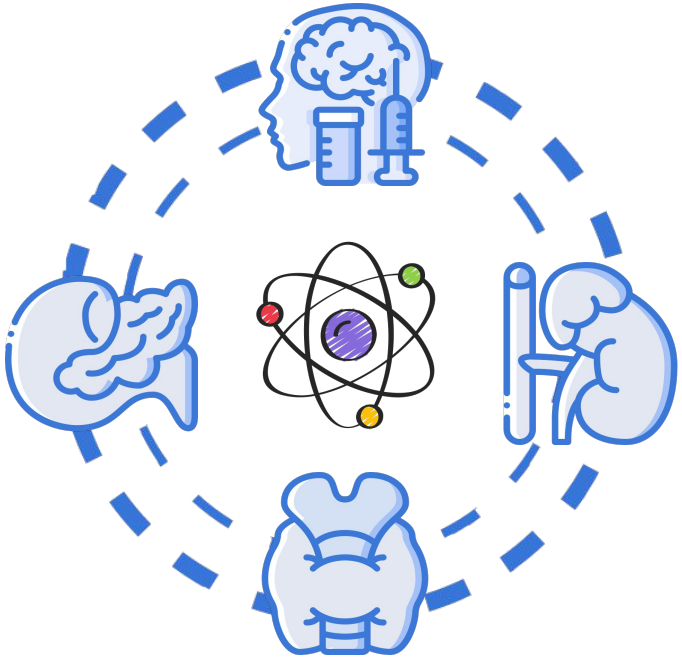
Thyroid Hormones and Thermogenesis



Color Index:

- Main Topic
- Main content
- Important
- Drs' notes
- Extra info

Editing File

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.

I'm gonna study at 5
I'm gonna study at 6
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Types and Biosynthesis of Thyroid Hormones

Types of Thyroid Hormones :

1. Thyroxine (T_4)
   - Major secretion

Mostly transported in plasma bound to:

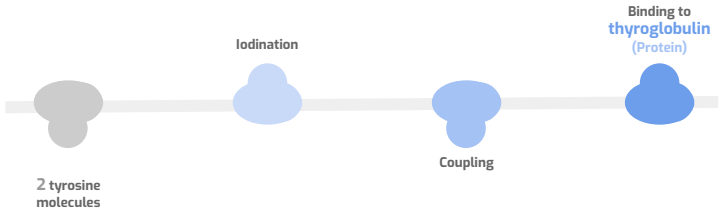
- **70%** Thyroxin Binding globulin (TBG)
- **25%** Albumin
- **5%** Transthyretin (pre-albumin)

2. Tri-iodothyronine (T_3)
   - More biologically active

The **unbound (free)** form of T_3 & T_4 are biologically active

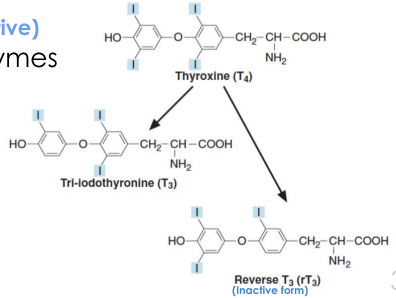
Thyroid Gland :

Synthesize T_3 & T_4



Peripheral tissues (liver, kidney, etc.) :

De-iodinate T_4 → T_3 or rT_3 (inactive)
Catalyzed by **deiodinase** enzymes



Thyroid hormone action

- Plays an essential role in maturation of all body tissues
- Involved in thermogenesis & metabolic regulation
- Increases cellular O_2 consumption & 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 **(short stature)**
- **Delayed puberty**

Hypothyroid patients have **high serum cholesterol**

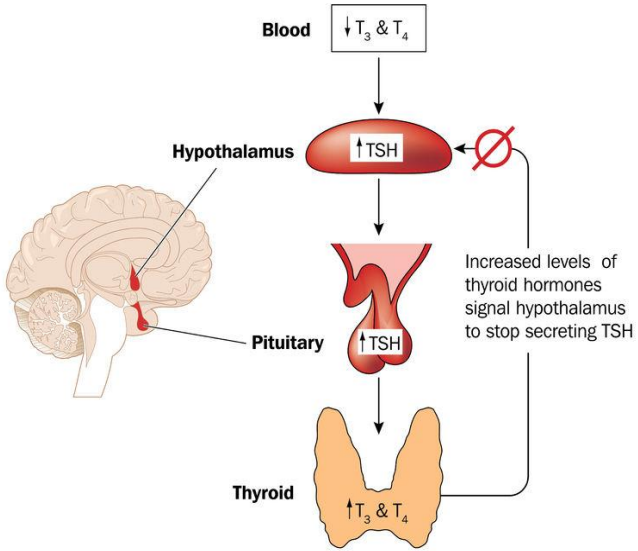
→ **Why?**

- **liver cells :** Down regulation of LDL receptors
- **Gut :** Failure of sterol excretion

Regulation of Thyroid Hormone Secretion

By The hypothalamic-pituitary-thyroid axis

1. The **hypothalamus** senses low levels of T3/T4 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
4. T3/T4 exert **negative feedback** control on 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

Highly sensitive
(detects very low conc.)

May take up to 8 weeks to adjust to new level during treatment [1]

Total or free T_4

Monitors thyroid **treatment**

→ **thyroid** replacement
→ **Anti-thyroid**

Total or free T_3

T_3 toxicosis
*hyperthyroidism in which rise in T3 is independent of T4 (normal T4)

Earlier identification of thyrotoxicosis

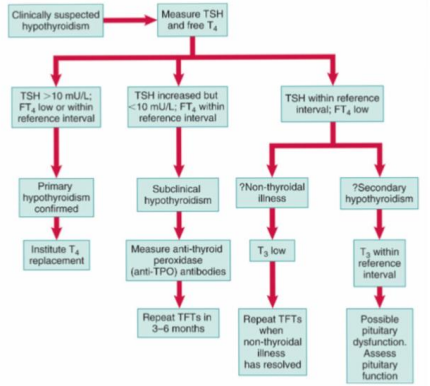
Antibodies

Autoimmune disease
*Diagnosis and monitoring

Hashimoto's thyroiditis
antibodies against TSH receptors that **suppress** thyroid secretion

Graves' disease
antibodies against TSH receptors that **stimulate** thyroid secretion[3]

Strategy for the Biochemical Investigation of Suspected Hypothyroidism



1. During that time we use T_4 as a measure
2. T3 is more important in hyperthyroidism as it's normally Lower in blood
3. Others e.g. antithyroglobulin antibodies

Goitre

Enlarged thyroid gland

May be associated with:

Hypofunction | Hyperfunction | Euthyroid

Normal thyroid hormone conc.

Causes

- Iodine, selenium deficiency.
- Hashimoto's thyroiditis.
- Graves' disease (hyperthyroidism)
- Congenital hypothyroidism
- thyroid cancer.

Hypothyroidism

Deficiency of thyroid hormones

1 Primary

Failure of thyroid gland

Elevated TSH

Deficiency of thyroid hormones

Causes

- Hashimoto's thyroiditis.
- Treatment of hyperthyroidism (Radioiodine or surgical)
- Drug effects.
- TSH deficiency.
- Congenital
  - defects in thyroid synthesis .
  - thyroid resistance
- Severe iodine deficiency.

Clinical features

- Tiredness .
- Cold intolerance .
- Weight gain .
- Dry skin .

2 Secondary

Failure of the pituitary gland to secrete TSH

Failure of the hypothalamic-pituitary-thyroid axis

Non-thyroidal illness

the normal regulation of TSH, T3 and T4 secretion and metabolism is disturbed

Most of T4 is converted to rT3 (inactive)

Deficiency of thyroid hormones

Secretion of T4 and T3 is decreased

Treatment

Replacement therapy with levothyroxine **(T4)**

hyperthyroidism

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

Causes

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

Clinical features

- Weight loss with normal appetite
- Sweating / heat intolerance
- Fatigue
- Palpitation / agitation, tremor
- Angina, heart failure
- Diarrhea
- Eyelid retraction and lid lag

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 → Causing hypersecretion of thyroid hormone

hyperthyroidism

Diagnosis

Suppressed / undetectable TSH level

Raised thyroid hormones levels

Confirms primary hyperthyroidism

Problems in diagnosis

Total serum T4 varies due to changes in binding protein levels

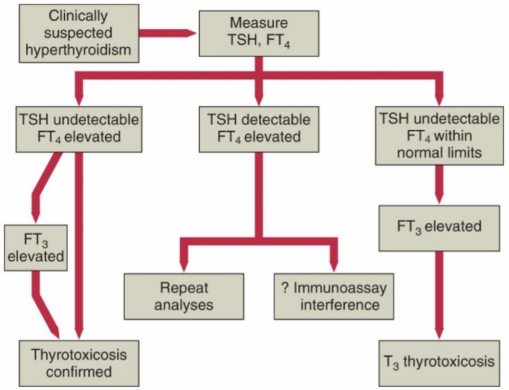
High estrogens in pregnancy increase TBG synthesis

- Congenital TBG deficiency can also influence results
- Free T4 and TSH are first-line tests for diagnosis of thyroid dysfunction

Treatment

1. Antithyroid drugs: carbimazole, propylthiouracil
2. Radioiodine: sodium ^{131}I inhibits T_4/T_3 synthesis
3. Surgery: thyroidectomy

Strategy for the Biochemical Investigation of Suspected Hyperthyroidism



Thermogenesis (Heat production)

Humans are **homeothermic** (keep constant body temp.)

Tightly controlled **temperature homeostasis**

Thermogenesis is of two types:

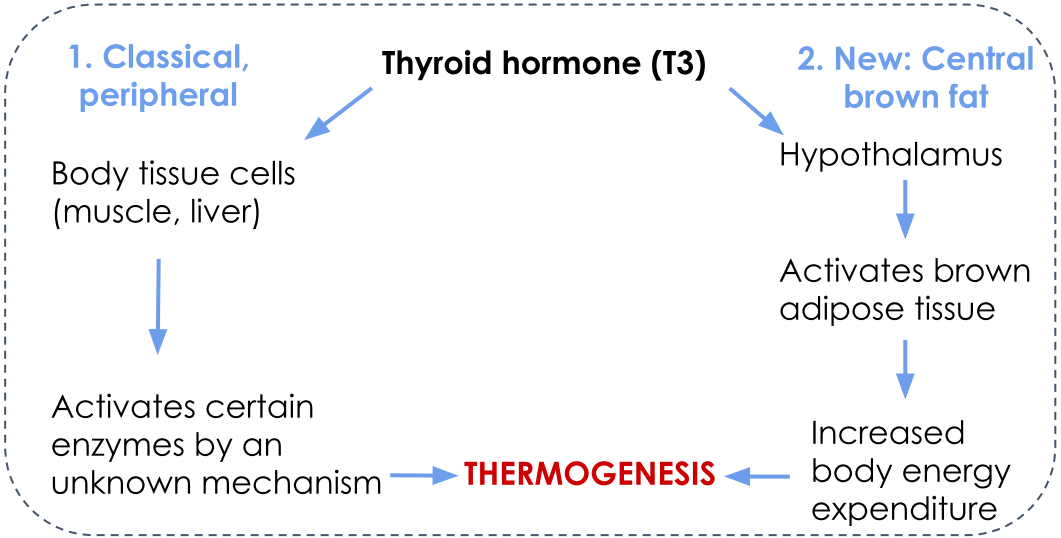
Facultative thermogenesis in brown adipose tissue is stimulated by sympathetic nervous system

Facultative: On-demand extra heat production from metabolic activity in brown adipose tissue, skeletal muscle, etc.

Obligatory: Heat production due to basal metabolic rate

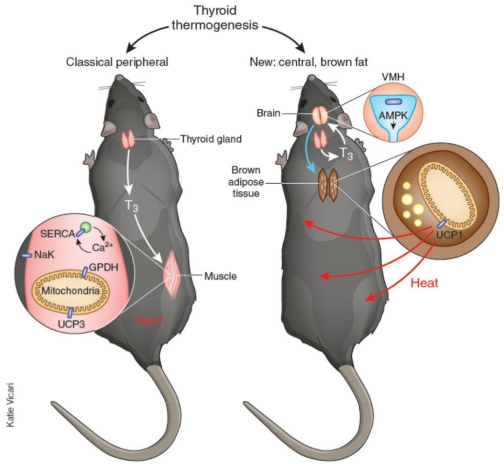
Thyroid Hormone and Thermogenesis

- 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



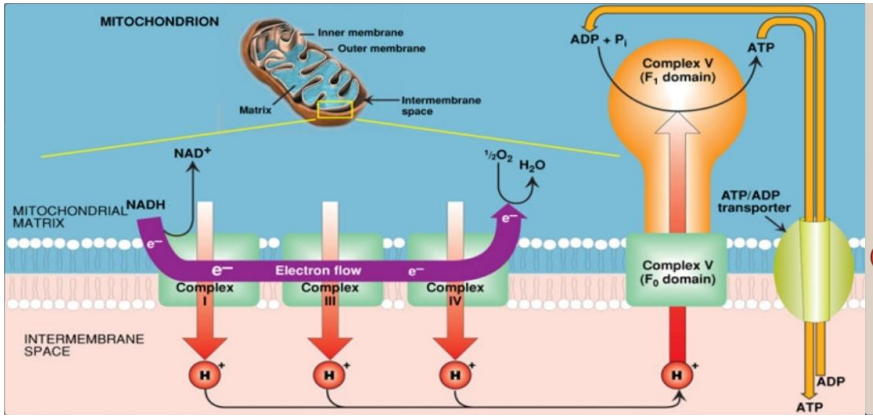
Thermogenesis

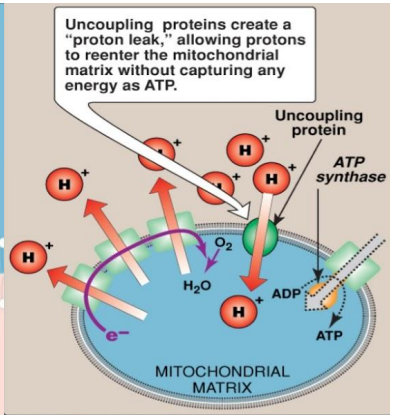
Two concepts of thyroid thermogenesis



- 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





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 T_4 and T_3, and antibodies help diagnose and follow up thyroid disorders
- Goiter, hypo- and hyperthyroidism are due to abnormalities in thyroid functions

Summary

	Thyroid Hormones			
Types	Thyroxine (T_4)		Tri-iodothyronine (T_3)	
Action	maturation	thermogenesis & metabolic regulation	stimulates the metabolic rate	Affects the rate of metabolisim
Clinical evidence	untreated congenital hypothyroidism →permanent brain damage		hyopthyroid pationts have high serum cholesterol	
Regulation of Secretion	hypothalamic-pituitary-thyroid axis: hypothalamus → thyrotropin releasing hormone (TRH) → pituitary→thyroid stimulating hormone (TSH)→ thyroid → produce T3/T4 → negative feedback (stops secretion)			
Thyroid Function Tests	TSH Highly sensitive	total or free T_4 Monitors thyroid **treatment**	total or free T_3 thyrotoxicosis	Antibodies **Autoimmune** disease

hypothyroidism
Deficiency of thyroid hormones

treatment

Replacement therapy with levothyroxine **(T4)**

- primary: failiar of thyroid gland
- secondary: Failure of the pituitary gland Failure of the hypothalamic-pituitary-thyroid axis
- Non-thyroidal illness

hyperthyroidism
Hyperstimulation of thyroid gland by pituitary gland

treatment

Antithyroid drugs
Radioiodine
Surgery

- Graves' disease
  Most common cause of hyperthyroidism
- Diagnosis
  Suppressed TSH level
  Raised thyroid hormones levels
  Confirms primary hyperthyroidism
- Problems in diagnosis
  - Total serum T4 varies
  - High estrogens in pregnancy

Quiz

MCQs :

Q1: hyperthyroidisim is caused by?
a) hypostimulation of thyroid gland **b)** graves'disease
c) hashimoto's thyroiditis **d)** severe iodine deficiency

Q2: which of the following function tests are first-line test for diagnosis of thyroid dysfunction in the case of hyperthyroidisim?
a)free T4 and free T3 **b)** free T3 and TSH
c)free T4 and TSH **d)** free T4 and antibodies

Q3: Thyroid hormone regulates which mitochondrial UCPs ?
a) UCP1 in brown adipose tissue **b)** UCP3 in the liver
c) UCP3 in brown adipose tissue **d)** UCP1 in muscle, and other tissues

Q4: One of the symptoms of hypothyroidism is:
a) Fatigue. **b)** Intolerance to cold
c) Weight gain. **d)** All of the above

Q5: A person with untreated hypothyroidism may also have:
a) High cholesterol. **b)** Low blood pressure
c) Low blood sugar **d)** None of the above

Q6: The symptoms of hypothyroidism may be difficult to detect, so the condition can best be diagnosed with:
a) An MRI scan. **b)** An ultrasound
c) A thyroid stimulating hormone test (TSH). **d)** A hemoglobin test or hematocrit test

SAQs :

Q1: explain the mechanism of regulation of thyroid hormone secretion

Q2: state the two types of thermogenesis and the difference between them?

Q3: list 3 of thyroid hormone action

Q4: enumerate 4 causes of hypothyroidism

★ **MCQs Answer key:**

1) b 2) c 3) a 4) d 5) a 6) c

★ **SAQs Answer key:**

1) Slide 5
2) obligatory: its due to basal metabolic rate
facultative: its an on-demand extra heat production
3) Slide 4
4) slide 7

Team members

Girls Team: 

- Ajeed Al-Rashoud
- Alwateen Albalawi
- Amira AlDakhilalla
- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
- Nouf Alhumaidhi
- Noura Alturki
- Sarah Alkhalife
- Shahd Alsalamah
- Taif Alotaibi

Boys Team: 

- Alkassem Binobaid
- Fares Aldokhayel
- Khayyal Alderaan
- Mashal Abaalkhail
- Naif Alsolais
- Omar Alyabis
- Omar Saeed
- Rayyan Almousa
- Yazen Bajeaifer

Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ **A goal should scare you a little and excite you a lot!**

438 BIOCHEMISTRY TEAM

We hear you