTIVES:

- ✓ Describe the types and biosynthesis, actions and the regulation of thyroid hormones.
- ✓ List and interpret the thyroid function tests.
- ✓ Define goiter and differentiate between hypo- and hyperthyroidism.
- ✓ Discuss the role of thyroid hormone in thermogenesis.

Types and biosynthesis of thyroid hormones

❖ Biosynthesis:

1. Synthesis:

Synthesized in the **thyroid gland** by:

- Iodination.
- Coupling of two tyrosine molecules.
- Binding to thyroglobulin protein "for transportation".

2.Secretion:

Thyroid gland **mostly secretes T_4.**

3. Deiodination:

- Peripheral tissues (liver, kidney, etc.) de-iodinate T_4 to T_3.
- Deiodination is catalyzed by **deiodinase enzymes.**
- T_4 can be metabolized to rT_3 (**in**active form)
  "to maintain balance and prevent thyrotoxicosis"

❖ Types:

Thyroxine (T_4)	tri-iodothyronine (T_3)
Most of T_4 is transported in plasma as **protein-bound**: **- Thyroxin Binding globulin** (TBG)-bound (70%) - **Albumin-bound** (25%). Don't get confused between thyroglobulin & TBG! - **Transthyretin (pre-albumin)-bound** (5%).	- **More** biologically **active form.** - T_3 is also transported in plasma as **protein-bound.** T_3 is maximally active → then T_4 → rT_3 is the inactive form.

The **un**bound (free) form of T_4 and T_3 are biologically **active.**

The free form is the form that is taken up by tissues, in which it exerts biological effects.

Note that the bound form is available as a source of the free form, so that that the bound form turns into free form whenever it is needed

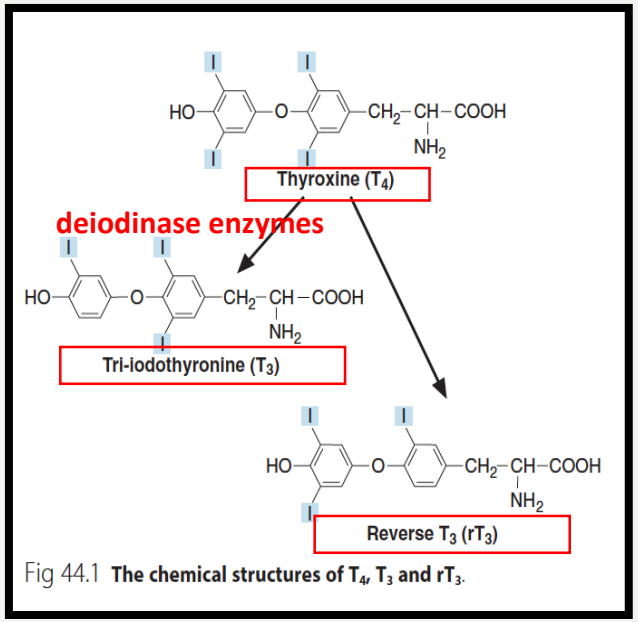


Fig 44.1 **The chemical structures of T_4, T_3 and rT_3.**

The only difference between the active form of T3 and the inactive form (rT3) is the arrangement of iodine.

Thyroid Hormone Production

You can skip it if you studied physiology lectures

Biosynthesis - Dr.sumbul's Explanation -.

1-We require **iodide** which is taken up by the iodide sodium symporter (**active transport**), we also require amino acids.

Note that the iodide taken in, is in the ionic form.

2- Iodide is **oxidized** by thyroid peroxidase.

3- **Thyroglobulin** is synthesized by follicular cells. This thyroglobulin contains many residues of tyrosine. Theses tyrosine residues are iodinated by **thyroid peroxidase enzyme**(iodination process)..

What are the products of iodination ? DIT and MIT

4- **The coupling process:** is the coupling of iodinated tyrosine molecules while these molecules are still bound (within) to the thyroglobulin protein.

MIT+DIT =T3 , DIT+DIT= T4 (majority)

- **How much of T3 is formed from the thyroid gland and how much by peripheral tissues ?**
  - 2/3 of t3 are formed at peripheral tissues by deiodination while 1/3 is formed at the thyroid gland

5- TSH must then trigger the **endocytosis** of the thyroglobulin with T3,T4.

6- Note that the formed T3 and T4 formed are still attached to the tyroglobulin (so these hormones need something to free them from thyroglobulin, in order to enter the circulation), What?)

Lysosomes containing **protease enzymes**

7- T3 and T4 are then **released** into the bloodstream while the remaining iodinated tyrosine molecules (MIT and DIT) **get recycled**

8- T4 is synthesized more than T3 in the peripheral tissues. T4 gets converted into T3(highly active) by **deiodinase enzymes**.

9- T4 can also be metabolized into reverse T3..

- ✓ So at the level of peripheral tissues, we have **three forms** of thyroid hormones (T4,T3 ,reverse T3) with **T3 as the highly active** form then T4 is the second most active then reverse T3 is inactive.

Thyroid hormone action

Maturation of **all** body tissues.	**Thermogenesis** and metabolic regulation.	**Increases** cellular oxygen consumption and **stimulates** the metabolic rate.	Affects the rate of: protein, carbohydrate and lipid **metabolism**.

❖ Clinical evidence of the wide spectrum of thyroid hormone action:

Case:	Consequences:
Untreated congenital **Hypo**thyroidism	Untreated within 3 months → **permanent brain damage.**
Hypothyroid **children** "for genetic and non-genetic causes":	• Delayed **skeletal maturation** →short stature. "Remember: Thyroid hormones promote fusion of bone plates." Delayed **puberty**. The term for hypothyroidism in infants or children is cretinism
Hypothyroid patients:	**High serum cholesterol** due to: • **Down** regulation of **LDL** receptors on liver cells. • Failure of **sterol excretion** via the gut.

Regulation of Thyroid Hormone Secretion

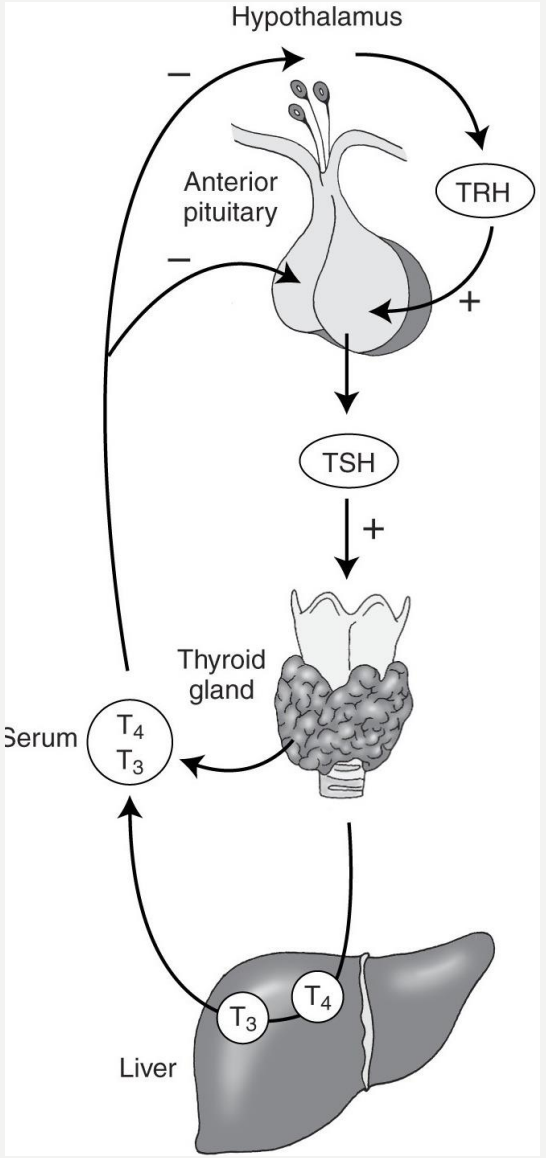
The **hypothalamus senses** low levels of T_3/T_4 and **releases** thyrotropin releasing hormone (**TRH**)

→ **TRH stimulates** the **pituitary** to produce thyroid stimulating hormone (**TSH**)

→ **TSH** stimulates the **thyroid** to produce T3/T4 until levels return to normal

T3/T4 exert **negative** feed back control on the **hypothalamus** and **pituitary**

→ Controlling the release of **BOTH** TRH and TSH.



Low thyroid hormone levels	High thyroid hormone levels
stimulate TRH, TSH to produce more hormone	**suppress** TRH, TSH

Thyroid Functions tests: IMPORTANT

Test:	Used for:
TSH measurement:	○ Assessment of **thyroid function**. Although TSH is not secreted by the thyroid gland, it indicates the thyroid function.. WHY? Because the level of TSH itself is regulated by thyroid hormones. ○ Highly sensitive test (detects very low conc.).
***Total** "bound + unbound" **T_4 or free T_4**	○ Assessment of **thyroid function**. ○ Monitors **thyroid treatment** (both anti-thyroid(to treat hyperthyroidism) and thyroid replacement treatment(to treat hypothyroidism)). ○ TSH may take up to 8 weeks to adjust to new level during treatment. So T4 is better in monitoring treatment response than TSH? Because TSH takes 8 weeks to change while T4 can be measured more frequently.
***Total** "bound + unbound" **T_3 or free T_3**	○ Useful for assessing **hyperthyroidism** in which rise in T_3 is **independent** of T_4rare condition ○ In some patients only T_3 rises (T_4 is normal): **T_3 toxicosis** ○ For earlier identification of **thyrotoxicosis.**
Antibodies:	○ Diagnosis and monitoring of **autoimmune thyroid disease**: • **Hashimoto's thyroiditis** (antibodies against TSH receptors that **suppress** thyroid secretion). • **Graves' disease** (antibodies against TSH receptors that **stimulate** thyroid secretion).

*the free form test is more Preferable → why? → in case of liver diseases → less synthesis of proteins → less amounts of the bound TH →So these changes do not depict the condition of the thyroid gland , hence the free hormones are a better indication for the function of the thyroid gland

Goitre – تضخم الغدة الدرقية

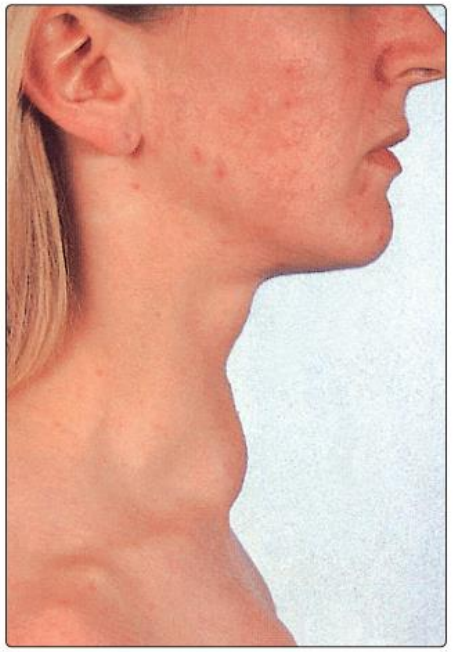


Fig 44.2 **A patient with a goitre.**

- Enlarged thyroid gland. Note that the way thyroid gland may enlarge is uninodular ,binodular, or diffused so that the whole gland will enlarge.
- **Goitre may be associated with:**
  - **Hypo**function
  - **Hyper**function
  - ***Normal** thyroid hormone conc. (euthyroid) For example when hypo or hyperthyroidism causes goiter, then the patient is treated so the levels of circulating thyroid hormones is normal but the goiter is still present
- **Causes:**

Iodine deficiency.most common cause "Hyperplasia of thyroid to compensate for decreased efficacy"	**Selenium deficiency.** "selenium is essential for the production of thyroid hormones (act as a co-factor)."	**Hashimoto's thyroiditis.**	**Graves' disease (hyperthyroidism).** "will be discussed"	**Congenital hypothyroidism / thyroid cancer.**

*ضروري تعرفون ان الغدة بتكون متضخمة وافراز الهرمونات ممكن يقل أو يزيد أو يبقى زي ماهو!

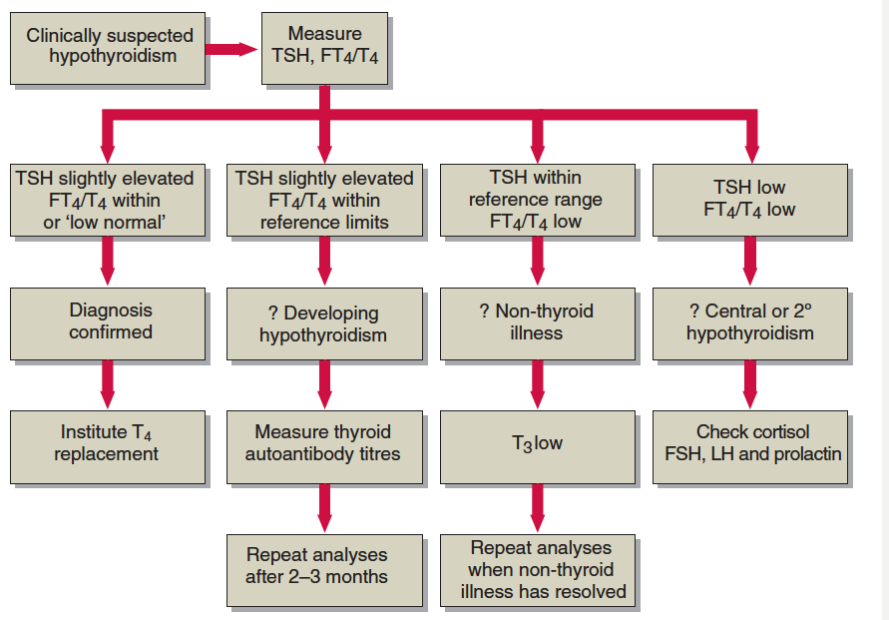
Hypothyroidism

Definition:	**Deficiency of thyroid hormones.**			
Types:	**Primary hypothyroidism:** "at the level of thyroid gland".		**Secondary hypothyroidism:**	
	Failure of **thyroid gland** (***Elevated** TSH, **deficiency** of thyroid hormones.		Failure of the **pituitary gland** to secrete TSH (rare)	
			Failure of the **hypothalamic-pituitary-thyroid axis**	
Causes:	• **Hashimoto's thyroiditis**. (Major cause) • **Radioiodine** or **surgical treatment** of hyperthyroidism. → Most common causes • **Drug effects.** • **TSH deficiency.** • **Congenital defects** in **thyroid synthesis** / thyroid resistance (where the cells are unable to uptake the thyroid hormone). • **Severe iodine deficiency.**			
	Non-thyroidal illness:			
	○ In some diseases, the normal **regulation** of TSH, T_3 and T_4 secretion and metabolism is **disturbed**. ○ Most of T_4 is converted to rT_3 (inactive) → Causing thyroid hormone deficiency. ○ **Secretion** of T_4 and T_3 is **decreased**.			
Clinical features:	**Tiredness**	**Cold intolerance.**	**Weight gain.** "metabolic rate slows down"	**Dry skin**
Treatment:	**Replacement therapy** with **levothyroxine** (T4)			

*__Why is TSH elevated?__ Because low levels of thyroid hormones will stimulate the hypothalamus to produce more TRH which will stimulate the anterior pituitary to secrete more TSH.

Biochemical investigation of suspected hypothyroidism

	1	2	3	4
TSH:	**Elevated**		**Within reference range**	**Low**
FT4\T4:	**Within or <u>low</u> normal**	**Within reference range**	**Low**	
Diagnosis:	**Conformed hypo-thyroidism**	**Developing hypo-thyroidism** لأن التي فور لسى ماتأثرت مستوياته بس عندنا ارتفاع بالتي اس اتش، فتوه قاعد يتطور.	**Non-thyroid illness**	**2ry or central hypo-thyroidism.** تي اس اتش قليل ← يعني المشكلة فوق ميب على لفل الثايرويد ← يعني سكندري
Further?	Institute T4 Replacement.	1- Measure thyroid autoantibody titers. why? Because the most common cause of hypo is hashimoto's thyroiditis. 2- Repeat analyses after 2-3 months.	1- T3 test → if low 2- Repeat analyses when non-thyroid illness has resolved.	Check cortisol FSH, LH and prolactin. لأنه هنا سكندري فنحتاج نشيكل على الهرمونات اللي تفرز من البتيوتاري



HYPERTHYROIDISM

- **Hyperstimulation** of thyroid gland by pituitary gland. By TSH
- **Hypersecretion** of thyroid hormones.
- **Tissues** are exposed to high levels of thyroid hormones (**thyrotoxicosis**).

What is the difference between hyperthyroidism and thyrotoxicosis?
Hyperthyroidism is a type of thyrotoxicosis
So thyrotoxicosis can be caused by other causes , hence thyrotoxicosis is a broader term

Causes:

- **Toxic multinodular goitre**
- **Thyroid adenoma**
- **Graves' disease**
- **Excessive intake of iodine \ iodine drugs**
- **Thyroiditis**
- **Excessive intake of T_4 and T_3**

Graves' disease

- Most **common cause** of hyperthyroidism.
- An **autoimmune** disease due to **antibodies against** TSH receptors on thyroid gland.
- The antibodies **mimic** the action of pituitary hormone → causing **hypersecretion** of thyroid hormone.

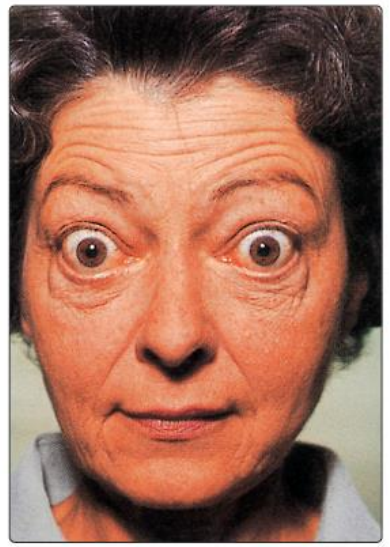


Fig 46.3 **Lid retraction and exophthalmos in a patient with Graves' disease.**

Graves' Disease - Hyperthyroidism

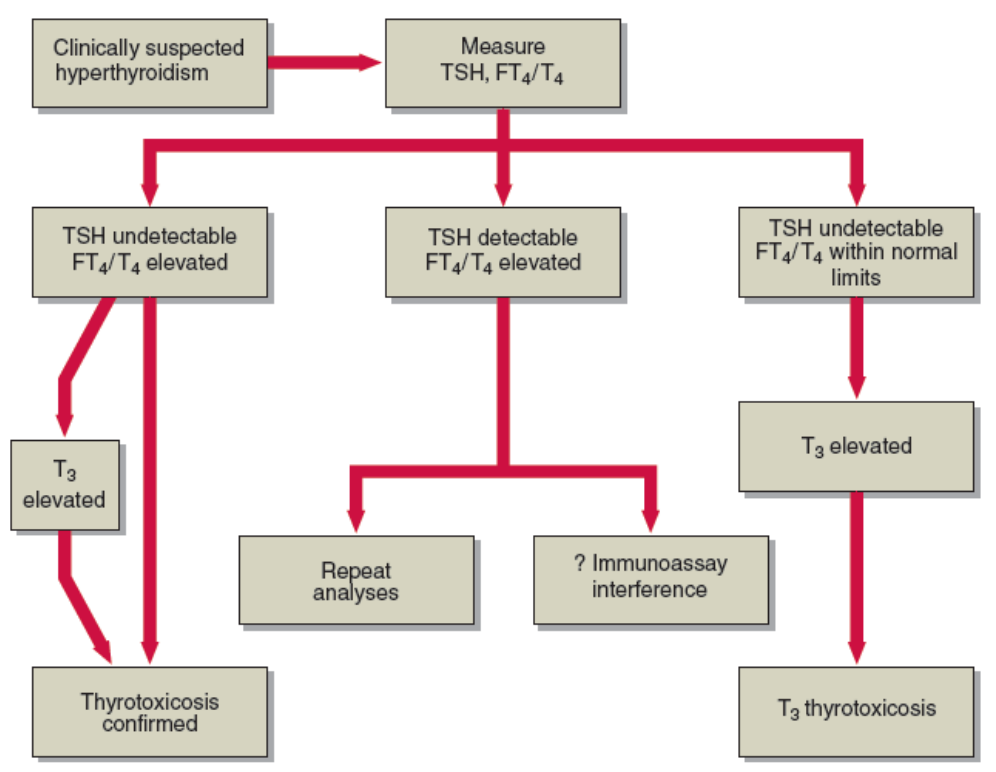
HYPERTHYROIDISM

Clinical features:	**Sweating / heat intolerance**	**Fatigue**	**Palpitation(by sympathetic stimulation) / agitation, tremor**
	Angina, heart failure	**Diarrhea** "by increasing motility"	***Eyelid retraction and lid lag.**
	Weight loss (due to increased metabolic rate) with normal appetite		
Diagnosis:	○ Suppressed / undetectable TSH level. ○ Raised thyroid hormones levels. ○ Confirms primary hyperthyroidism**.** Free T_4 and TSH are **first-line tests** for diagnosis of thyroid dysfunction		
Problems in diagnosis:	○ Total serum T_4 varies due to changes in binding protein levels ○ High estrogens in pregnancy increase TBG synthesis ○ Total T_4 will be high, free T_4 will be normal Congenital TBG deficiency can also influence results		
Treatment:	✓ **Antithyroid drugs:** carbimazole, propylthiouracil "for younger patients". ✓ **Radioiodine** "more aggressive treatment": sodium ^{131}I inhibits T_4/T_3 synthesis "for older patients". ✓ **Surgery:** thyroidectomy "subtotal".		

*The antibodies which are being produced against thyroid gland have similar antigen to those of the orbital muscles → inflammatory reaction→ edema + exophthalmos.

Biochemical investigation of suspected hyperthyroidism

	1	2	3
TSH:	**Undetectable**	**Detectable**	**Undetectable**
FT4\T4:	**Elevated**		**Within normal limits**
Further?	**T3 levels**	- Repeat analyses. - Immunoassay interference.	**T3 levels**
Diagnosis:	If T3 is elevated → **thyrotoxicosis conformed.**	-	If **T3 is elevated** → T3 **thyrotoxicosis**. لاحظوا ان بهالحالة فقط التي 3 هو المرتفع.. rare



What are the lab results in pituitary adenoma?
increased TSH, increased t3 and t4 levels

Thermogenesis (Heat production)

- Humans are **homeothermic** (keep constant body temp.).
- Tightly controlled **temperature homeostasis.**

Thermogenesis is of two types:	
Obligatory:	**Facultative**:
○ Heat production due to ***basal metabolic rate.** طاقة حرارية تنتج لمن يتحول الاي تي بي الى أي دي بي "بنطلع فوسفات ← بتطلع معه طاقة معظمها يستخدم في العمليات الحيوية والباقي يطلع على شكل حرارة".	○ **On-demand** extra heat production from metabolic activity in <u>brown adipose tissue</u>, <u>skeletal muscle</u>, etc. مثلا: لمن تدخل غرفة باردة حرارة جسمك بترتفع.. فالحرارة بتنتج حسب الحاجة.. ○ Facultative thermogenesis in ****brown adipose tissue** humans is stimulated by **sympathetic** nervous system.

Notes:

- Newborns have a lot of brown adipose tissue which decreases as the infant grows (as the person grows brown adipose tissue is converted into white adipose tissue.)
- **What is brown adipose tissue ?**
  - Contains a lot of mitochondria, and has a lot of capillaries, (what is the benefit of the abundance of capillaries? they will allow the fast circulation of the heat produced in the adipose tissue).

*the minimal rate of energy expenditure per unit time at rest.

THYROID HORMONE AND THERMOGENESIS

❖ **Two concepts of thyroid thermogenesis:**

1. Classical: peripheral

2. New: Central brown fat

Thyroid hormone (T_3)

Body **tissue cells** (muscle, liver)

↓

Activates certain **enzymes** by an <u>unknown mechanism</u>

Hypothalamus

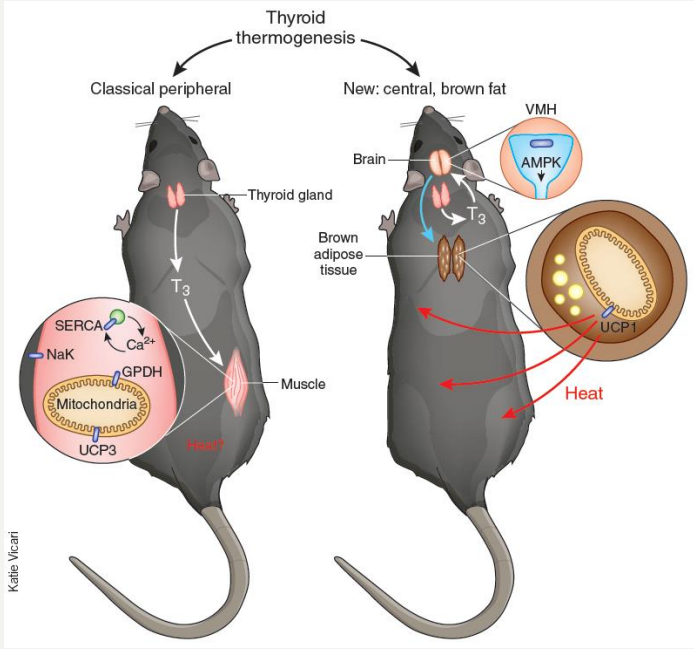
↓

Activates **brown adipose tissue**

↓

Increased body energy expenditure

THERMOGENESIS



Classical peripheral	New: central, brown fat
TH → t3 → muscles → there are different enzymes which are involved and producing heat and the most important ones are: **GPDH**, **NaK-ATPase**, smooth endoplasmic reticulum ATPase (**SERCA**), and Uncoupling protein 3 (**UCP3**) → **thermogenesis**.	**TH → T3** → acts on the **hypothalamus** and inhibits **AMPK** enzyme → signals go the **brown adipose tissue** → activation of one the uncoupling proteins which is known as **UCP1** → **thermogenesis**.

THYROID HORMONE AND THERMOGENESIS

- Thyroid hormone plays essential roles in thermogenesis.
- It **upregulates** body temperature set by the brain.
- It acts centrally on the **hypothalamus** that controls **brown adipose tissue** for thermogenesis

- In respiratory chain, some protons reenter the mitochondrial matrix through uncoupling proteins (UCPs) without ATP synthesis.
- These protons are released as **heat**.
- Thyroid hormone regulates mitochondrial UCPs.

Examples:

- UCP1 in brown adipose tissue
- UCP3 in muscle, other tissues . علشان ماتنسونها شوفوا ال3 كأنه حرف الام واقف

You can skip it if you understood last slide

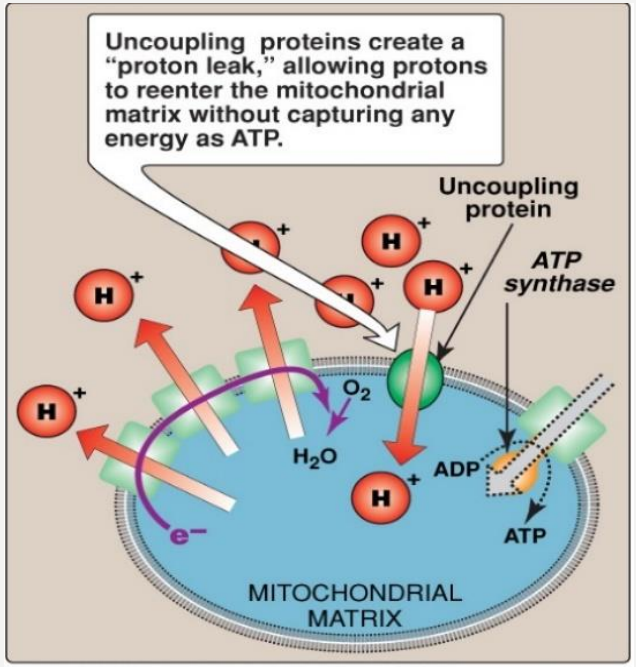
UNCOUPLING PROTEINS – EXPLANATION -

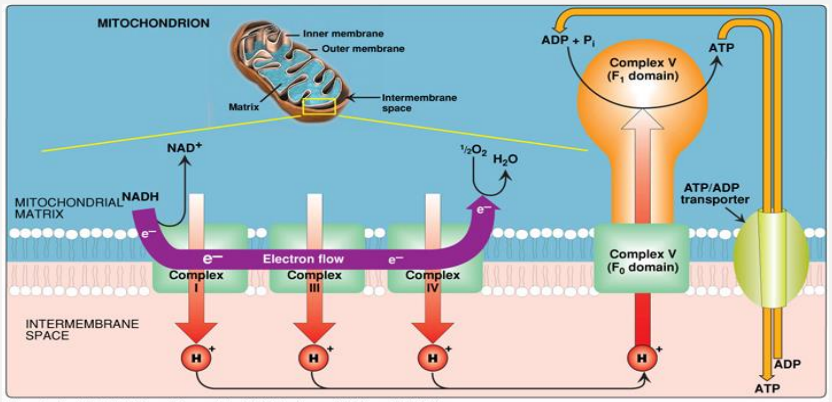
❖ How uncoupling proteins work?

- As the electrons are flowing through the complexes, there is a concurrent flow of protons into the intermembrane space from the mitochondrial matrix.
- So when that happens, a proton gradient is generated → So when these protons go back into the matrix, this will rotate the F1-0 ATPase which will lead to the production of ATP.

❖ What do the uncoupling proteins do?

- Without the protons going through the f1-0 ATPASE enzyme, the uncoupling proteins just bring the protons back in through the uncoupling proteins.
- These uncoupling proteins kind of create holes in the membrane
- So when the protons pass through them instead of the enzyme, heat is released instead of the synthesis of ATP
- ATP is not produced if the protons do not pass through the ATPase >the rotation if the enzyme will not occur → ATP not produced >the energy is released instead as heat





Check your understanding!

Q1: Hypothyroid patients have low serum cholesterol due to down regulation of LDL receptor on liver cell :

A. True
B. False

Q2: T4 is mostly converted to T3 in:

A. thyroid
B. when needed
C. peripheral tissue
D. never converted

Q3: T3/T4 exert negative feedback control on :

A .Hypothalamus
B. Thyroid gland
c. Pituitary and hypothalamus
D. All of the above

Q4: in primary hypothyroidism there is :

A. Failure of thyroid gland
B. Deficiency of thyroid hormones
C. Elevated TSH
D. All of the above

Q5: UCP1 are found in :

A. In muscle, other tissue
B. brown adipose tissues
C. white adipose tissues
D. Liver

Q6:Most common cause of hyperthyroidism :

A. Grave's disease
B. Excessive intake of T3 AND T4
C. Thyroid adenoma
D. Hashimoto's thyroiditis

Q7: in which if these states is TBG synthesis is high:

A. liver diseases
B. stress
C. pregnancy
D. Kidney diseases

1-B 2-C 3-C 4-D 5-B 6-A 7-C 8-A

Check your understanding!

Q8:which of the following is considered a first line test in TFT:

A.TSH measurement
B. total T4
C. total T3
D.TRH measurement

Q9: if a patient TSH is high and T4 is high what does it indicate:

A. Primary hyperthyroidism
B. Secondary hyperthyroidism

Q10:the thyroid gland mostly secretes:

A. T3
B. T4
C. equal
D. neither

Q11: The thyroid hormones are regulated by:

A. positive feedback mechanism
B. hypothalamic-pituitary-thyroid axis
C. Both
D. Neither

Q12: thyroid hormones have an important func3on in thermogenesis through:

A. Na/k gradient
B. Na/Ca gradient
C. Na/Cl gradient

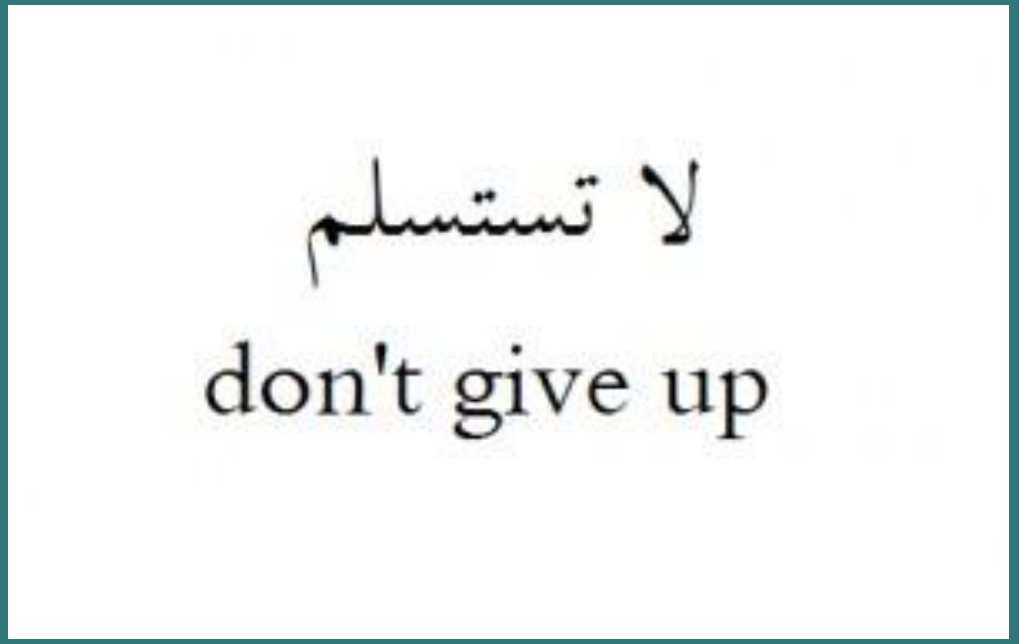
9-B 10-B 11-B 12-A

Done by:

- شهد العنزي.
- عبدالله الغزي.
- ريفان هاشم.
- نوف الرشيد.
- عبدالله الشنيفي.

Revised by:

- فارس المطيري.



Resources:

- 435's slides and notes.

@435biochemteam
435biochemistryteam@gmail.com
@biochemteam435