

# ENDOCRINE SYSTEM



## LECTURE 2 :

### THYROID HORMONES

#### Objectives:

- Types and biosynthesis of thyroid hormones
- Thyroid hormone action
- Regulation of thyroid hormones
- Thyroid function tests
- Goitre
- Hypo and hyperthyroidism
  - Causes
  - Diagnosis
  - Treatment
- Thermogenesis

# Thyroid hormones

- Thyroxine (T4) and tri-iodothyronine (T3)
- Synthesized in **the thyroid gland** by:
  - ❑ Iodination (organification)
  - ❑ Coupling of two tyrosine molecules
  - ❑ Attaching to thyroglobulin protein
- Thyroid gland **mostly secretes T4**
- Peripheral tissues (liver, kidney, etc.) deiodinate T4 to T3
  
- T3 is more biologically active form**
- T4 can be converted to rT3 (reverse T3) – inactive form**
- Most of T4 is transported in plasma as protein-bound**
  - ✓ **Thyroxin-binding globulin TBG (70%)**
  - ✓ **Albumin-bound (25%)**
  - ✓ **Transthyretin-bound (5%)**
- The unbound (free) form of T4 and T3 are biologically active**

# Thyroid hormone

## Action:

- Essential for normal maturation and metabolism of all body tissues
- Affects the rate of protein, carbohydrate and lipid metabolism
- Regulates thermogenesis

## Regulation of TH secretion:

### By the hypothalamic-pituitary-thyroid

The **hypothalamus** senses low levels of T3/T4 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 feedback** control on the **hypothalamus** and **pituitary** Controlling the release of both **TRH and TSH**

# Thyroid function tests:

- **TSH measurement:** Indicates thyroid status  
(TSH may take up to **8 weeks** to adjust to new level during treatment)
- **Total T4 or free T4:**
  - ✓ Indicates thyroid status
  - ✓ **Monitors anti-thyroid treatment**
  - ✓ **Monitors thyroid supplement treatment**

**TSH and T4 (total or free) are sensitive, first-line test**

**N.B: Some labs only measure TSH as first-line test**

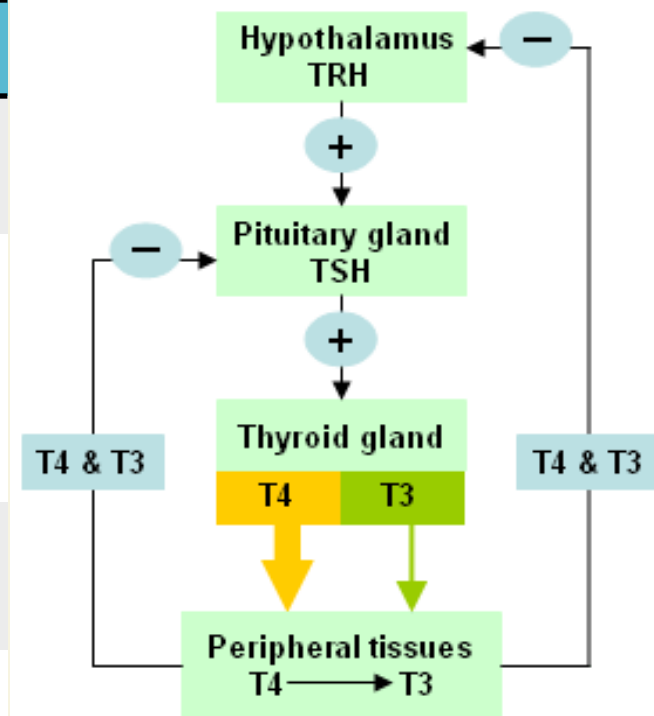
- **Total T3 or free T3:**
  - ✓ **Rise in T3 is independent of T4**  
(In some patients only T3 rises (T4 is normal))
  - ✓ **For earlier identification of T3 thyrotoxicosis**

- **Antibodies:**

**Diagnosis and monitoring of autoimmune thyroid diseases**

**(Hashimoto's thyroiditis):** Anti-thyroid peroxidase in hypothyroidism

**(Grave's disease):** Antibodies against TSH receptors on thyroid cells



**High thyroid levels suppress TRH and TSH**

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

# Goiter:

Enlarged thyroid gland

May be associated with:

1. Hypofunction
2. Hyperfunction
3. Normal concentration of thyroid hormones (euthyroid)

## Causes:

- Iodine deficiency
- Selenium deficiency
- Hashimoto's thyroiditis
- Congenital hypothyroidism
- Grave's disease
- Thyroid cancer

- : Hypothyroidism
- : Hyperthyroidism

## Hyperthyroidism

Over-activity of thyroid gland.

## Hypothyroidism

Deficiency of thyroid hormones.

- ❑ Hypothyroid children have delayed skeletal maturation, short stature, delayed puberty
- ❑ Untreated congenital hypothyroidism causes permanent brain damage
- ❑ Hypothyroid patients have high serum cholesterol levels due to:
  - 1 Down regulation of LDL receptors on liver cells
  - 2 Failure of sterol excretion via the gut

# Hypothyroidism:

## ❖ Primary hypothyroidism: (Most common)

- Failure of thyroid gland.
- Secondary hypothyroidism: - Failure of the pituitary to secrete TSH (*rare*).
- Failure of the hypothalamic-pituitary-thyroid axis.

## Causes:

- Hashimoto's disease.
- Radioiodine or surgical treatment of hyperthyroidism.
- Drug effects.
- TSH deficiency.
- Congenital defects.
- Severe iodine deficiency.

## Diagnosis:

- Elevated TSH levels confirms hypothyroidism (primary).

## Clinical features:

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

## Treatment:

- **T4** replacement therapy (tablets).
- Monitoring **TSH level** to determine dosage.
- Patient has to continue treatment for life.

# Hyperthyroidism:

- **Increased secretion** of thyroid hormones
- Tissues are exposed to high levels of thyroid hormones (**thyrotoxicosis**).
- Increased pituitary stimulation of the thyroid gland (**secondary**).

## Causes:

- Grave's disease.
- Toxic multinodular goiter.
- Thyroid adenoma.
- Thyroiditis.
- ↑ Intake of iodine / iodine drugs.
- ↑ intake of exogenous T4 and T3.

## Treatment:

- **Antithyroid drugs:**  
carbimazole, propylthiouracil.
- **Radioiodine:**  
Sodium  $^{131}\text{I}$  inhibits T4/T3 synthesis.
- **Surgery:** Thyroidectomy.

## Clinical features:

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

## Diagnosis:

**Suppressed TSH level**

**Raised thyroid hormone level**

=> Confirms primary hyperthyroidism

❑ Problems in diagnosis:

- **Total serum T4 changes due to changes in binding protein levels.**
- **In pregnancy, high estrogens increase TBG synthesis**  
(- Total T4 will be high, free T4 will be normal )
- **Congenital TBG deficiency can also influence results.**

# Hyperthyroidism

## ☐ Grave's disease :

- An autoimmune disease.
- Most common cause of hyperthyroidism.
- Antibodies against TSH receptors on thyroid cells mimic the action of pituitary hormone.
- Normal regulation of synthesis/control is disturbed

# Hypothyroidism

## ☐ NEONATAL HYPOTHYROIDISM

- Due to genetic defect in thyroid gland of newborns.
- Diagnosed by TSH screening.
- Hormone replacement therapy.
- May cause cretinism, if untreated.
- Cretinism is manifested by:
  1. puffy face and protuberant tongue
  2. umbilical hernia
  3. mental retardation and short stature
  4. deaf mute and neurological signs.

## ☐ 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)
- ⇒ Causing thyroid hormone deficiency
- TSH secretion is suppressed
- ⇒ Secretion of T4 and T3 is decreased



# Steps for investigating suspected Hypothyroidism & Hyperthyroidism

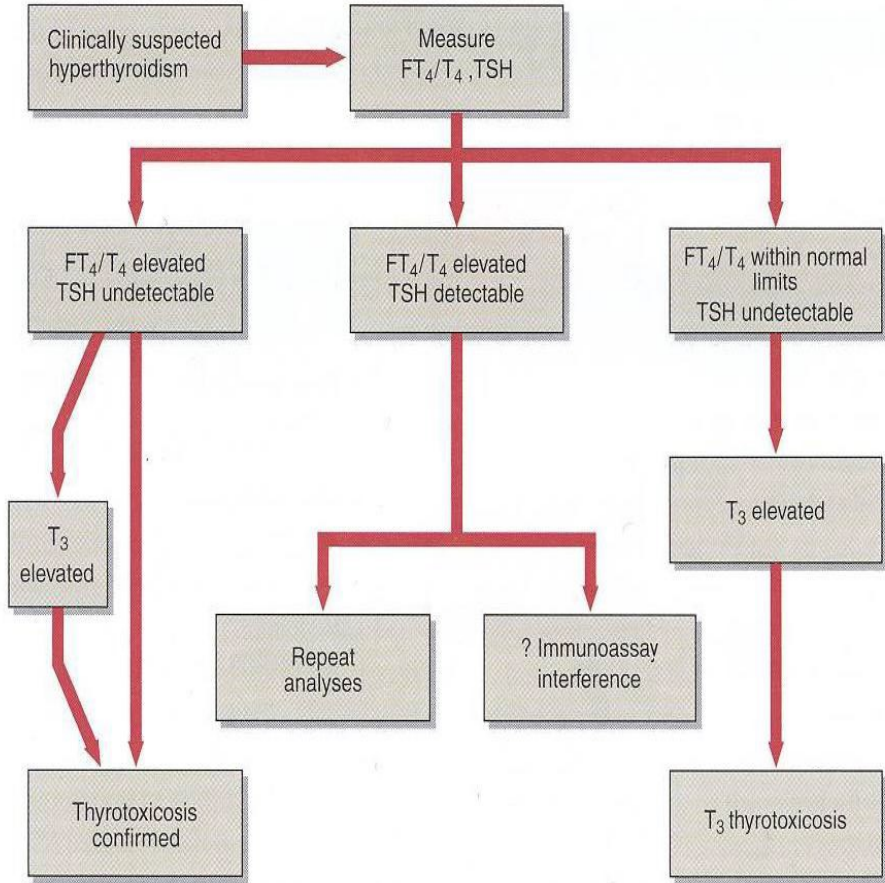


Fig. 2 Strategy for the biochemical investigation of suspected hyperthyroidism.

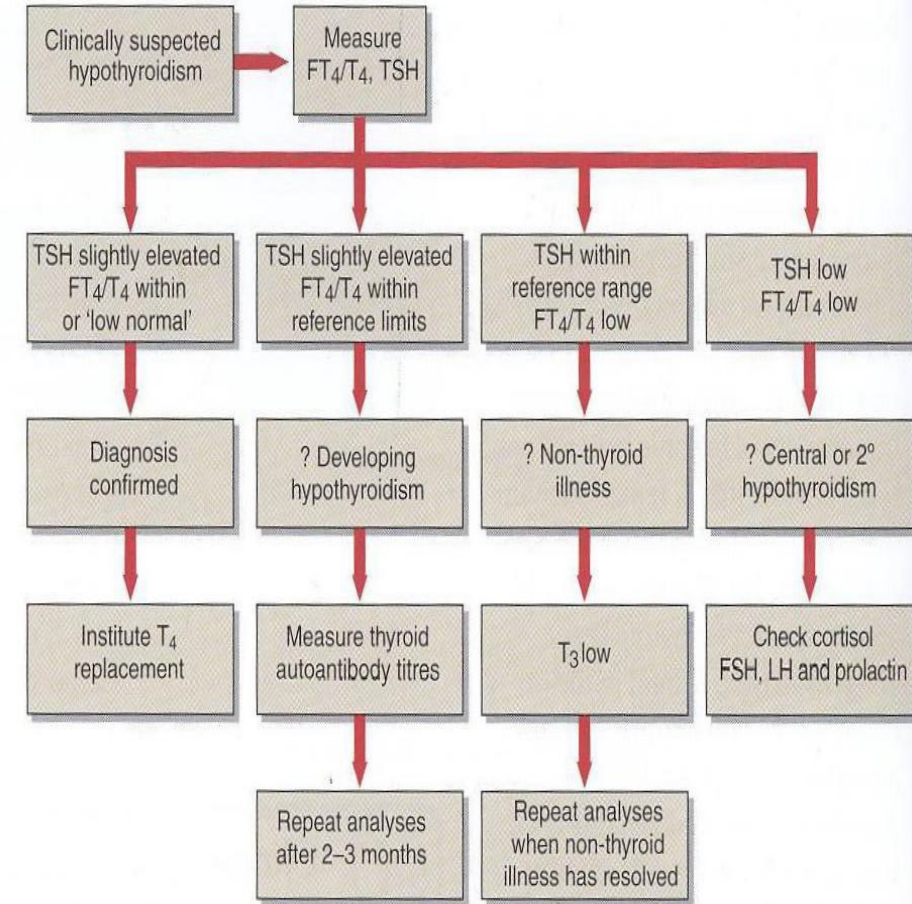


Fig. 1 Strategy for the biochemical investigation of suspected hypothyroidism.

## Thermogenesis:

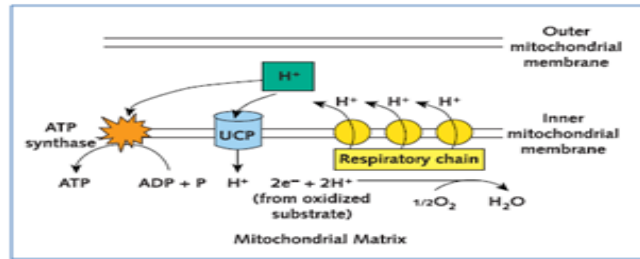
- Thyroid hormone has an **active** role in thermogenesis.
- About 30% thermogenesis depends on thyroid.
- **Thyroid regulates metabolism and ATP turnover.**
- **It increases ATP synthesis and consumption by many possible mechanisms.**
- Na/K gradient requires ATP to maintain it.
- The gradient is used to transport nutrients inside the cell.

- Thyroid **reduces** Na/K gradient across the cell membrane.  
=> Caused by more nutrient transport in the cell (**increasing metabolism**).
- This increases the **demand for ATP** to maintain the gradient.
- ATP synthesis and consumption is **increased => produce heat.**



- Thyroid hormones causes **increased** proton leak into the matrix across the inner mitochondrial membrane.
- Protons are pumped back into the matrix by **uncoupling proteins (UCPs)** without ATP synthesis.
- This process **produces heat.**
- **The mitochondria of brown adipose tissue contain UCP-1 (thermogenin).**
- The brown adipose tissue mostly **present in children.**
- **Produces heat via uncoupling of electron transport chain and oxidative phosphorylation.**

## Mechanism of action of uncoupling proteins (UCP):



The energy released in the oxidation of substrates in the mitochondria → proton gradient

The energy accumulated in this gradient is used by the ATP Synthase to produce ATP

UCPs reduce the proton gradient, bypassing the ATP synthase → **exothermic** movement of protons down the gradient → heat

### Uncoupling proteins (UCPs):

- **UCP1** is the best known and best characterized of the UCPs, is present in the inner mitochondrial membrane of brown adipose tissue.
- Other UCP are found in the inner mitochondrial membrane of organs and tissues other than the brown adipose tissue (**Ubiquitous distribution**).

Cold



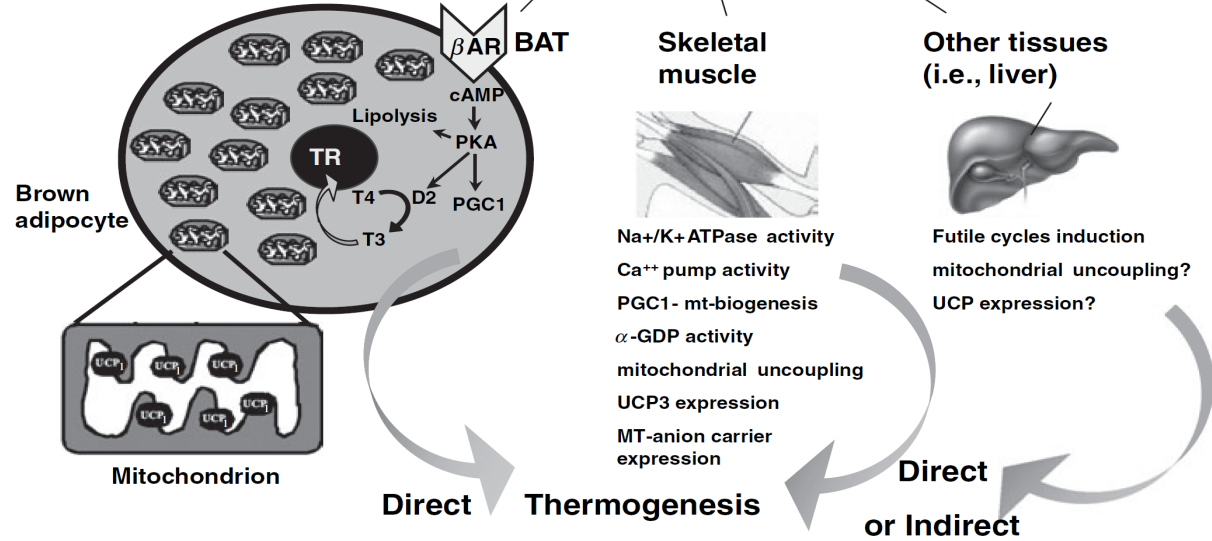
Sympathetic nervous system

Hypothalamic-pituitary-thyroid axis

NE



T3



For reading:

[http://ksumsc.com/download\\_center/2nd/03%20Endocrine%20Block/Male/Biochemistry/Extra%20reading/Thermogenesis.pdf](http://ksumsc.com/download_center/2nd/03%20Endocrine%20Block/Male/Biochemistry/Extra%20reading/Thermogenesis.pdf)

# Summary

□ Thyroxine (T4) and tri-iodothyronine (T3) are synthesized in the thyroid gland by:

1. Iodination

2. Coupling of two tyrosine molecules

3. Attaching to thyroglobulin protein

- Essential for normal maturation and metabolism of all body tissues
- Affects the rate of protein, carbohydrate and lipid metabolism
- Regulate thermogenesis
  
- The hypothalamic-pituitary-thyroid axis regulates thyroid secretion
- Goiter is an Enlarged thyroid gland
- Hypothyroidism is caused by deficiency of thyroid hormones
- Hyperthyroidism is caused by overproduction of thyroid hormones
- They could occur due to primary diseases ( occurs in the thyroid gland) or secondary (occurs in the pituitary gland or the hypothalamus)

# TEST YOURSELF!

**1- the thyroid gland mostly secretes:**

- A- T3
- B- T4
- C- equal quantities
- D- neither

**2- T4 is mostly converted to T3 in:**

- A- thyroid
- B- when needed
- C- peripheral tissues
- D- never converted

**3- which is more biologically active?**

- A- T3
- B- T4
- C- equally active
- D- TBG- bound T3

**4- which if the following could be found in hypothyroidism patients:**

- A- high cholesterol
- B- high blood sugar
- C- high calcium
- D- high iodine

**5- the thyroid hormones are regulated by:**

- A- positive feedback mechanism
- B- negative feedback mechanism
- C- neither.

**6- which of the following is considered a first line test in TFT:**

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

**7- in which if these states is TBG synthesis is high:**

- A- liver diseases
- B- stress
- C- pregnancy

**8- a patient is presented with diarrhea, palpitations and weight loss, he most probably has:**

- A- Hyperthyroidism
- B- Hypothyroidism
- C- Euthyroid

**9- thyroid hormones have an important function in thermogenesis through**

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

**10- UCP1 are found in**

- A- all body tissues
- B- brown adipose tissues
- C- white adipose tissues
- D- liver



# THANK YOU ...

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