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BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY

Thyroid Hormones and Thermogenesis

Editing File

Color Index

- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

Objectives

- Describe the types and biosynthesis, actions and the regulation of thyroid hormones.
- List and interpret the thyroid function test.
- Define goiter and differentiate between hypo- and hyperthyroidism
- Discuss the role of thyroid hormone in thermogenesis
- Understand the nutritional importance of dietary macro and micronutrients.
- Understand the nutritional importance of dietary macro and micronutrients.

Types of Thyroid Hormones

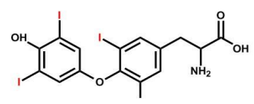
Thyroxine (T_4)

Major secretion

thyroxine or tetraiodothyronine: all the four sides are Iodinated.

Most likely transported to plasma bound to:

- 70% Thyroxine binding globulin **(TBG)**
  Do not confuse it with thyroglobulin (involved in the synthesis whereas TBG is involved in the transport)
- 25% albumin
- 5% transthyretin **(prealbumin)**

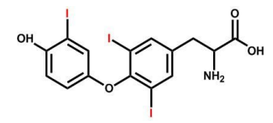


3,5,3',5'-tetraiodothyronine (aka thyroxine)

Tri-iodothyronine (T_3)

More biologically active

- Thyroxine has one iodine atom more than T3 however T3 is more active
- The functional form of the thyroid hormone T4.



3,5,3'-triiodothyronine (T3)

- Once the hormone is bound to protein it becomes inactive and then it goes to the tissue and becomes unbound form (active) and then acts on the cells
- The unbound free form of T3 and T4 are biologically active (most of the actions of the thyroid hormones are formed by this T3 and T4).

-thyroid gland secrets 90% of T4 and 10% of T3.
-they belong to steroid thyroid superfamily "lipophilic", which require smoothing to carry them in the bloodstream. What carries them? Thyroxine binding globulin TBG.
-When the hormones are produced, They produce:
90% of T4: 99.95% is bound to protein and 0.05% is free
10% of T3: 99.5% is bound to protein and 0.5% is free
So ,when we compare 0.05 and 0.5, the percentage of free T3 is ten times that of T4.

Biosynthesis of Thyroid Hormones

A thorough explanation of the entire process can be found **here**.

Thyroid Gland :

Synthesize T_3 and T_4

2 tyrosine molecules tyrosine deficiency leads to thyroid deficiency

↓

Iodination/Organification

↓

Coupling

↓

Binding to thyroglobulin (protein)

Peripheral tissues (liver, kidney, etc.):

- De-iodinate[(1)] T_4 ⇒ T_3 (active) catalyzed by **deiodinase** enzyme
- T4 can be metabolized to rT3 (inactive form)

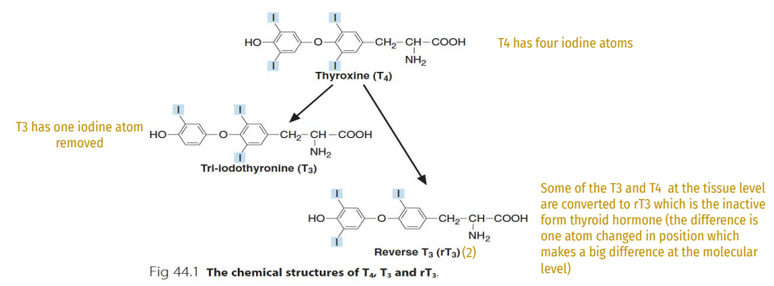


Fig 44.1 **The chemical structures of T_4, T_3 and rT_3.**

(1): De-iodination? Because T3 is the more effective and it is the functional form.
(2): inactive form of the thyroid hormone, and the only difference between T3 and reverse T3 is the site of de-iodination.

Thyroid Hormone Action **Require for growth**

Plays an essential role in maturation of all body tissues

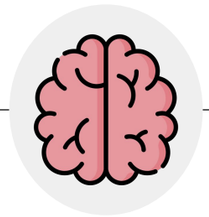
Involved in production of 30% of heat ,non shivering thermogenesis and metabolic regulation

affect the metabolism and the rate of the metabolism (change the need and oxygen consumption by the cells)

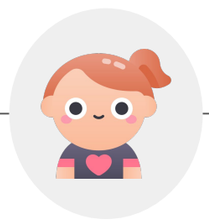
Increase cellular O2 consumption, ATP production and stimulates the metabolic rate

Affects the rate of protein, carbohydrate and lipid metabolism

Clinical evidence of the wide spectrum of thyroid hormone action:



Untreated congenital hypothyroidism⇒ **Permanent brain damage**



Hypothyroid children have:

- Delayed skeletal maturation ⇒ a short stature (stunted growth)
- Delayed puberty

Hypothyroid patients have high serum cholesterol due to:

- Down regulation of LDL receptors on liver cells
- Failure of sterol excretion via the gut, a feedback mechanism: internally in the cells there's a deficiency of cholesterol but in the circulation there's a lot of cholesterol available which can't be used -> the cells send signals that we need more cholesterol -> more production and down regulation of LDL receptors
- **mainly carrying cholesterol, so if the downregulated, they will not taken up cholesterol and they will not be cleared from Bloodstream.**
- The cholesterol will be building up leading to atherosclerosis or risk of heart disease

Regulation of Thyroid Hormone Secretion

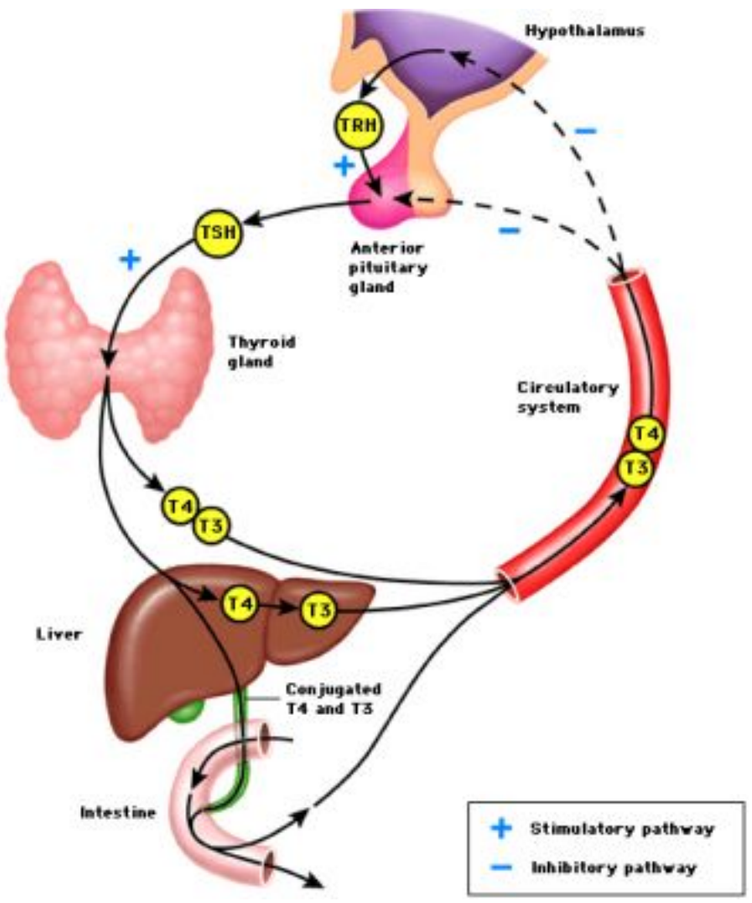
The hypothalamic-pituitary-thyroid axis regulates thyroid secretion

1. the hypothalamus senses low levels of T_3/ T_4 and releases thyrotropin releasing hormone (TRH)

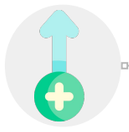
2. TRH stimulates the pituitary to produce thyroid stimulating hormone(TSH)

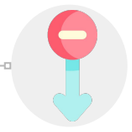
3. TSH stimulates the thyroid to produce T3/T4 until levels return to normal , causes the breakdown / degradation of thyroglobulin, then T4 and T3 are released.

4. T_3/ T_4 exerts **negative feedback** to control the hypothalamus and pituitary controlling the release of both TRH and TSH:



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





High thyroid hormone levels **suppress** TRH, TSH

Thyroid function tests

We used these test to diagnosis and insure that patient is responding well to the treatment

Tests and interpretation are important

	Test	Interpretation
Most common Both will help to assess the thyroid function, but TSH is more sensitive. Any changes in the thyroid function will lead to change in the level of TSH (hypo and hyper will picked up by TSH level). But it has draw back, that you have to wait for at least 2 months to see changes in TSH level).	**TSH measurement**	- **Assessment of thyroid function** - highly sensitive test (detects very low concentration) - Even if there is low or minimal changes in T4 levels, the level of TSH changes significantly.
	Total T_4 or free T_4	- **Assessment of thyroid function** - **Monitors thyroid treatmen**t (both anti-thyroid for hyperthyroidism and thyroid replacement for hypothyroidism treatment) - TSH may take up to 8 weeks to adjust to new level during treatment - The accurate diagnosis will be able to make with free T4 (functional form). - Free T4 is more relevant in people with hyperthyroidism because they can develop hypothyroidism quickly after initiating treatment. People being treated must measure thyroid hormone (titration)
Less common	**Total T_3 or free T_3:**	- **Useful for assessing hyperthyroidism** in which rise in T_3 is independent of T_4 - In some patients only T_3 rises independently (T_4 is normal): T_3 toxicosis (in some cases the thyroid gland itself from the beginning is producing high amounts of T3 which will lead to toxicosis (not related to T4 being converted to T3). Rarely used, useful only in ↓ TSH with normal T4 - For earlier identification of **thyrotoxicosis**
	Antibodies	Diagnosis and monitoring of autoimmune thyroid disease: 1. Hashimoto's thyroiditis (antibodies against TSH receptors that suppress the thyroid secretion) the most common cause of hypothyroidism. 2. Graves disease (antibodies against TSH receptor is that stimulate thyroid secretion) hyperthyroidism.

Goiter (enlarged thyroid gland)

Goiter may be associated with:

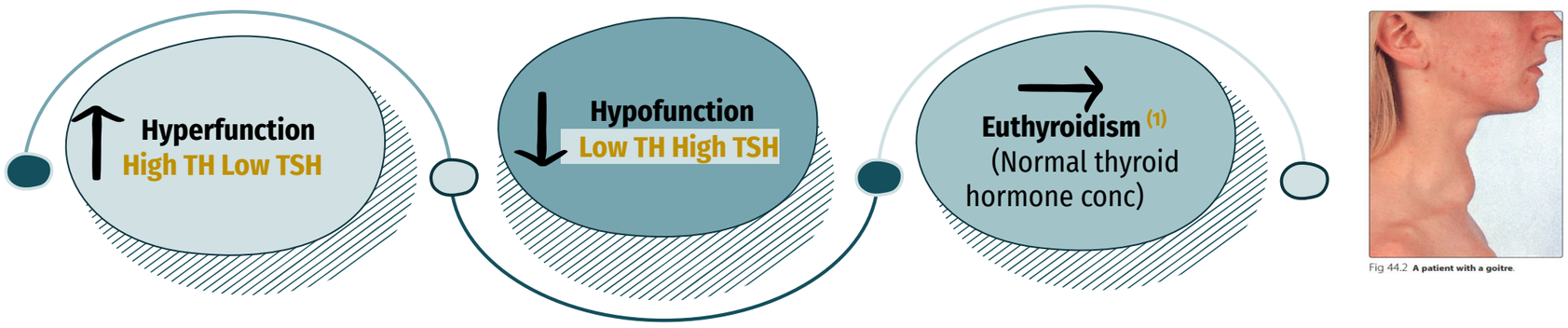


Fig 44.2 **A patient with a goitre.**

(1): when you give patients with hypothyroidism "thyroxine/hormone replacement therapy" and the TSH and T4 have come to normal. At that moment we call them Euthyroid, because the thyroid hormones are normal due to replacement. And vice versa.

Goiter causes:

- Iodine, selenium[2] deficiency
- Hashimoto's thyroiditis
- Graves disease (hyperthyroidism)
- Congenital hypothyroidism/ Thyroid cancer

(2) Selenium is a cofactor involved in thyroid synthesis and is essential for the enzyme function (thyroxine peroxidase requires selenium for its activation).

Hypothyroidism

- Deficiency of thyroid hormones

Hypothyroidism	
Types of hypothyroidism	**1. Primary hypothyroidism:** Failure of thyroid gland. (at the level of thyroid gland itself) • Elevated TSH (because when there is less amount of hormones→the hypothalamus will pick it up→ release TRH→ that will release TSH). • Deficiency of thyroid hormone (normal or low, but normal it will be in the lower end of the range). **2. Secondary hypothyroidism:** at the level of pituitary, hypothalamus or some other disease • Failure of pituitary to secrete TSH • Failure of hypothalamic pituitary axis
Causes of hypothyroidism	• Hashimoto's thyroiditis • Radioiodine inhibit/ destruction of thyroid cells or surgical (removal of thyroid gland) treatment of hyperthyroidism • Drug effects • TSH deficiency • Severe iodine deficiency • Congenital defects in thyroid synthesis / thyroid resistance
Clinical features due to low metabolic rate	• Tiredness • Cold intolerance • Weight gain • Dry skin
Treatment	• Replacement therapy with levothyroxine (T_4) use it every day for whole life (there's no treatment). Very successful after titration.
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) at the level of the tissue • Causing thyroid hormone deficiency • Secretion of T_4 and T_3 is decreased (Why do we have this reverse T3 in our body ? Reverse T3 is protective, how? When T4 level is going high to protect our body from thyrotoxicosis , the body convert this excess into reverse T3 . So , formation of reverse T3 Is protective in some cases when there's excess of thyroid hormones).

Dr. sumbul: Important

Strategy for the biochemical investigation of suspected hyperthyroidism

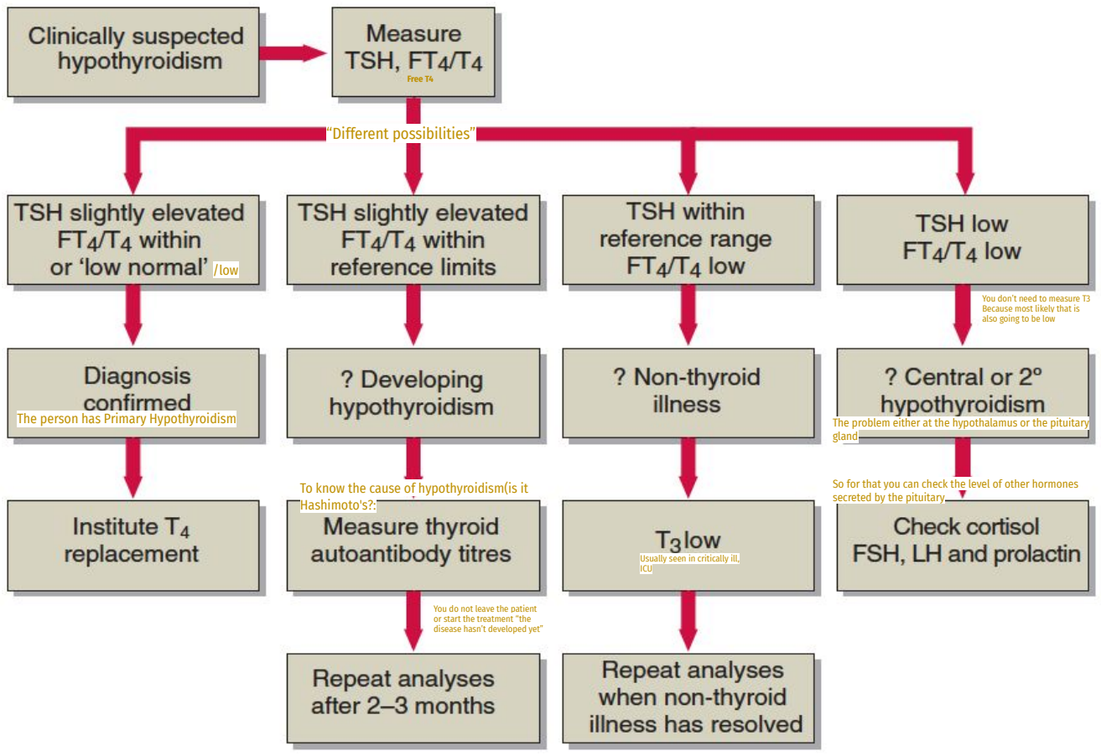
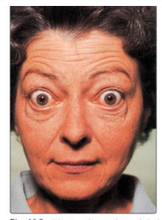
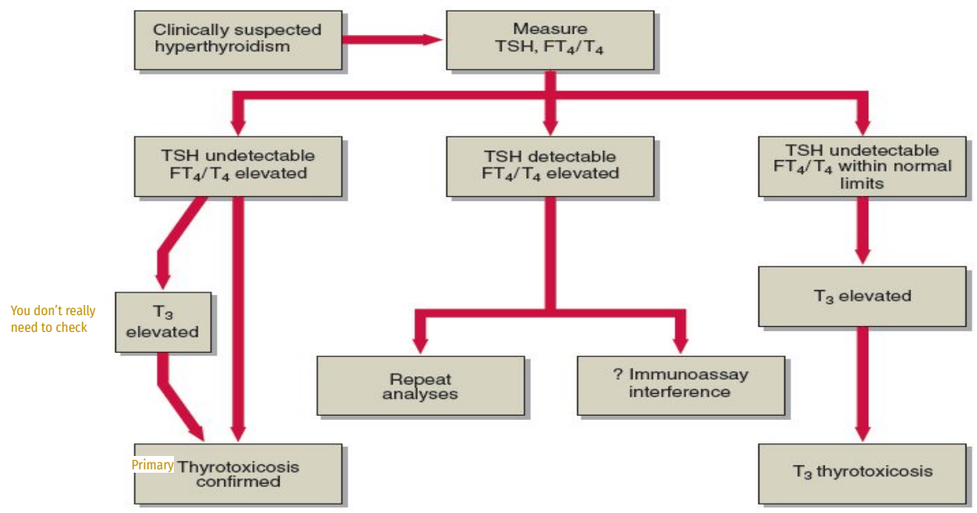


Fig 45.1 **Strategy for the biochemical investigation of suspected hypothyroidism.**

Hyperthyroidism

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

Hyperthyroidism	
Causes	• Graves' disease • Toxic multinodular goitre • Thyroid adenoma • Thyroiditis • Excessive intake of iodine / iodine drugs • Excessive intake of T_4 and T_3 (If person is benign treated for hypothyroidism, he have to take the medication throughout their life, but there is a guideline that every few mounts they have to go for thyroid hormones check up, because the body physiology keep changing with time and their bodies requirement of the thyroid hormone may decrease or increase. So for instance, If somebody's thyroid hormones requirement has decrease, maybe he has done lifestyle modification, exercise and losing weight. So in that case there is excess intake of the hormone and that can leads to the symptoms of hyperthyroidism)
Clinical features	• Weight loss with normal appetite (due to the high metabolic rate) • Sweating / heat intolerance (because thermogenesis is high) • Fatigue (because the body is working excessively) • Palpitation / agitation, tremor • Angina, heart failure • Diarrhea • Eyelid retraction and lid lag (because of the Antibodies, which are responsible for the hyper stimulation of the TG. some of those Antibodies they are sharing the antigens with the orbital muscle of the eye, so they can go and bind to those orbital muscles and start an Inflammation leading to edema. That cause exophthalmos).  Fig 46.3 **Lid retraction and exophthalmos in a patient with Graves' disease.**
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 (stimulation) • Causing hypersecretion of thyroid hormone
Diagnosis	• Suppressed / undetectable TSH level due to negative feedback on pituitary • Raised thyroid hormones levels • Confirms primary hyperthyroidism
Problems in diagnosis **When you're measuring total T4**	• Total serum T_4 varies due to changes in binding protein levels • High estrogens in pregnancy increase TBG synthesis -> you'll have more bound form • Total T_4 will be high, free T_4 will be normal • Congenital TBG deficiency can also influence results • **Free T4 and TSH are first-line tests for diagnosis of thyroid dysfunction**
Treatment	• Antithyroid drugs: carbimazole, propylthiouracil > if the patient is young, to protect him from Radioiodine. • Radioiodine: sodium ^{131}I inhibits T_4/T_3 synthesis • Surgery: thyroidectomy complete of partial removal of thyroid gland
Strategy for the biochemical investigation of suspected hyperthyroidism	 Fig 46.2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

Thermogenesis (Heat production)

- Humans are **homeothermic** (keep constant body temp.) human are warm-blooded, they didn't change their temperature according to the external environment unlike cold-blooded animals
- Tightly controlled **temperature homeostasis**

Thermogenesis is of two types:

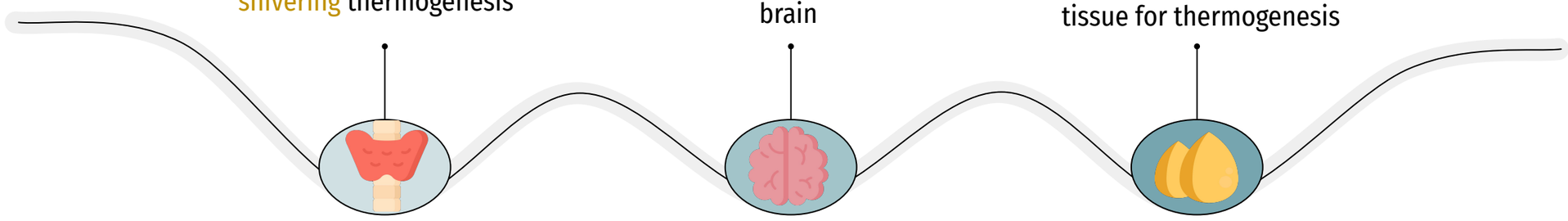
- **Obligatory**: Heat production due to basal metabolic rate ex: eating, sleeping
- **Facultative**: On-demand extra heat production from metabolic activity in brown adipose tissue, skeletal muscle, etc. Facultative thermogenesis in brown adipose tissue is stimulated by sympathetic nervous system ex: exercise

Thyroid Hormone and Thermogenesis

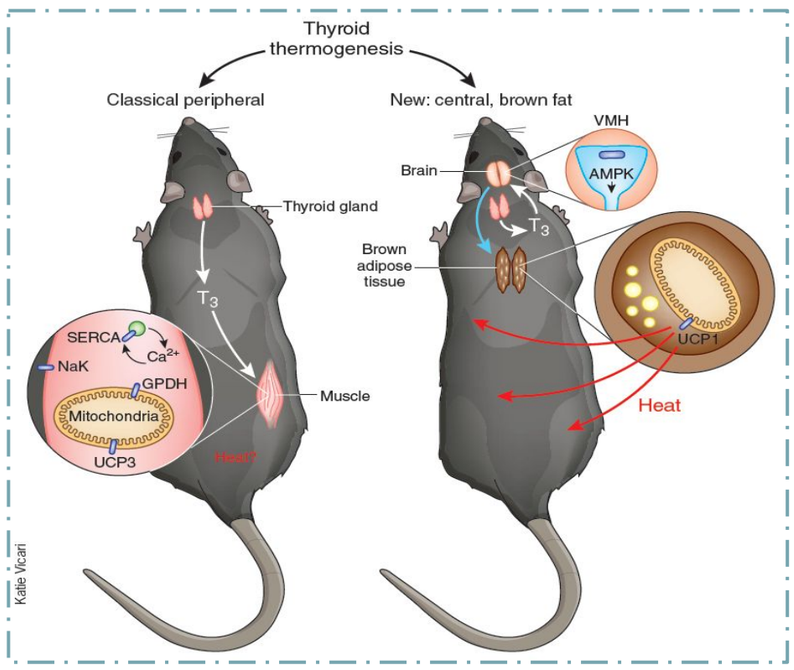
Thyroid hormone plays essential roles in non shivering thermogenesis

It upregulates body temperature set by the brain

It acts centrally on the hypothalamus that controls brown adipose tissue for thermogenesis



Two concepts of thyroid thermogenesis



Classical	Central
1. TG Produces T3. 2. Stimulate muscle cells and liver to Activate certain enzymes and certain molecules to increase Production of heat, and the kind of UCP here is UCP3. Some enzymes mention here NaK ATPase, Glucose phosphate dehydrogenases and smooth endoplasmic Reticulum Ca^{++} ATPase	Thyroid hormone stimulate hypothalamus, and that leads to the inactivation of AMPk (which initiate the sympathetic stimulation → increased synthesis and activity of UCP1 "Present in brown adipose tissue", and that causes Thermogenesis.)

1. Classical, peripheral

Thyroid hormone (T_3)

Stimulates

Body tissue cells (muscle, liver)

Activates certain enzymes by an unknown mechanism

THERMOGENESIS

2. New: Central, brown fat

Thyroid hormone (T_3)

Stimulates

Hypothalamus

Activates brown adipose tissue

Increased body energy expenditure

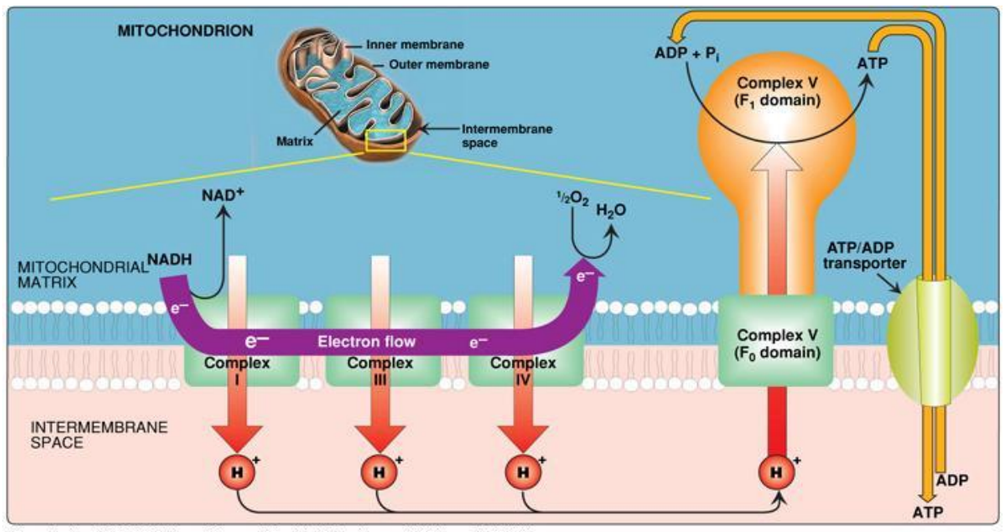
THERMOGENESIS

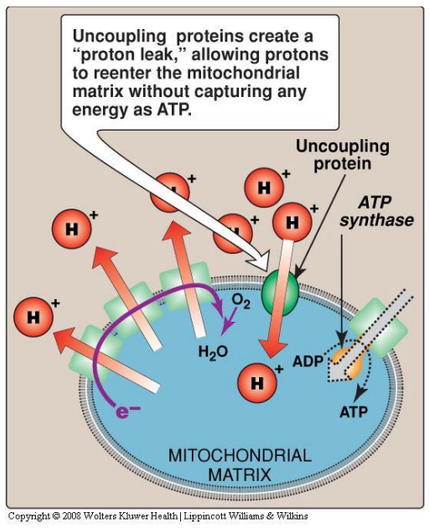
Two concepts of thyroid thermogenesis con.

- In respiratory chain, some protons re-enter the mitochondrial matrix thru **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**

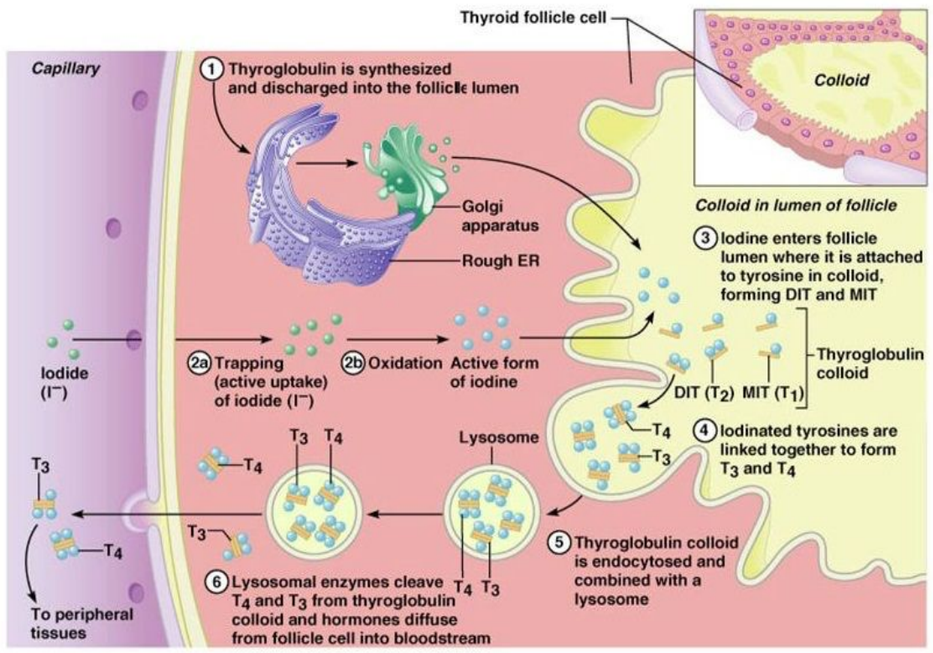




during Electron transport chain, when you were Making this proton gradient which required for synthesis of ATP. But UCPs They disturbed this proton gradient (They allow Protons to leak out cause" Proton leak). These protons are carrying energy and they Just go and leak out of the matrix into the cytosol. That cause increase Production of heat.

Thyroid Hormone Synthesis

Note: The picture is extra. Both M and F doctors explained the thyroid hormone synthesis process. Please refer to physiology for a more detailed explanation.



Synthesis of thyroid hormones (Dr sumbul):

- Thyroglobulin secreted in the lumen (colloid) "synthesis by Follicular cells of thyroid Gland".
- Iodide come from Bloodstream, and changes to Iodine by an enzyme called peroxidase.
- Thyroglobulin protein is iodinated. Where exactly? 2 Tyrosine residues, they are coupled.
- Iodinated Thyroglobulin is sent back again to Follicular cell, where the thyroglobulin protein part is degrade.
- and what left? T4, T3 depending upon How many molecules were added. 4 Iodine ⇒T4 , 3 Iodine ⇒ T3.
- There are other molecules: MonoiodoThyronine and diidoThymnin.
- When TSH is released from anterior Pituitary gland is stimulate the thyroid to produce T4 and T3 (cause breach down of thyroglobulin > T4 and T3 are released.

Take Home Messages

- Thyroid hormones are synthesized in the thyroid gland by iodination, coupling and binding to thyroglobulin protein
- Thyroid hormones regulate metabolism and thermogenesis in the body
- It is regulated by hypothalamic-pituitary-thyroid axis
- Thyroid function tests such as TSH, total and free T4 and T3, and antibodies help diagnose and follow up thyroid disorders
- Goiter, hypo- and hyperthyroidism are due to abnormalities in thyroid functions

Summary

Thyroid Hormones: - Thyroxine (T4): Major secretion, - Triiodothyronine (T3): More biologically active	Biosynthesis	1. Thyroid Gland : Synthesize T3 and T4 2. Peripheral tissues (liver, kidney, etc.): De-iodinate T4 ⇒ T3 (inactive) by deiodinase enzyme
	Action	• maturation of all body tissues • thermogenesis and metabolic regulation • Increase cellular O2 consumption and stimulates the metabolic rate • Affects the rate of protein, carbohydrate and lipid metabolism
	Clinical evidence	• Untreated congenital thyroidism ⇒ Permanent brain damage • Hypothyroid children have: short stature, Delayed puberty • Hypothyroid patients have high serum cholesterol
	Regulation of Thyroid Hormone Secretion	T3/T4 exerts negative feedback to control the hypothalamus and pituitary controlling the release of both TRH and TSH: • High thyroid hormone levels suppress TRH, TSH • Low thyroid hormone levels stimulate TRH, TSH to produce more hormone
	Thyroid function tests	• TSH measurement: assessment of thyroid function • Total T4 or free T4: monitors thyroid treatment • Total T3 or free T3: hyperthyroidism, thyrotoxicosis • Antibodies :autoimmune thyroid disease (hashimoto's thyroiditis, graves disease)
Goiter	Goiter may be associated with:	Hyperthyroidism , Hypothyroidism, Euthyroidism (Normal thyroid conc)
	Goiter causes:	Iodine, selenium deficiency,, Hashimoto's thyroiditis, Graves disease (hyperthyroidism), Congenital hypothyroidism/ Thyroid cancer
Hypothyroidism (Deficiency of thyroid hormones)	Types	**1. Primary hypothyroidism:** elevated TSH, deficiency of thyroid hormone **2. Secondary hypothyroidism:** Failure of pituitary to secrete TSH, Failure of hypothalamic pituitary axis
	Causes	Hashimoto's thyroiditis, Radioiodine or surgical treatment of hyperthyroidism, Drug effects TSH deficiency, Congenital defects in thyroid synthesis / thyroid resistance, Severe iodine deficiency
	Clinical features	Tiredness / cold intolerance / weight gain / dry skin
Hyperthyroidism: - Hyperstimulation of thyroid gland by pituitary gland - Hypersecretion of thyroid hormones	Causes	Graves' disease, Toxic multinodular goitre, Thyroid adenoma, Thyroiditis, Excessive intake of iodine, Excessive intake of T4 and T3
	Clinical features	Weight loss with normal appetite, Sweating / heat intolerance, Palpitation / agitation, tremor, heart failure, Diarrhea, Eyelid retraction and lid lag
	Graves' disease	• An autoimmune disease • Due to antibodies against TSH receptors on thyroid gland • The antibodies mimic the action of pituitary hormone
Thermogenesis	Thermogenesis is of two types:	• Obligatory: Heat production due to basal metabolic rate • Facultative: On-demand extra heat production from metabolic activity in brown adipose tissue, skeletal muscle, etc.
	Two concepts of thyroid thermogenesis	• Classical, peripheral: Affects Body tissue cells (muscle, liver) • New: Central, brown fat: Stimulates the hypothalamus

MCQs

1- The inactive form of thyroid hormone is:			
A- rT3	B- T3	C- T4	D- all forms are active
2- A 53-year-old woman complains of progressive weight loss, nervousness, and sweating.Physical examination reveals tachycardia.Her thyroid is diffusely enlarged and warm on palpation. Serum levels of thyroid-stimulating hormone (TSH) are low, and levels of thyroid hormones (T3 and T4) are elevated. What is most likely her diagnosis?			
A- Primary hyperthyroidism	B- Secondary hyperthyroidism	C- secondary hypothyroidism	D- Hashimoto's disease
3- Regarding Thyroid hormone regulation mitochondrial UCPs which of the following is true:			
A- UCP3 in brown adipose tissue	B- UCP3 in muscle, other tissues	C- UCP1 in muscle, other tissues	D-UCP2 in brown adipose tissue
4- The first-line tests for the diagnosis of thyroid dysfunction			
A-TSH / T4	B- TSH /T3	C- TRH/T3	D- TRH/T4
5- A patient has an extremely high T3 and T4 level. Which of the following signs and symptoms DO NOT present with this condition			
A- Diarrhea	B- Intolerance to cold	C- Weight loss	D-Smooth skin
6- _____is an autoimmune disorder where the body attacks the thyroid gland that causes it to stop releasing T3 and T4. The patient is likely to have the typical signs/symptoms of hypothyroidism			
A- Hashimoto's disease	B- Grave's disease	C- myasthenia gravis	D- SLE

Answers key

1- A 2- A 3- B 4- A 5- B 6- A

SAQs

1- Fill in the blank regarding the negative feedback loop for thyroid hormone production: The _____ produces TRH (Thyrotropin-Releasing Hormone) which causes the anterior pituitary gland to produce _____ which in turn causes the thyroid gland to release _____ and _____.

Hypothalamus, TSH (thyroid-stimulating hormone), T3 and T4

2- List three actions of thyroid hormones

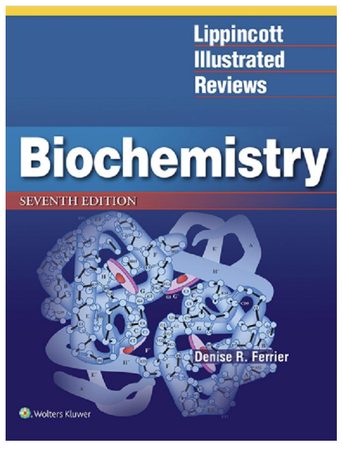
1. maturation of all body tissues
2. thermogenesis and metabolic regulation
3. Increase cellular O2 consumption and stimulates the metabolic rate

3- You are reviewing a 44-year-old woman in the endocrinology outpatient clinic. Her thyroid function test reveals that she has slightly elevated TSH and her T4 is within reference limit a.what is most likely her diagnosis b. What is your next step

a. Developing hypothyroidism
b. Measure thyroid autoantibodies titer then repeat the analysis after 2-3 months

Resources

Click on the book to download the resource



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