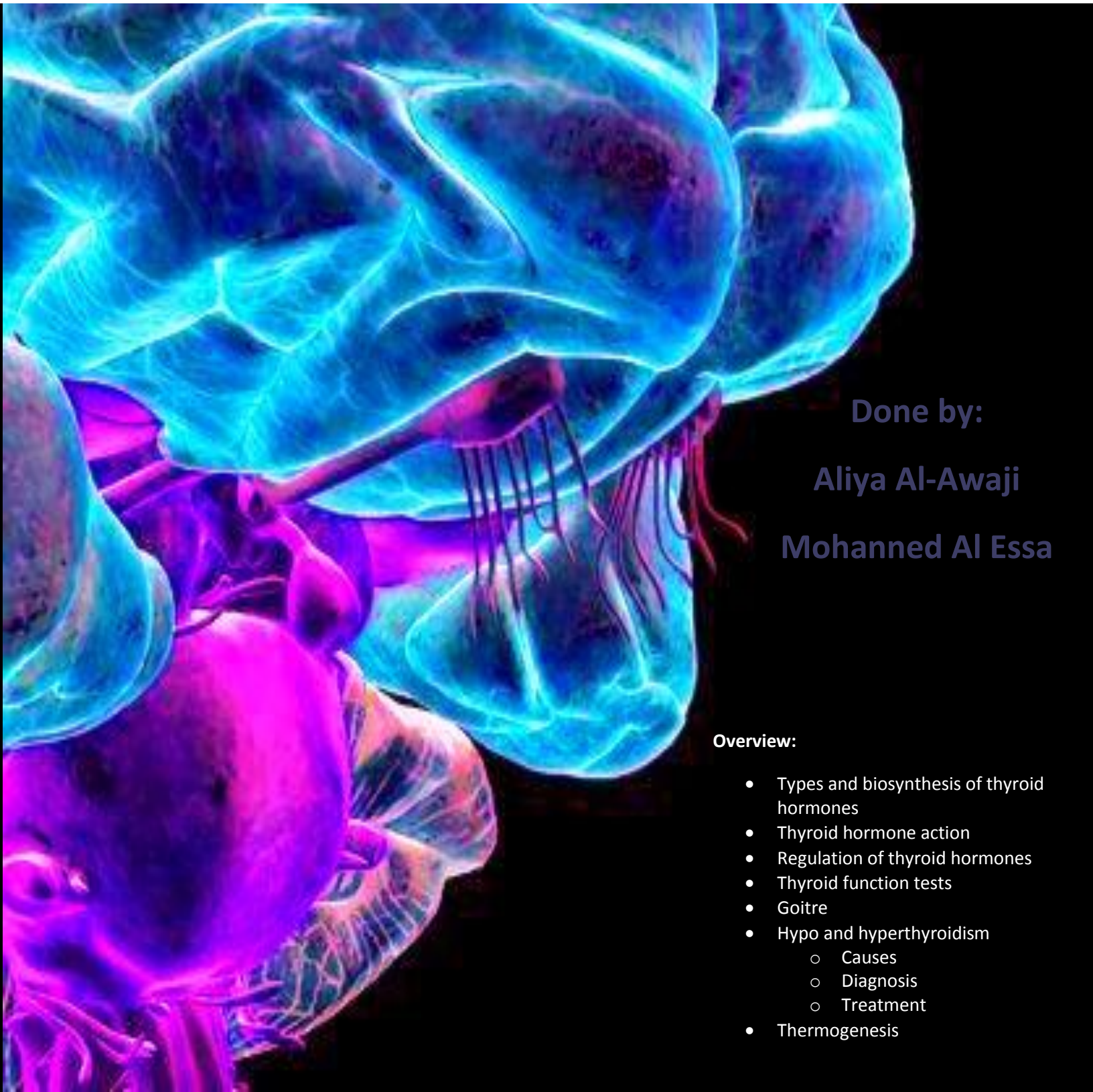


Thyroid Hormones and Thermogenesis



Done by:

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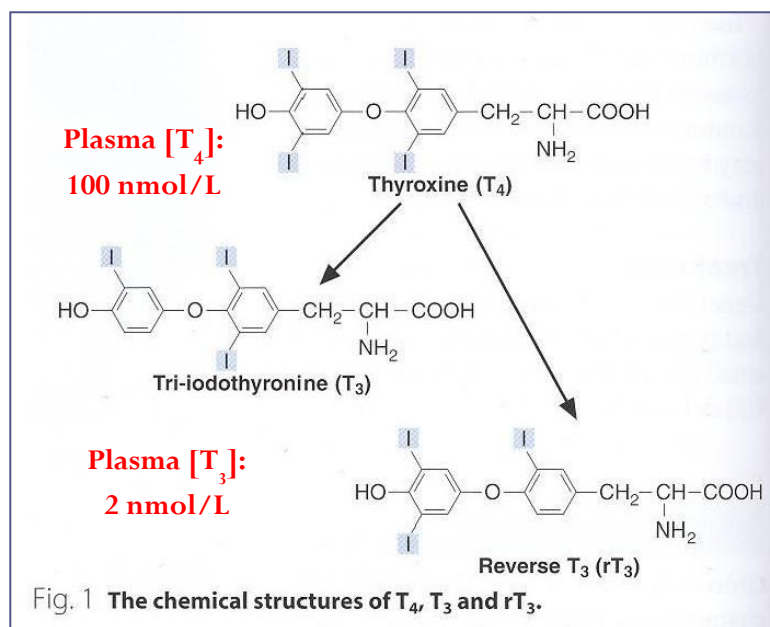
Overview:

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

Types and biosynthesis of thyroid hormones :

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

Thyroxine-binding globulin (TBG) is a protein carrier that carry thyroid hormones, But its levels depends on the physiological state (e.g. during pregnancy estrogen level goes up which ↑ thyroglobulin level).



- Tyrosine is an amino acid, which comes from phenylalanine.
- We link 2 tyrosine together then we add the iodine atoms (if 3 tri- , if 4 tetra-).
- If we took plasma sample for a normal person T₄ levels can reach 100 nMol/L (i.e. 50 times T₃). T₃ level reach to 2 nMol/L.
- So T₄ circulate in plasma more than **T₃ levels (which is more active)**. But in the tissue T₃ is the active form.

Thyroid Hormone Action:

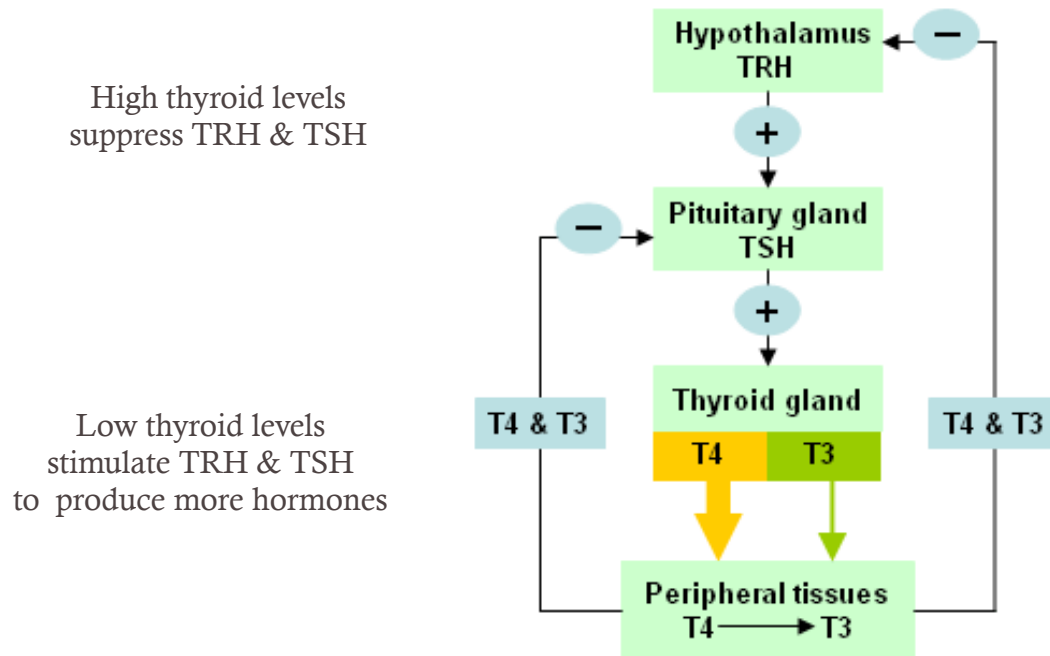
- Essential for normal maturation and metabolism of all body tissues
- Affects the rate of protein, carbohydrate and lipid metabolism
- Thermogenesis
- **Hypothyroid children have:**

Thermogenesis: is production of heat, its importance occurring during certain physiological conditions (e.g. cold weather).

- delayed skeletal maturation → short stature
- delayed puberty
- **Untreated congenital hypothyroidism** causes permanent brain damage
- **Hypothyroid patients** have **high serum cholesterol** due to:
 - Usually adult patients with hypothyroidism will be having ↑ serum cholesterol for many reasons, such as:
 1. Down regulation of LDL receptors on liver cells “decreased uptake” (e.g. familial LDLR deficiency).
 2. Failure of sterol “LDL” excretion via the gut (by secreting bile).

Regulation of Thyroid Hormone Secretion:

- The hypothalamic-pituitary-thyroid axis regulates thyroid secretion
- 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 (TFT):

- **TSH measurement:**
 - Indicates thyroid status “e.g. if ↑TSH with ↓T₃ T₄ → primary Hypothyroidism. If ↓TSH with ↑T₃ T₄ → primary Hyperthyroidism”
 - Sensitive, first-line test
- **Total T4 or free T4:**
 - Indicates thyroid status (↑Hyper ↓Hypo)

- Monitors anti-thyroid treatment
- Monitors thyroid supplement treatment
- 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
 - Diagnosis of **Grave's disease**: Antibodies against TSH receptors on thyroid cells

Grave's Disease is caused by thyroid autoantibodies (TSHR-Ab) that activate the TSH-receptor (TSHR), thereby stimulating thyroid hormone synthesis and secretion, and thyroid growth causing goiter.

Goitre

- Enlarged thyroid gland
- May be associated with:
 - Hypofunction
 - Hyperfunction
 - Normal function of thyroid gland

Causes:

- Iodine deficiency. **Worldwide, over 90% cases of goitre are caused by iodine deficiency.**
- Selenium deficiency
- Hashimoto's thyroiditis
- Congenital hypothyroidism
- Grave's disease (hyperthyroidism)
- Thyroid cancer

Selenium deficiency: Selenium mineral is a trace mineral and an important nutrient to fight many diseases including hypothyroidism.

*selenium deficiency symptoms typically associated with a hypothyroid condition.

Hypothyroidism

- Deficiency of thyroid hormones
- **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

Clinical features

- Tiredness
- Cold intolerance
- Weight gain
- Dry skin

Diagnosis

- Elevated TSH level confirms hypothyroidism (primary)

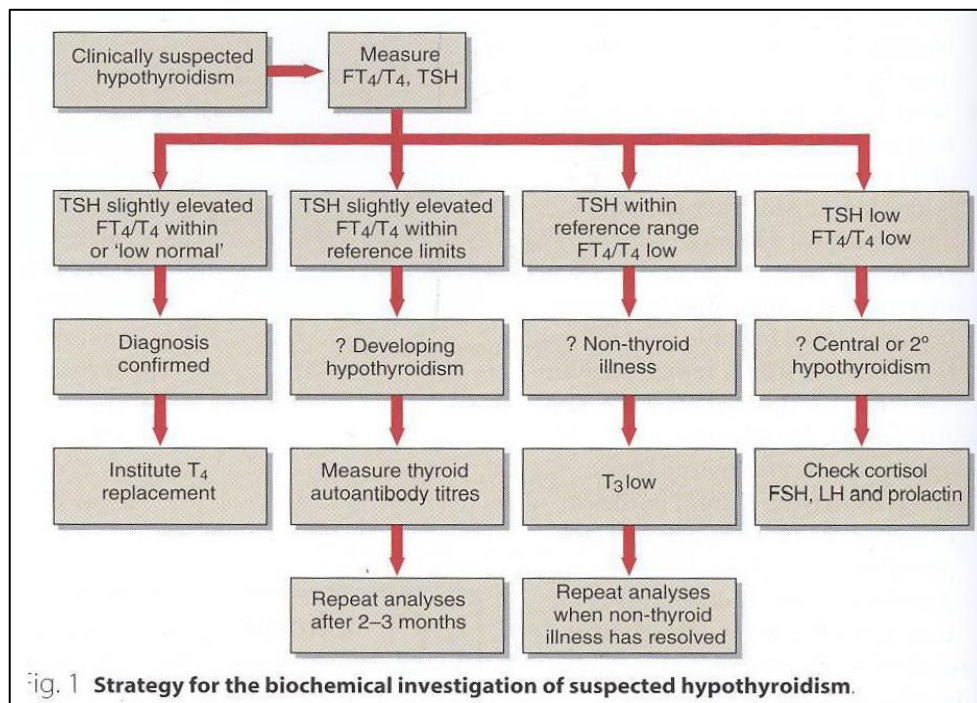
Treatment

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

Neonatal hypothyroidism

- Due to genetic defect in thyroid gland of newborns
- Diagnosed by TSH screening
- Hormone replacement therapy
- May cause cretinism, if untreated

This diagram is not important



Non-thyroidal illness (secondary)

- 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

Hyperthyroidism

- Over-activity of the thyroid gland
- 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 goitre
- Thyroid adenoma
- Thyroiditis
- Intake of iodine / iodine drugs
- Excessive intake of T4 and T3

Clinical features

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

Diagnosis

- in primary hyperthyroidism:
- Suppressed TSH level
- Raised thyroid hormone level

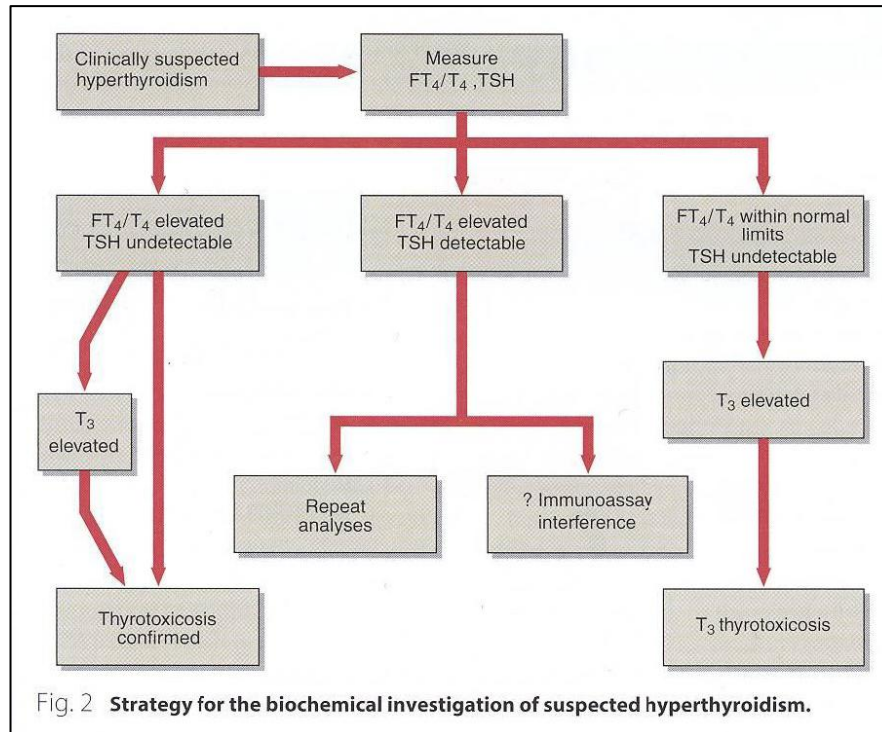
Problems in diagnosis

- Total serum T4 conc. 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

- Free T₄ and TSH are first-line tests for thyroid dysfunction

Treatment

- Antithyroid drugs: carbimazole, propylthiouracil
- Radioiodine: sodium ¹³¹I inhibits T₄/T₃ synthesis
- Surgery: thyroidectomy.



This diagram is not important

Grave's Disease

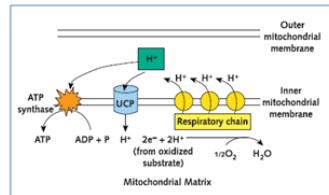
- Most common cause of hyperthyroidism
- An autoimmune disease
- Antibodies against TSH receptors on thyroid cells mimic the action of pituitary hormone
- Normal regulation of synthesis/control is disturbed

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
- Causing more nutrient transport in the cell (increasing metabolism)
- This increases the demand for ATP to maintain the gradient
- ATP synthesis and consumption is increased that 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):



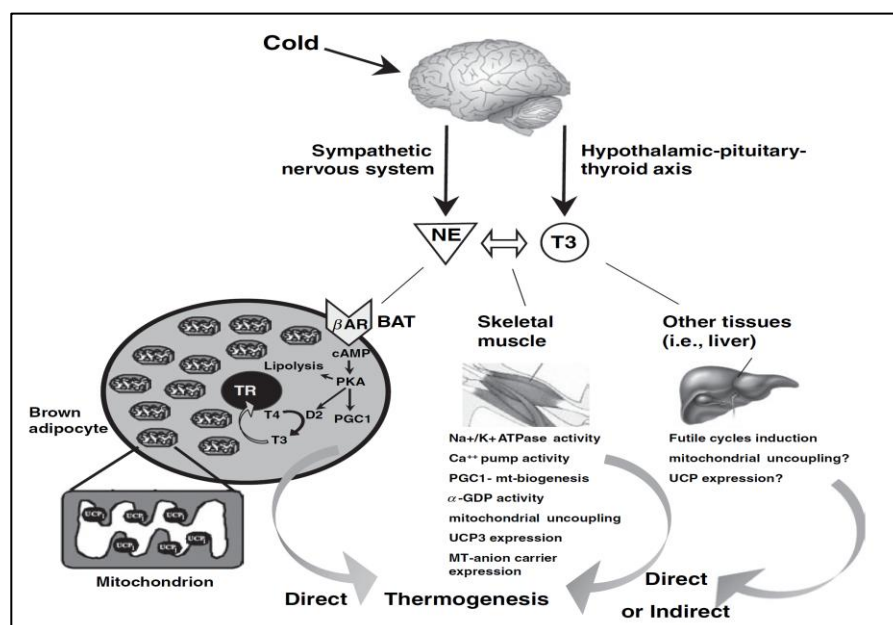
The energy released in the oxidation of substrates in the mitochondria → proton gradient

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), continued...

- 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**)



Summary:**Types and biosynthesis of thyroid hormones:**

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- Synthesized in the thyroid gland
- Thyroid gland mostly secretes T4
- T3 is more biologically active form
- T4 can be converted to rT3 (reverse T3) – inactive form

Thyroid Hormone Action:

- Essential for normal maturation and metabolism of all body tissues
- **Hypothyroid children have:**
 - delayed skeletal maturation → short stature
 - delayed puberty
- **Untreated congenital hypothyroidism** causes permanent brain damage

Regulation of Thyroid Hormone Secretion:

- High thyroid levels **suppress** TRH & TSH
- Low thyroid levels **stimulate** TRH & TSH to produce more hormones

Thyroid Function Tests (TFT):

• TSH measurement • Total T4 or free T4 • Total T3 or free T3 • Antibodies

Goitre • Enlarged thyroid gland • May be associated with:

- Hypofunction
- Hyperfunction

Hypothyroidism Diagnosis Elevated TSH level confirms hypothyroidism

Hyperthyroidism Diagnosis Suppressed TSH level, Raised thyroid hormone level, Confirms primary hyperthyroidism

Thermogenesis:

About 30% thermogenesis depends on thyroid gland, it regulates metabolism and ATP turnover and increases its synthesis and consumption by many possible mechanisms. Na/K gradient which is used to transport nutrients inside the cell requires ATP to maintain it. Thyroid reduces Na/K gradient across the cell membrane causing more nutrient transport in the cell (increasing metabolism) This increases the demand for ATP, ATP synthesis and consumption is increased that 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). Produces heat via uncoupling of electron transport chain and oxidative phosphorylation.