Biochemistry Bandits 434

THYROID HORMONES AND THERMOGENESIS

OBJECTIVES:

- Describe types and steps of biosynthesis of thyroid hormones
- Discuss the thyroid hormone actions
- Determine different levels for the regulation of thyroid hormones
- List the thyroid function tests
- Define goiter
- Differentiate between hypo and hyperthyroidism based on:
  - ✓ Causes
  - ✓ Diagnosis
  - ✓ Treatment
- Discuss the role of thyroid hormone in thermogenesis

❖ **Important** ❖ Extra ❖ Biochemistry Edit

TYPES AND BIOSYNTHESIS OF THYROID HORMONES

- Thyroxine (T4) & tri-iodothyronine (T3)
- Synthesized in the thyroid gland by:
  1. Iodination
  2. Coupling of two tyrosine molecules
  3. Binding to thyroglobulin protein

- Thyroid gland mostly secretes T4, then the Peripheral tissues (liver, kidney, etc.) de-iodinate T4 to T3 by **deiodinase enzymes**
- T4 can be converted to rT3 (reverse T3) inactive form "i.e.to maintain the balance and prevent thyrotoxicosis"

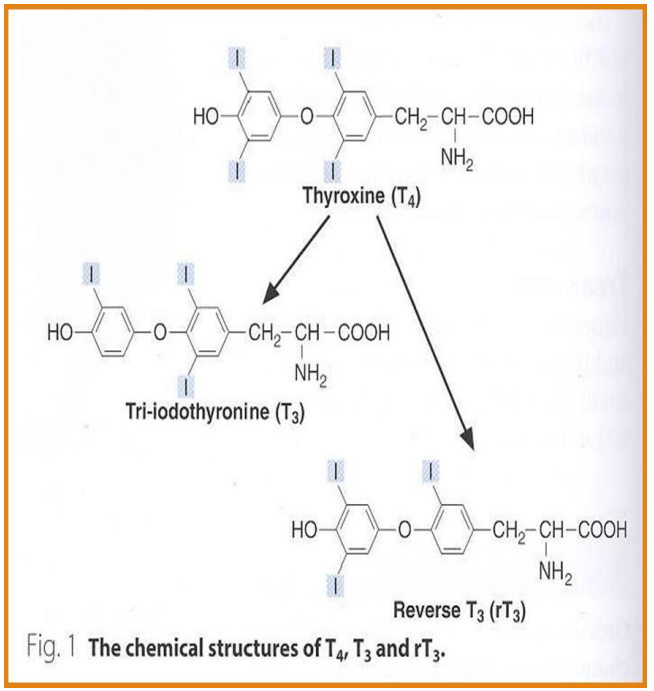


Fig. 1 **The chemical structures of T_4, T_3 and rT_3.**

BOUND	UNBOUND

• Most of T_4 are protein bound
  • Thyroxin Binding globulin (TBG)-bound (70%)
  • Albumin-bound (25%)
  • Transthyretin (prealbumin)-bound (5%)
	• The unbound (free) form of T4 and T3 are biologically active "Unbound T3 is the most biologically active"

THYROID HORMONES

❖ ACTION:

- Plays an essential role in maturation of all body tissues, coordinating development and specific cell functions
- Involved in thermogenesis and metabolic regulation
- Increases cellular oxygen consumption and stimulates the metabolic rate
- Affects the rate of protein, carbohydrate and lipid metabolism

❖ REGULATION THEIR SECRETION BY HYPOTHALAMIC-PITUITARY-THYROID AXIS:

The hypothalamus senses low levels of T3/T4

↓

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

↓

High thyroid hormone levels suppress TRH & TSH

❖ Elements Involved in Hypothalamic-Pituitary-Thyroid regulation

1. **Hypothalamus nuclei**
   - Regulation of *Trh* gene transcription and processing
   - Regulation in response to nutrient status
2. **Pituitary:**
   - Regulation of TRH degradation
   - Regulation of TSH synthesis and activation
3. **Thyroid:**
   - Synthesis, release, regulation of T_4 and its conversion to T_3 by deiodinase 2 (D2) enzyme

❖ 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 due to:
  - ➢ Down regulation of LDL receptors on liver cells
  - ➢ Failure of sterol excretion via the gut

❖ Goiter

may be associated with:

✓ Hypofunction
✓ Hyperfunction
✓ Normal concentration of thyroid hormones (euthyroid)

Causes:

✓ Iodine, selenium[1] deficiency ,thyroid cancer
✓ Hashimoto's thyroiditis
✓ Graves' disease (hyperthyroidism)
✓ Congenital hypothyroidism

THYROID FUNCTION TESTS

TSH measurement:

- Indicates thyroid status
- Sensitive, first-line test

- Total T4 or free T4:

- Indicates thyroid status
- Monitors thyroid treatment (both anti-thyroid and thyroid supplement treatment), since TSH may take up to 8 weeks to adjust to new level during treatment

Total T3 or free T3:

- Rise in T3 is independent of T4
- In some patients only T3 rises (T4 is normal): T3 toxicosis
- For earlier identification of thyrotoxicosis

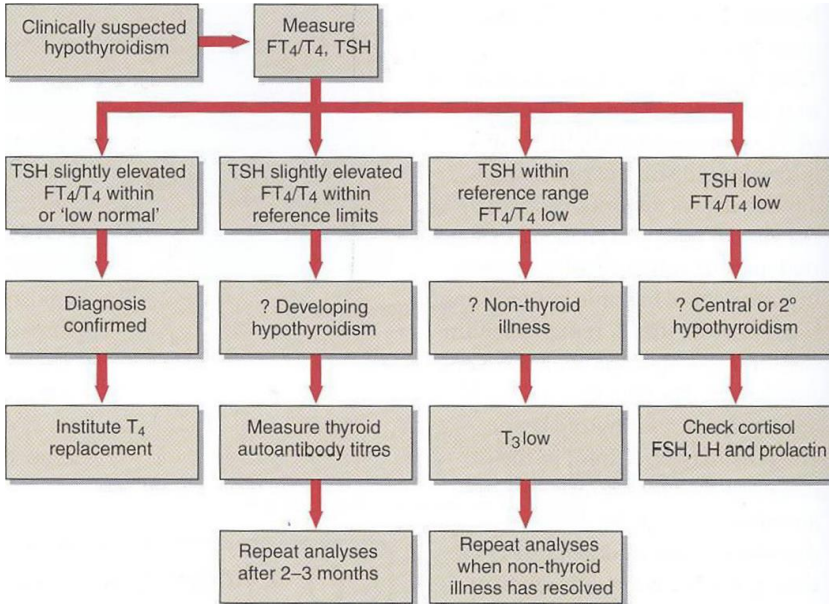
Antibodies:

-Diagnosis and monitoring of autoimmune thyroid disease
- Hashimoto's thyroiditis; anti-thyroid peroxidase in hypothyroidism
- Graves' disease: antibodies against TSH receptors on thyroid cells

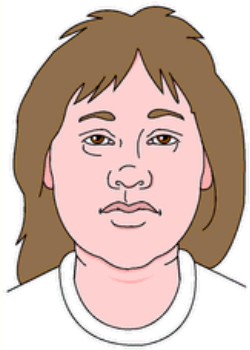
1. selenium is essential for the production of thyroid hormones

Hypothyroidism Deficiency of thyroid hormones

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



- **Causes:**
  - Hashimoto's disease
  - Radioiodine or surgical treatment of hyperthyroidism
  - Drug effects e.g. Anti thyroidal
  - TSH deficiency
  - Congenital defects
  - Severe iodine deficiency
- **Clinical features**
  - Tiredness
  - Cold intolerance
  - Weight gain
  - Dry skin



- **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 & T_3 decreased

*NTIS: Non-thyroidal illness syndrome refers to a syndrome found in seriously ill or starving patients with low fT3, usually elevated rT3, normal or low TSH, It is found in a high proportion of patients in the ICU setting.

Hyperthyroidism

Over-activity of the thyroid gland→ ↑secretion of thyroid hormones> Tissues are exposed to ↑ levels of thyroid hormones (thyrotoxicosis) >↑ pituitary stimulation of the thyroid gland

❖ **Causes**:

Grave's disease[1]
Toxic multinodular goitre
Thyroid adenoma
Thyroiditis
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

❖ **Diagnosis**

-Suppressed TSH level
-Raised thyroid hormones levels
-Confirms primary hyperthyroidism

❖ **Treatment**

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

❖ **Problems in diagnosis**

- Total serum T4 varies due to changes in binding protein levels e.g. High estrogens in pregnancy increase TBG synthesis>>Total T4 will be high, free T4 will be normal.
- Congenital TBG deficiency can also influence results

Free T_4 and TSH are first-line tests for thyroid dysfunction

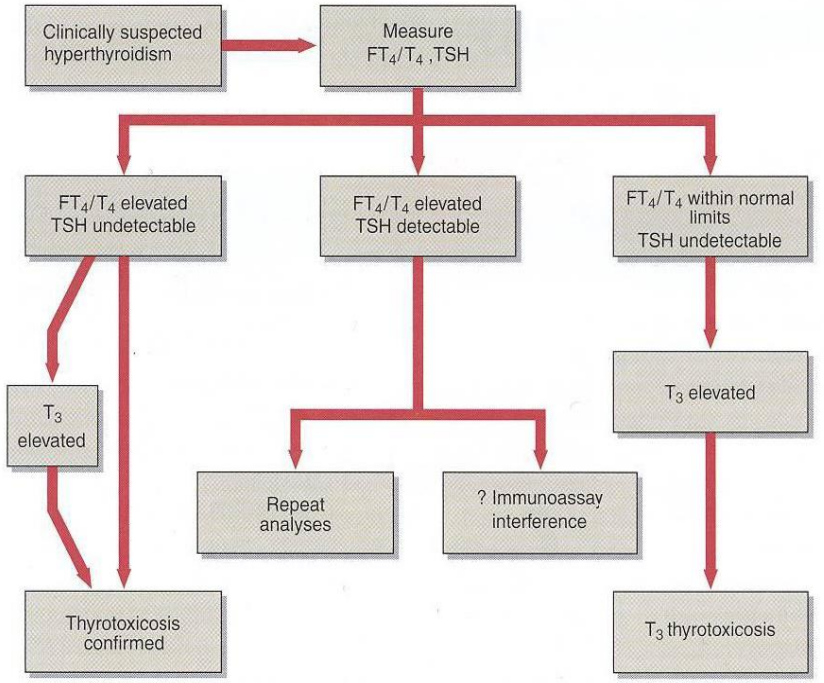


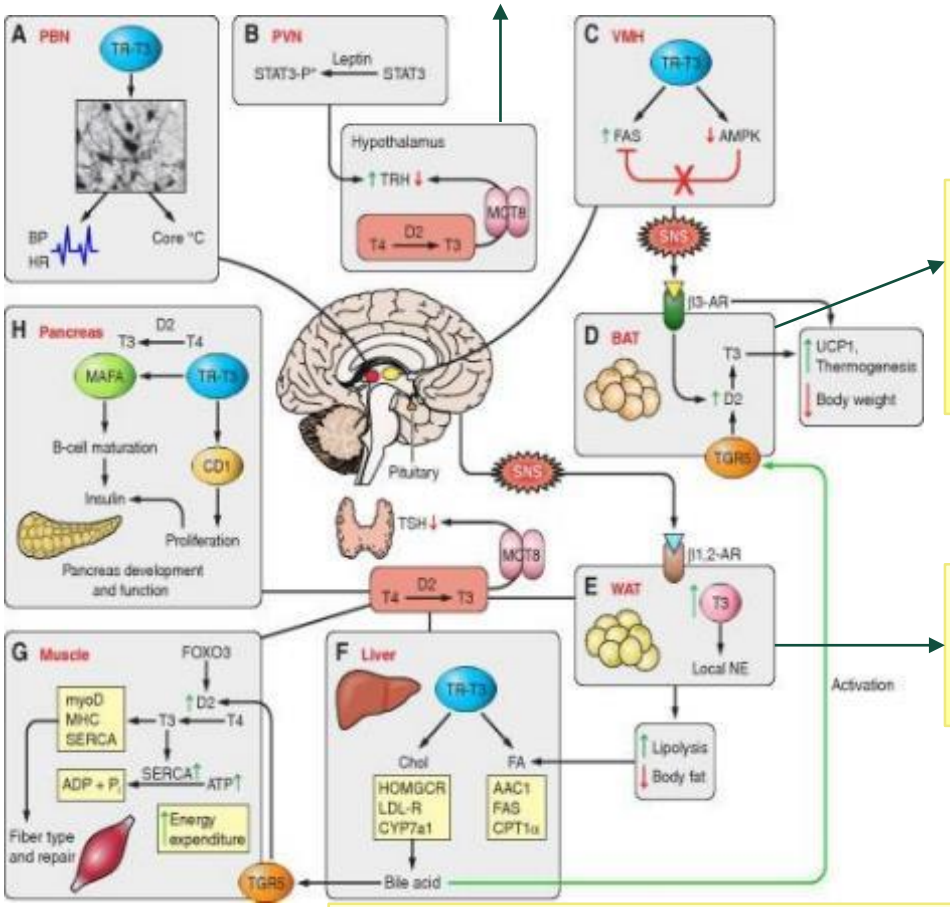
Fig. 2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

1. Most common cause of hyperthyroidism. It's an autoimmune disease, Antibodies against TSH receptors on thyroid cells mimic the action of pituitary hormone

SITES OF THYROID HORMONE REGULATION OF METABOLISM

(SOME EXAMPLES, IT EFFECTS ALL TISSUES)

1.Hypothalamus-Pituitary-Thyroid Axis
In response to feedback regulation, nutrition status and stress level→ regulation of TRH, TSH, and T4 release and central conversion of T4 toT3



2.Pancreas
In response T4 → ↑ local T3 → effect on β cell function & proliferation

3.Muscle
In response T4 and to bile acid → ↑ D2 & ↑ local T3 → ↑ energy expenditure

6.Brown adipose tissue
In response to sympathetic nervous system and bile acids → ↑ D2 → ↑ T3 → ↑UCP1 & thermogenesis and ↓body weight

5.White adipose tissue
In response to sympathetic nervous system → ↑ T3 → ↑ lipolysis & ↓ body fat

4.Liver
In response to ↑ lipolysis in WAT → effect on cholesterol and lipid metabolism and synthesis and release of bile acid

THERMOGENESIS
(HEAT PRODUCTION)

- Humans are **homeothermic** (keep constant body temperature 37º) Tightly controlled.
- There are two types:
  - **Obligatory**: **Basic** heat production due to basal metabolic rate needed for brain,heart,enzyme,etc function
  - **Facultative**: **On-demand** extra heat production from metabolic activity in **brown adipose tissue** (BAT), skeletal muscle, etc.In BAT, the facultative thermogenesis is stimulated by sympathetic nervous system in response to cold temperature

❖ THYROID HORMONE AND THERMOGENESIS

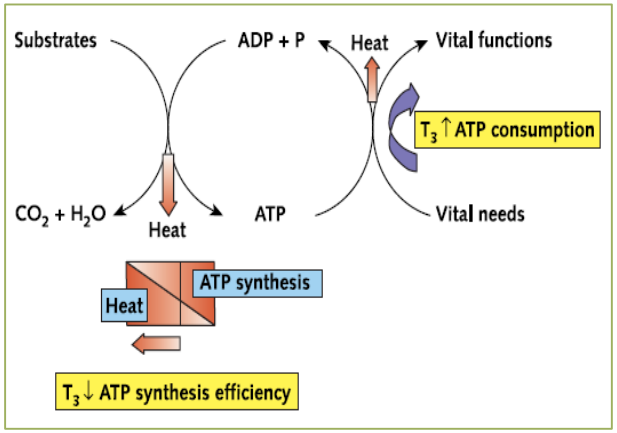
has an essential role in thermogenesis:

1- **Obligatory thermogenesis**: 30% of obligatory thermogenesis depends on thyroid hormone which is essential for temperature homeostasis

2- **Facultative thermogenesis**: thyroid hormone is important for facultative thermogenesis; in the absence of thyroid hormone, the thermo genic response of brown adipose tissue is substantially reduced "emphasizing its importance for thermogenesis in these tissues"

❖ MECHANISMS BY WHICH THYROID HORMONE REGULATES THERMOGENESIS

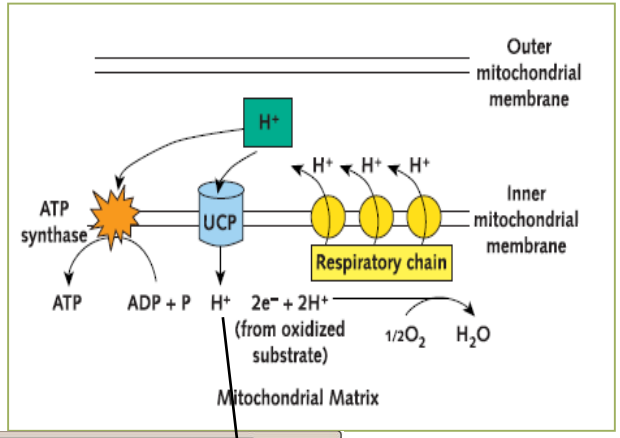
- The energy released from substrate oxidation is captured in ATP, then The energy is transferred from ATP to provide energy for biological processes
- However, A fraction of the energy is lost as heat without ATP production & consumption
- Thyroid hormone increases heat production by: **Increasing** ATP utilization / **Reducing** the thermodynamic efficiency of ATP synthesis

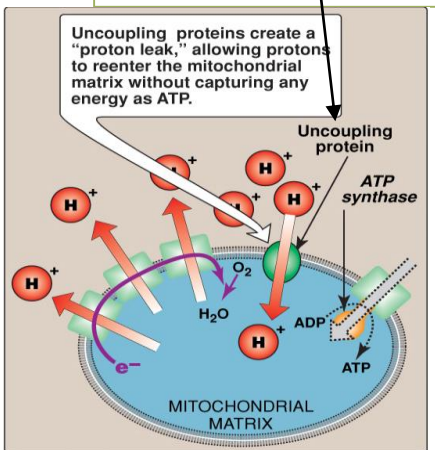


❖ ACTION MECHANISM OF UNCOUPLING PROTEINS (UCPS)

The energy released in the oxidation of substrates in the mitochondria →proton gradient → The energy accumulated in this gradient is used the ATP Synthase to produce ATP i.e. oxidation is coupled to phosphorylation of ADP to ATP

UCPs reduce the proton gradient, bypassing the ATP synthase → exothermic movement of protons down the gradient→ heat (because oxidation is uncoupled to phosphorylation)





Example: UCP1 is present in **the inner mitochondrial membrane** of **BAT. Other UCPs are ubiquitous.**

In other words: high proton gradient is usually build up to be used by ATPase synthase for ATP synthesis, UCPs are transmembrane proteins that decrease the proton gradient by increasing the permeability of the inner mitochondrial membrane, allowing protons that have been pumped into the intermembrane space to return to the mitochondrial matrix.

SUMMARY

- ✓ Thyroid hormones include T4 , T3, and rT3 (which is inactive), they are synthesized by iodination, coupling and attaching to thyroglobulin protein.
- ✓ T3 is the active form of thyroid hormone and is synthesized by deiodinase in peripheral and central tissues.
- ✓ Thyroid hormone has wide spectrum of actions, for instance maturation of all body tissues, coordinating development and specific cell functions, metabolic regulation, and thermogenesis.
- ✓ Thyroid hormone is regulated by feed back mechanism. Several elements are involved in the regulation at the level of the hypothalamic nuclei, pituitary gland, thyroid, and peripheral tissues.
- ✓ TFT include measurement of TSH, total and free T4, total and free T3, and thyroid antibodies.
- ✓ Goiter is and enlarged thyroid gland, that can be associated with: Hypo-, Hyper, or Eu (normal) thyroid function
- ✓ Hypo and hyperthyroidism are differentiated based on their clinical picture, causes, diagnostic criteria, and treatment
- ✓ Thyroid hormone regulates both obligatory and facultative thermogenesis.
- ✓ It increases obligatory thermogenesis, by accelerating ATP turnover and reducing the efficiency of ATP synthesis
- ✓ It increases facultative thermogenesis: Thyroid hormone is necessary for an efficient response of BAT to cold

MCQS

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 of 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- Eruthyroid

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

1-B 2-C 3-A 4-A 5-B 6-A 7-C 8-A 9-A 10-B

SAQS

1-what are the types of thyroid hormones?

1)T4 which is mostly protein bound

2)T3>> unbound to proteins + most active Or The reverse T3 form which is inactive.

2-Hypo and hyperthyroidism are differentiated based on what?

clinical picture

Causes

diagnostic criteria

treatment

3-T4 gets converted to rT3 (reverse T3) why?

to maintain the balance and prevent thyrotoxicosis

4-if a patient TSH is high and T4 is high what does it indicate?

Secondary hyperthyroidism

5- if a patients TSH is high and T4 is low what does it indicate?

Primary hypothyroidism

Biochemistry Bandits 434

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عند حاجتي إليه إنك على كل شيء قدير

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