Thyroid Hormones and Thermogenesis

Biochemistry Teamwork

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Do not memorize numbers nor structures.

Thyroxine (T_4), Tri-iodothyronine (T_3) & Reverse T_3 (rT_3)

Plasma [T_4]: 100 nmol/L

Plasma [T_3]: 2 nmol/L

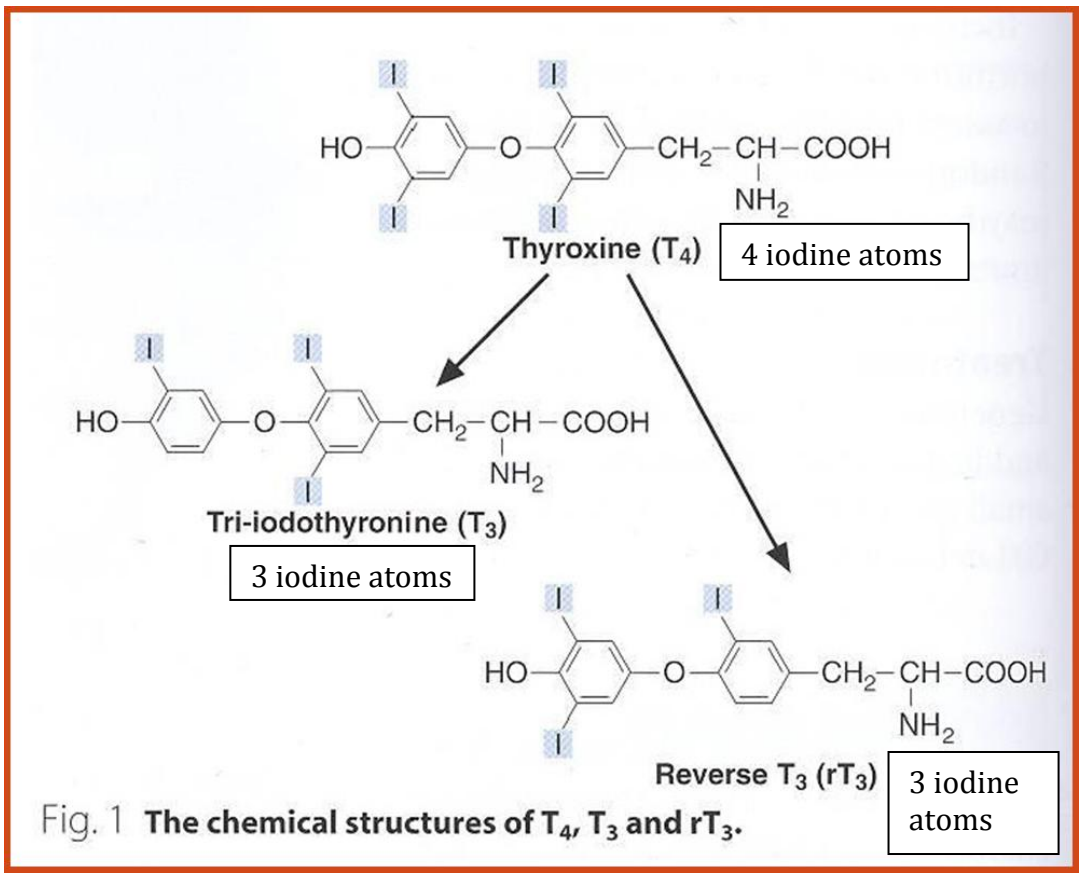


Fig. 1 **The chemical structures of T_4, T_3 and rT_3.**

Types & Biosynthesis of Thyroid Hormones:

- Thyroxine (T_4) and tri-iodothyronine (T_3)
- Synthesized in the thyroid gland by:
  - Iodination
  - Coupling of two tyrosine molecules

  } Whilst attached to thyroglobulin protein
- Thyroid gland secretes mostly T_4
- Peripheral tissues (liver, kidney, etc.) de-iodinate T_4 to T_3
- T_3 is the more biologically active form
- T_4 can be converted to rT_3 (reverse T_3) – inactive form (this is a regulatory mechanism) (when there is increased serum T_3, the body converts it to reverse T_3, which is inactive, instead of converting it to the active T_3)
- Most of T_4 is transported in plasma as protein-bound
  - Thyroxin Binding globulin (TBG)-bound (70%)
  - Albumin-bound (25%)
  - Transthyretin (prealbumin)-bound (5%)
- The unbound (free) form of T_4 and T_3 exert their biologic effects.

Thyroid hormone action:

- Essential for normal maturation and metabolism of **all** body tissues.
- Affects the rate of protein, carbohydrate and lipid metabolism.
- Thermogenesis

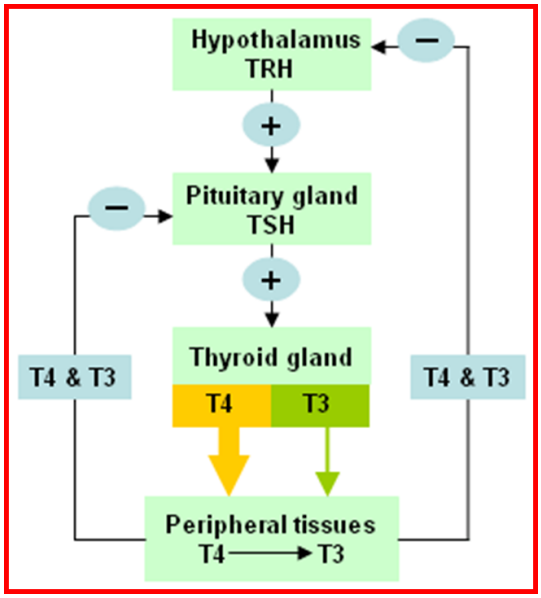
Evidences for the essential actions of thyroid hormones:

1. Congenital hypothyroidism: if untreated within 3 months of birth → permanent brain damage
2. Hypothyroid children have:
   - -delayed skeletal maturation →short stature
   - -delayed puberty
3. Hypothyroid patients have high serum cholesterol due to:
   - -Down regulation of LDL receptors on liver cells
   - -Failure of sterol excretion via the gut

Regulation of Thyroid Hormone Secretion:

-Components of hypothalamic-pituitary-thyroid axis:

- -TRH (tripeptide)
- -TSH (large Glycoprotein)
- -Thyroid hormones



- **High thyroid hormone levels** suppress TRH (thyrotropin releasing hormone) & TSH (thyroid stimulating hormone)
- **Low thyroid hormone levels** stimulate TRH & TSH to produce more hormones.
- The hypothalamic-pituitary-thyroid axis regulates thyroid secretion.
- The hypothalamus senses low levels of T_3/T_4 and releases thyrotropin releasing hormone (TRH)
- TRH stimulates the pituitary to produce thyroid stimulating hormone (TSH)
- TSH stimulates the thyroid to produce T_3/T_4 until levels return to normal
- The **Circulating Unbound T_3/T_4** exert negative feed-back control on the hypothalamus and pituitary
- Controlling the release of both TRH and TSH

Thyroid Function Tests (TFT):

1. TSH measurement:

- Indicates thyroid status
- Sensitive, first-line test

2.Total T_4 or free T_4:

- Indicates thyroid status
- Monitors thyroid treatment (both anti-thyroid and thyroid supplement treatment)
- Why don't we measure TSH to monitor treatment? Because TSH may take up to 8 weeks to adjust to a new level during treatment

3. Total T_3 or free T_3:

- In hyperthyroidism, the rise in T_3 is disproportionate (independent) of T_4
- For earlier identification of thyrotoxicosis
- In some patients only T_3 rises (T_4 is normal): T_3 toxicosis

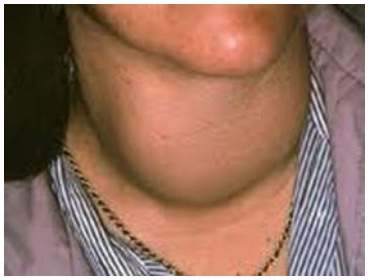
4.Antibodies:

- Diagnosis and monitoring of autoimmune thyroid disease (Hashimoto's thyroiditis); anti-thyroid peroxidase (anti-TPO) in hypothyroidism.
- Diagnosis of Grave's disease: stimulating antibodies against TSH (anti-TSH) (Thyroid Stimulating Immunoglobulin) receptors on thyroid cells in thyrotoxicosis.

Drugs affecting TFT: (not important)

- Amiodarone
- Lithium
- Anticonvulsants
- Heparin
- Aspirin

Goitre:



- Enlarged thyroid gland (enlarged doesn't mean it is hyper functioning)
- **Functionally**: Goitre may be associated with:
  - Hypofunction
  - Hyperfunction
  - Normal concentration of thyroid hormones (euthyroid)

- **Causes**:
  - Iodine deficiency
  - Selenium deficiency
  - Hashimoto's thyroiditis
  - Congenital hypothyroidism
  - Grave's disease (hyperthyroidism)
  - Thyroid cancer

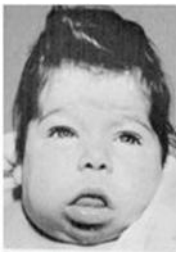
Hypothyroidism:

- Deficiency of thyroid hormones
- ***Primary hypothyroidism:***
  - Failure of thyroid gland (Elevated TSH level is diagnostic)
- ***Secondary hypothyroidism:***
  - Failure of the pituitary to secrete TSH (rare)
  - Failure of the hypothalamic-pituitary-thyroid axis (e.g. any pituitary disease)
- **Causes:**
  - **Hashimoto's disease (autoimmune destruction of the thyroid gland)**
  - **Radioiodine or surgical treatment of hyperthyroidism** (side effect of aggressive treatment of hyperthyroidism)

  } Over 90% of cases

  - Drug effects (e.g. lithium)
  - TSH deficiency (may be with panhypopituitarism – it means all the pituitary gland is affected)
  - Congenital defects (e.g. defective synthesis of T_4 & T_3, or organ resistance to their actions)
  - Severe iodine deficiency
- **Clinical features**
  - Tiredness
  - Cold intolerance
  - Weight gain
  - Dry & coarse skin and hair
  - Others (constipation, bradycardia,…)
- **Diagnosis**
  - Elevated TSH level confirms hypothyroidism (because in Hypothyroidism ,Circulating Thyroid hormones are very low which will stimulate the hypothalamus (to release TRH) and anterior pituitary gland (to release TSH) >>Result : Elevated TSH

- **Treatment**
  - T_4 replacement therapy (tablets)
  - Monitoring TSH and T_4 level to determine dosage & the adequacy of treatment.
  - Patient has to continue treatment for life



- **Neonatal hypothyroidism (primary)**
  - 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 puffy face, protuberant tongue, umbilical hernia, mental retardation, short stature, deaf mute, and neurological signs
- **Non-thyroidal illness (acute illness)**
  - In some systemic diseases, the normal regulation of TSH, T_3 and T_4 secretion and metabolism is disturbed & the concentrations of the transport proteins (albumin and transthyretin) are low.
  - Most of T_4 is converted to rT_3 (inactive)→ ↓thyroid hormone activity (low T_3 syndrome)
  - This does not increase TSH secretion (TSH is suppressed) → secretion of T_4 and T_3 is decreased

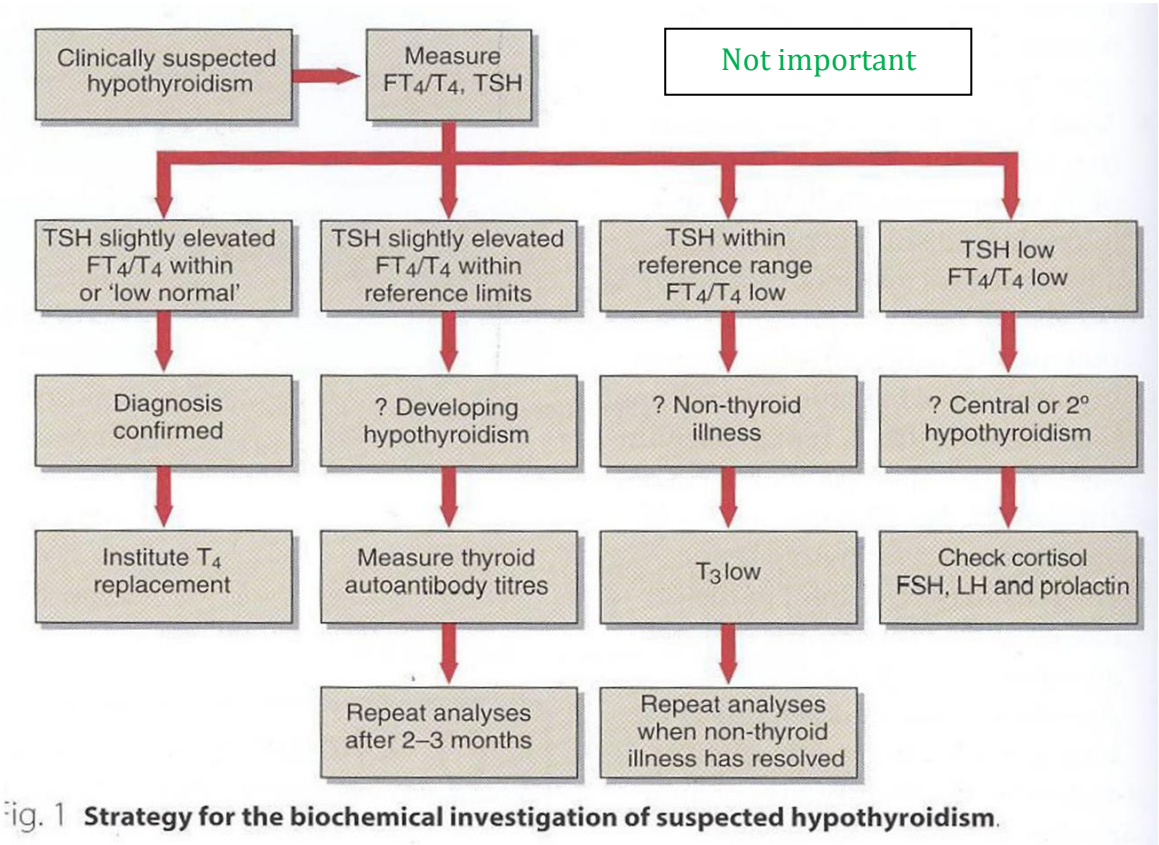


Fig. 1 **Strategy for the biochemical investigation of suspected hypothyroidism.**

Hyperthyroidism:

- **Hyperthyroidism** is over-activity of the thyroid gland→ ↑secretion of thyroid hormones (primary)
- Tissues are exposed to ↑ levels of thyroid hormones (**thyrotoxicosis**) (Not all thyrotoxicosis is caused by hyperthyroidism)
- ↑ Pituitary stimulation of the thyroid gland (rare) (secondary)
- **Causes**:
  - **Grave's disease** (the most common cause)
  - Toxic multinodular goitre
  - Thyroid adenoma
  - Thyroiditis
  - Intake of iodine / iodine-containing drugs e.g. amiodarone
  - Excessive intake of T_4 and T_3 (Factitious hyperthyroidism)
- **Clinical features:**
  - Weight loss with normal appetite
  - Sweating / heat intolerance
  - Fatigue & generalized muscle weakness, proximal myopathy
  - Palpitation / agitation, tremor
  - Angina, heart failure
  - Diarrhea
  - Eyelid retraction and lid lag
  - Goiter
  - Oligomenorrhoea & subfertility
- **Diagnosis**
  - Suppressed TSH level
  - Raised thyroid hormones level

  } Confirms primary hyperthyroidism
- **Problems in diagnosis**
  - Total serum[T_4] changes due to changes in binding protein levels
  - In pregnancy, high estrogens → increase TBG synthesis in the liver (TBG will bind to T_4)
    - Total [T_4] will be high, free [T_4] will be normal (because when TBG binds to free T_4, the decrease in free T_4 will stimulate TRH release ➔ increases TSH ➔ increases free T_4 synthesis to normal.)
  - Congenital TBG deficiency → problem in screening of thyroid hormones.
  - Free T_4 and TSH are first-line tests for thyroid dysfunction
- **Treatment**
  - Antithyroid drugs: carbimazole, propylthiouracil
  - Radioiodine: sodium ^{131}I inhibits T_4/T_3 synthesis
  - Surgery: thyroidectomy

Grave's Disease: Diffuse Toxic Goiter

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

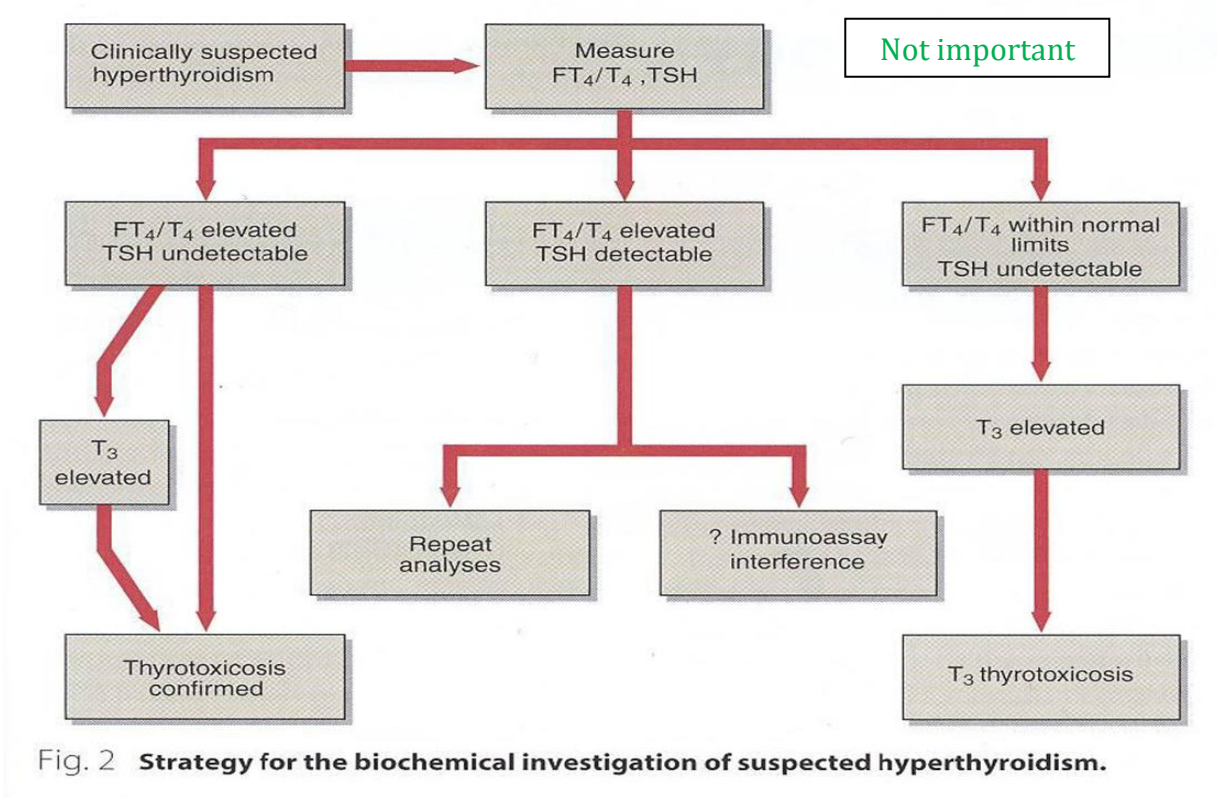
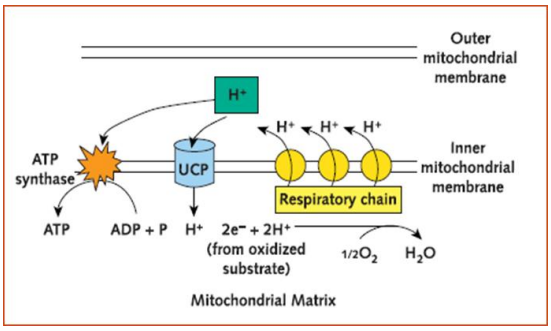


Fig. 2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

Thermogenesis:

- Thyroid hormone has an active role in thermogenesis
- About 30% of thermogenesis depends on thyroid hormone
- Thyroid hormone regulates metabolism and ATP turnover
- It increases ATP synthesis and consumption
- Na+/K+ gradient requires ATP to maintain it
- The gradient is used to transport nutrients inside the cell
- Thyroid hormone reduces Na+/K+ gradient across the cell membrane by increasing metabolism (more nutrient transport in the cell)
- This increases the demand for ATP to maintain the gradient
- ATP synthesis and consumption that produce heat is increased

Mechanism of action of uncoupling proteins (UCP):



The energy released in the oxidation of substrates in the Mitochondria → causes a proton gradient

⇩

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

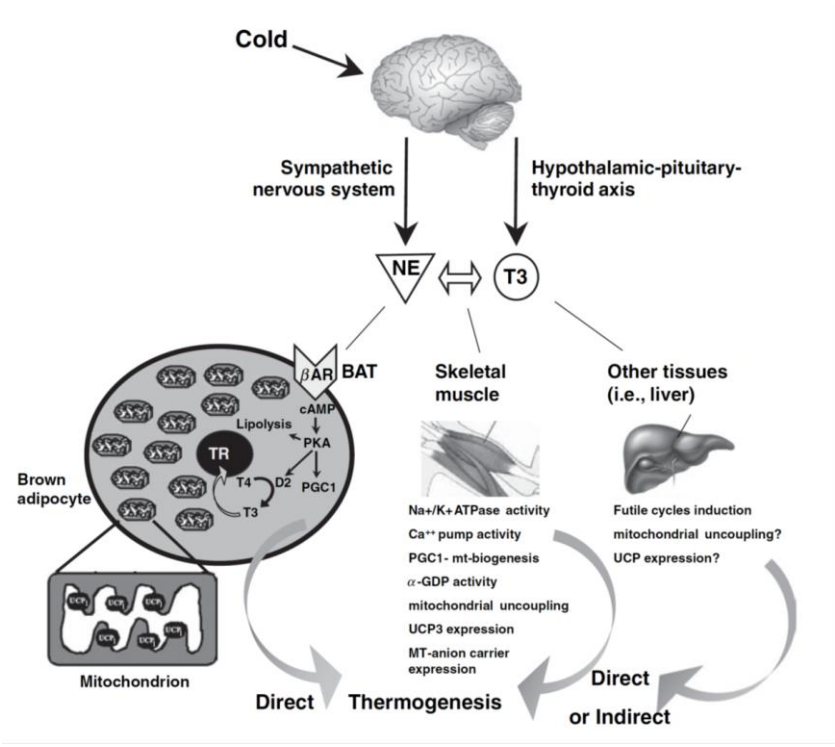
⇩

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**) (ubiquitous meaning it is spread in all organs)

The only thing we need to know about this picture is that T_3 helps in release of heat through hypothalamic-pituitary-thyroid axis by controlling UCP.



Questions:

1. Which one of the following will be seen in case of primary hyperthyroidism?
    A. T_4 is low
    B. T_3 is low
    C. TSH is low
    D. All are wrong

2. Which one of the following will happen in case of neonatal hypothyroidism?
    A. Acromegaly
    B. Dwarfism
    C. Cretinism
    D. Gigantism

3. Administration of TSH increases serum T3 and T4 in:
    A. Hyperthyroidism of pituitary origin (secondary)
    B. Hypothyroidism of pituitary origin (secondary)
    C. Hyperthyroidism of thyroid origin (primary)
    D. Hypothyroidism of thyroid origin (primary)

4. High level of T3 and T4 and low TSH in serum indicates:
    A. Hyperthyroidism of pituitary origin (secondary)
    B. Hypothyroidism of pituitary origin (secondary)
    C. Hypothyroidism of thyroid origin (primary)
    D. Hyperthyroidism of thyroid origin (primary)

Answers: 1-C, 2-C, 3-B, 4-D