

2- Thyroid Hormones and Thermogenesis

Types and Biosynthesis of Thyroid Hormones

Biosynthesis :

- **Synthesized** in the thyroid gland by:
 - **Iodination** and **coupling** of two tyrosine molecules
 - Binding to **thyroglobulin protein**
- Thyroid gland mostly **secretes** T₄
- Peripheral tissues (liver, kidney, etc.) **de-iodinate** T₄ to T₃
- Deiodination is catalyzed by **deiodinase enzymes**
- T₄ can be metabolized to **rT₃** (inactive form)

Types :

- **Thyroxine** (T₄) and **tri-iodothyronine** (T₃)
- **T₃ is more biologically active form**
- Most of T₄ is transported in plasma as protein-bound
 - **Thyroxin Binding globulin** (TBG)-bound (70%)
 - **Albumin-bound** (25%)
 - **Transthyretin (pre-albumin)**-bound (5%)
- The unbound (**free**) form of T₄ and T₃ are **biologically active**

Thyroid hormone action

- Plays an essential role in maturation of **all body tissues**
- Involved in **thermogenesis and metabolic regulation**
- **Increases cellular oxygen consumption** and **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 | Hypothyroid children have: | Hypothyroid patients have high serum cholesterol due to: |
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| permanent brain damage | <ul style="list-style-type: none"> • Delayed skeletal maturation → short stature • Delayed puberty | <ul style="list-style-type: none"> • Down regulation of LDL receptors on liver cells • Failure of sterol excretion via the gut |

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

High thyroid hormone levels suppress TRH, TSH

Low thyroid hormone levels stimulate TRH, TSH to produce more hormone

Thyroid Function Tests

| TSH measurement: | Total T ₄ or free T ₄ : | Total T ₃ or free T ₃ : | Antibodies |
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| <ul style="list-style-type: none"> ◦ Assessment of thyroid function ◦ Highly sensitive test (detects very low conc.) | <ul style="list-style-type: none"> ◦ Assessment of thyroid function ◦ Monitors thyroid treatment (both anti-thyroid and thyroid replacement treatment) ◦ TSH may take up to 8 weeks to adjust to new level during treatment | <ul style="list-style-type: none"> • Useful for assessing hyperthyroidism in which rise in T₃ is independent of T₄ • In some patients only T₃ rises (T₄ is normal): T₃ toxicosis • For earlier identification of thyrotoxicosis | <ul style="list-style-type: none"> ➤ Diagnosis and monitoring of autoimmune thyroid disease: <ul style="list-style-type: none"> • Hashimoto's thyroiditis (antibodies against TSH receptors that suppress thyroid secretion) • Graves' disease (antibodies against TSH receptors that stimulate thyroid secretion) |

Goitre : Enlarged thyroid gland

Goitre may be associated with:

- Hypofunction
- Hyperfunction
- Normal thyroid hormone conc. (euthyroid)

Causes:

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

Hypo and Hyperthyroidism

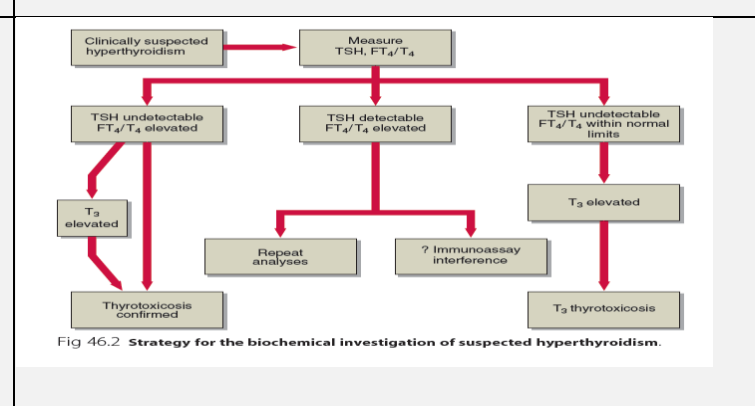
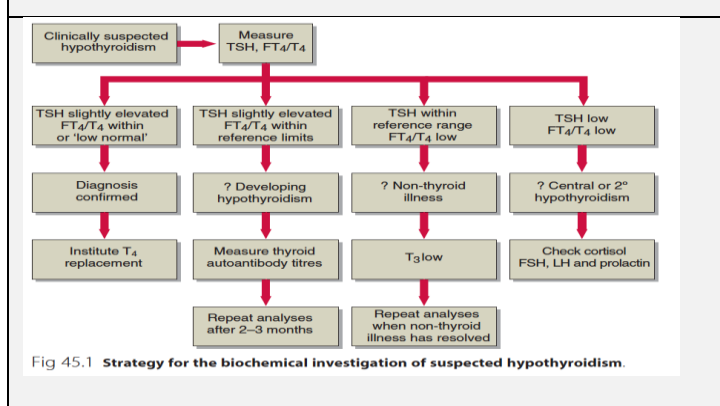
| Hypothyroidism | | Hyperthyroidism |
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| Deficiency of thyroid hormones | | <ul style="list-style-type: none"> ◦ Hyperstimulation of thyroid gland by pituitary gland ◦ Hypersecretion of thyroid hormones ◦ Tissues are exposed to high levels of thyroid hormones (thyrotoxicosis) |
| Primary hypothyroidism: | Secondary hypothyroidism: | |
| <ul style="list-style-type: none"> ◦ Failure of thyroid gland (Elevated TSH, deficiency of thyroid hormones) | <ul style="list-style-type: none"> ◦ Failure of the pituitary gland to secrete TSH (rare) ◦ Failure of the hypothalamic-pituitary-thyroid axis | |

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| Causes : <ul style="list-style-type: none"> • Hashimoto's thyroiditis • Radioiodine or surgical treatment of hyperthyroidism • Drug effects • TSH deficiency • Congenital defects in thyroid synthesis / thyroid resistance • Severe iodine deficiency | Causes: <ul style="list-style-type: none"> • Graves' disease • Toxic multinodular goiter • Thyroid adenoma • Thyroiditis • Excessive intake of iodine / iodine drugs • Excessive intake of T₄ and T₃ |
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| Clinical features <ul style="list-style-type: none"> ➢ Tiredness ➢ cold intolerance ➢ weight gain ➢ dry skin | Clinical features: <ul style="list-style-type: none"> ➢ Weight loss with normal appetite ➢ Sweating / heat intolerance ➢ Fatigue ➢ Palpitation / agitation, tremor ➢ Angina, heart failure ➢ Diarrhea ➢ Eyelid retraction and lid lag |
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| | Diagnosis <ul style="list-style-type: none"> ➢ Suppressed / undetectable TSH level ➢ Raised thyroid hormones levels ➢ Confirms primary hyperthyroidism ➢ Free T₄ and TSH are first-line tests for diagnosis of thyroid dysfunction Problems in diagnosis <ul style="list-style-type: none"> ➢ Total serum T₄ varies due to changes in binding protein levels ➢ High estrogens in pregnancy increase TBG synthesis ➢ Total T₄ will be high, free T₄ will be normal ➢ Congenital TBG deficiency can also influence results |
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| Treatment Replacement therapy with levothyroxine (T₄) | Treatment <ul style="list-style-type: none"> ➢ Antithyroid drugs: carbimazole, propylthiouracil ➢ Radioiodine: sodium ¹³¹I inhibits T₄/T₃ synthesis ➢ Surgery: thyroidectomy |
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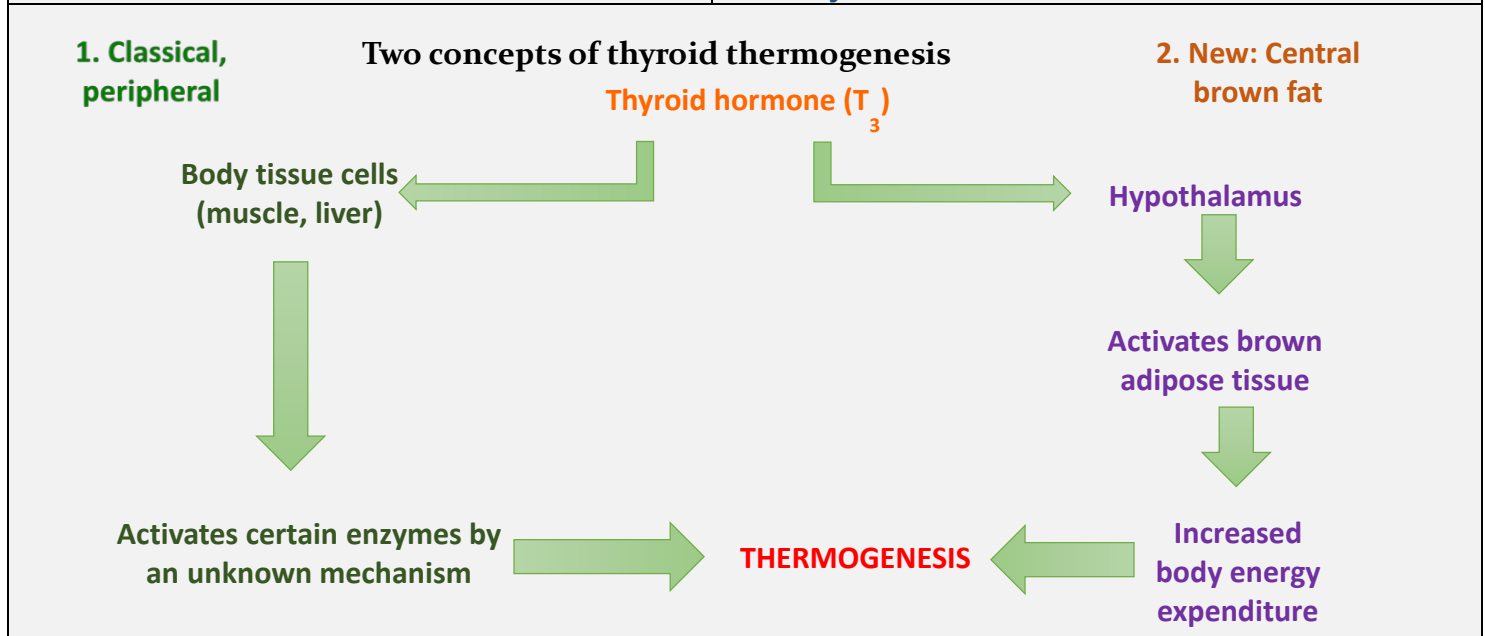


| Non-thyroidal illness | Graves' disease |
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| <ul style="list-style-type: none"> In some diseases, the normal regulation of TSH, T₃ and T₄ secretion and metabolism is disturbed Most of T₄ is converted to rT₃ (inactive) Causing thyroid hormone deficiency Secretion of T₄ and T₃ is decreased | <ul style="list-style-type: none"> 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 |

Thermogenesis (Heat production)

- Humans are homeothermic (keep constant body temp.)
- Tightly controlled temperature homeostasis
- **Thermogenesis is of two types:**

| Obligatory | Facultative |
|--|--|
| Heat production due to basal metabolic rate | On-demand extra heat production from metabolic activity in brown adipose tissue , skeletal muscle, etc. <ul style="list-style-type: none"> ➤ Facultative thermogenesis in brown adipose tissue is stimulated by sympathetic nervous system |



| Classical peripheral | New: central, brown fat |
|---|--|
| TH→t ₃ →muscles→there are different enzymes which are involved and producing heat and the most important ones are: GPDH, NaK-ATPase, smooth endoplasmic reticulum ATPase (SERCA), and Uncoupling protein 3 (UCP3)→thermogenesis. | TH→T ₃ →acts on the hypothalamus and inhibits AMPK enzyme→signals go the brown adipose tissue→activation of one the uncoupling proteins which is known as UCP1 → thermogenesis. |

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
- In respiratory chain, some protons reenter 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**