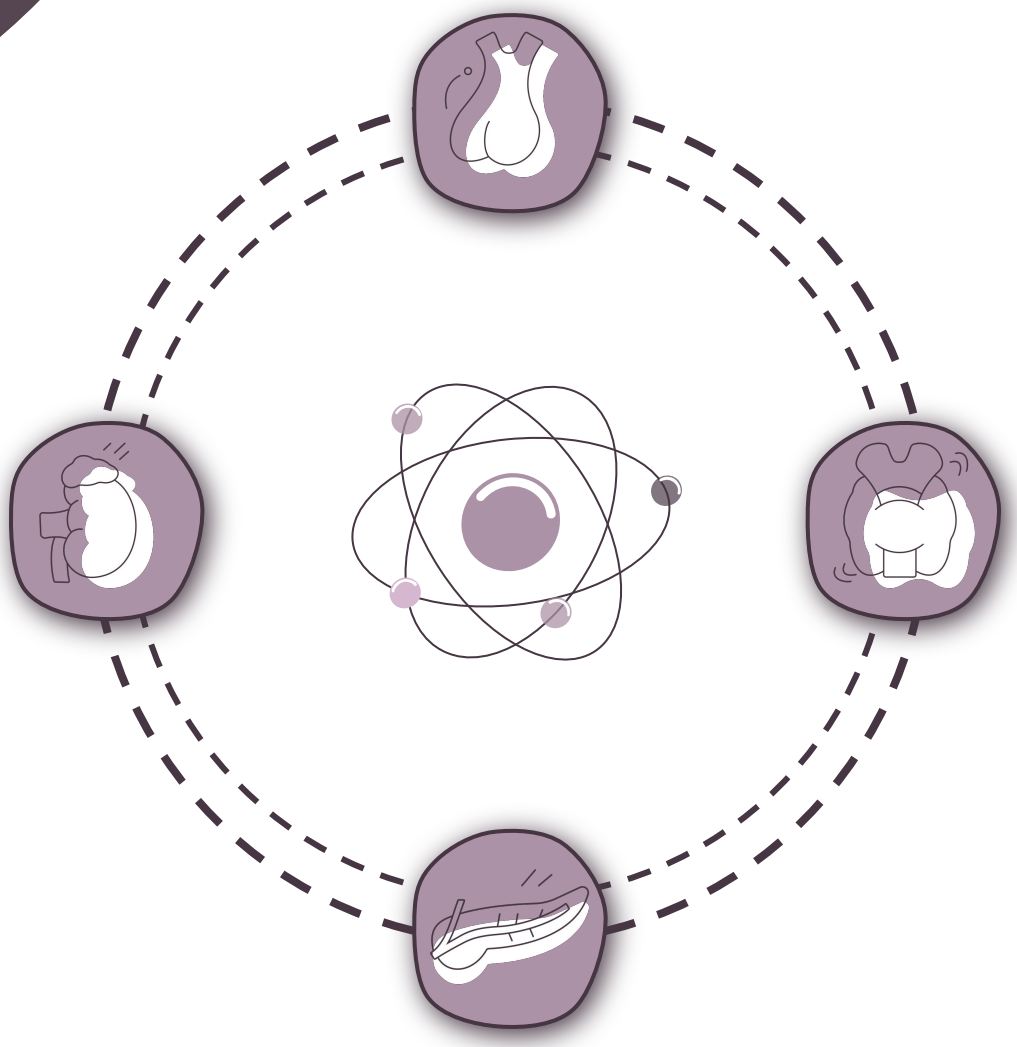
Biochemistry
Team 443



L1: Thyroid hormone and thermogenesis

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Color Index:
Main Text
Male's Slides
Female's Slides
Important
Doctor's Notes
Extra Info

Editing File link:

Objectives

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

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Types of Thyroid Hormones

Thyroxine (T4)

Major secretion

thyroxine or tetraiodothyronine: all the four sides are iodinated.

Most likely transported in 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)**

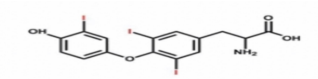
Since the hormone is bound to protein it becomes inactive and then it goes to the tissue and becomes unbound form (active) and then acts on the cells

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).

Triiodothyronine (T3)

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)

-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

Thyroid Gland:

Synthesize T3 and T4

2 tyrosine molecules tyrosine deficiency leads to thyroid deficiency

↓

Iodination/ Organification

↓

Coupling

↓

Binding to thyroglobulin (protein)

Peripheral tissues (liver, kidney, etc.):

- **De-iodinate T4 => T3** (active) **catalyzed by deiodinase enzyme**
- **T4 can be metabolized to rT3 (inactive form)**

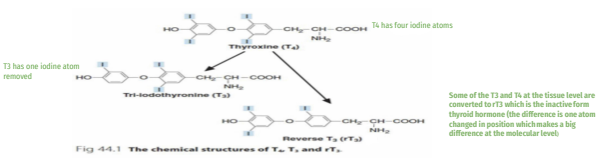


Fig 44.1 **The chemical structures of T4, T3, and rT3**

(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 02 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

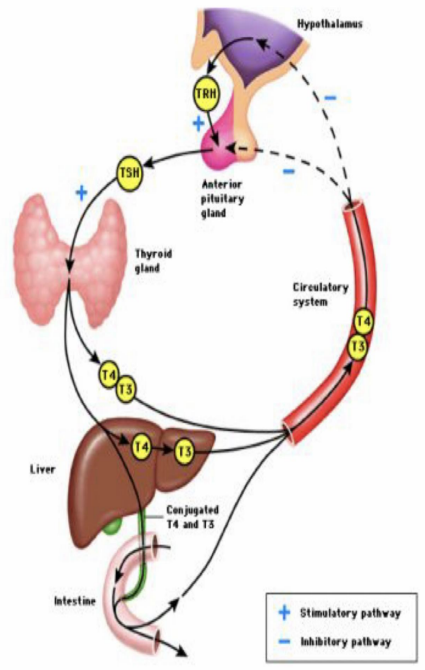
The hypothalamic-pituitary-thyroid axis regulates thyroid secretion

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. T3/ T4 exert **negative feedback** to control the hypothalamus and pituitary controlling the release of both TRH and TSH :



Low thvroid 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

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).

Less common

Test	Interpretation
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 T4 or free T4	- Assessment of thyroid function - Monitors thyroid treatment (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)
Total T3 or free T3	- Useful for assessing hyperthyroidism in which rise in T3 is independent of T4 - In some patients only T3 rises independently (T4 is normal): T3 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).

Goiter (enlarged thyroid gland)

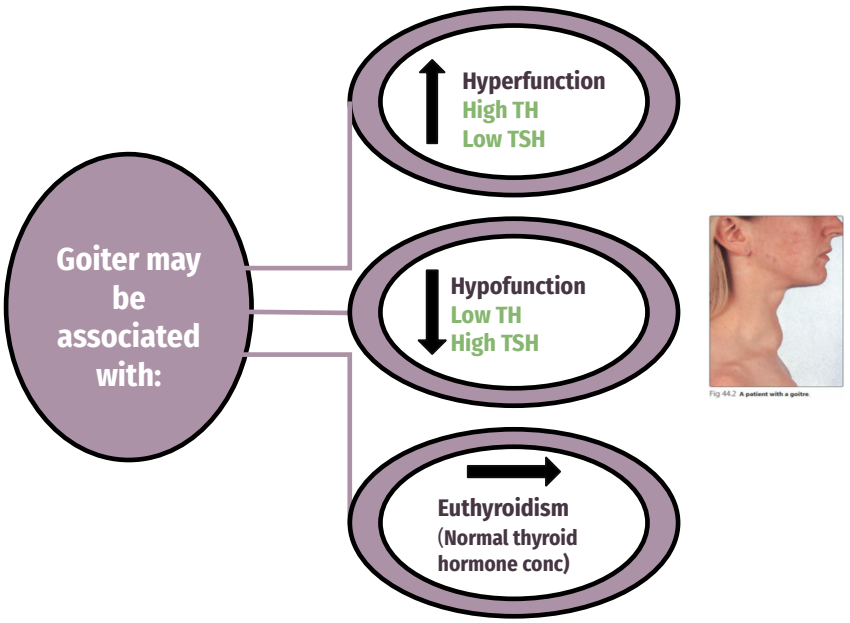


Fig 44.2 A patient with a goitre.

Goiter causes

1. Iodine, selenium deficiency
2. Hashimoto's thyroiditis
3. Graves disease (hyperthyroidism)
4. Congenital hypothyroidism/ Thyroid cancer

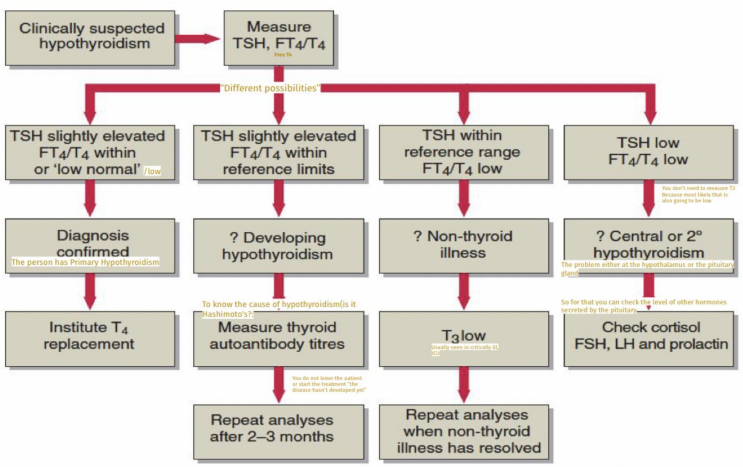
(1): when you give patients with hypothyroidism "thyroxine/hormone replacement therapy" and the TSH and T4 have come to normal. At that moment we call them Euthyroid, because the thyroid hormones are normal due to replacement. And vice versa

(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 (rare). • 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 (T4) 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, T3 and T4 secretion and metabolism is disturbed • Most of T4 is converted to rT3 (inactive) at the level of the tissue • Causing thyroid hormone deficiency • Secretion of T4 and T3 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).
Strategy for the biochemical investigation of suspected hypothyroidism	**Dr. sumbul: Important**  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).

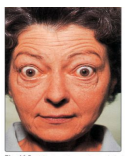


Fig 46.3 **Lid retraction and exophthalmos in a patient with Graves' disease.**

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

Strategy for the biochemical investigation of suspected hyperthyroidism

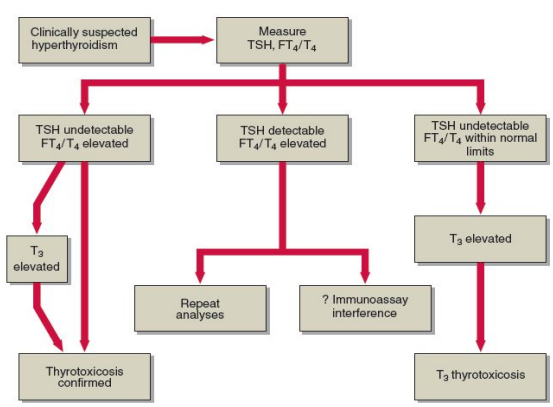


Fig 46.2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

Thermogenesis (Heat production)

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

human are warm-blooded, they don't change their temperature according to the external environment unlike cold-blooded animals

Thermogenesis is of Two Types:

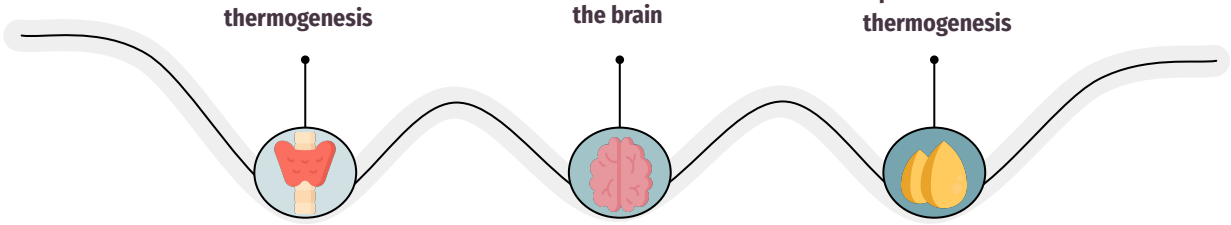
- **Obligatory**: Heat production due to basal metabolic rate ex: Eating, Sleeping
- **Facultative**: On-demand extra heat production from metabolic activity in brown adipose tissue, skeletal muscle, etc.
- Facultative thermogenesis in brown adipose tissue is stimulated by Sympathetic Nervous System ex: Exercise

Thyroid Hormone and Thermogenesis

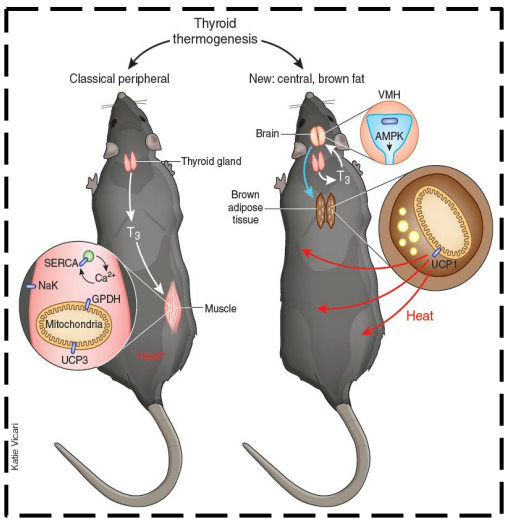
Thyroid hormone plays essential roles in non shivering thermogenesis

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.)

Thyroid hormone (T_3)

1. Classical, peripheral → Stimulates → Body tissue cells (muscle, liver) → Activates certain enzymes by an unknown mechanism → THERMOGENESIS

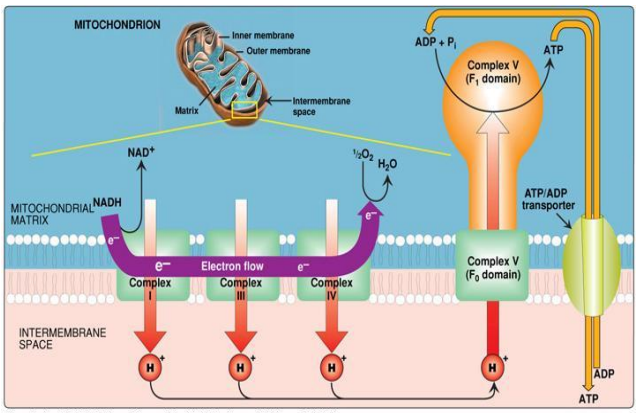
2. New: Central, brown fat → Stimulates → Hypothalamus → Activates brown adipose tissue → Increased body energy expenditure → THERMOGENESIS

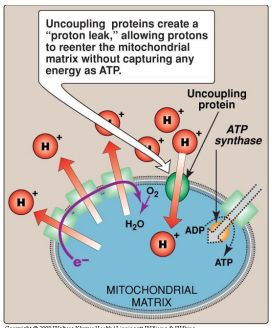
Two concepts of thyroid thermogenesis con.

- 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.

We advise you to watch this video to understand the concepts

Take home massage

- **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

Test Yourself!

MCQs

Answers: 1-D 2-A 3-A 4-A

Q1: Which of the following is a feature of hyperthyroidism?
A. weight gain
B. constipation
C. cold intolerance
D. heat intolerance

Q2: The inactive form of thyroid hormone is?
A. rT3
B. T3
C. T4
D. all are active

Q3: The 1st line for the diagnosis of thyroid dysfunction ?
A. TSH\T4
B. TSH\T3
C. TRH\T3
D. TRH\T4

Q4: Which of the following cause hypothyroidism?
A. Hashimoto's disease
B. Graves disease
C. Myasthenia gravis
D. SLE

SAQs

Q1: List 3 actions of thyroid hormone?
1-Maturation of all body tissues
2-Thermogenesis and metabolic regulation
3-Increase cellular O2 consumption

Q2: Mention the causes of hyperthyroidism?
Graves disease, Thyroiditis, Thyroid adenoma, excessive intake of iodine\T3,T4.

Meet The Team!

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