

Done By :

Ismael Raslan

Arwa Al-Madani

Sarah Bin-Hussain

Bedoor Al-Qadrah

Reham Al-Henaki

Special thanks to :

Abdullah alaqeel

Overview:

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

Team Notes:

- When there is excess thyroid hormones some of the T4 will be converted to rT3 (as regulation)
- T3 has a weaker binding th the plasma protein → that's why it's biologically active

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

In Peripheral tissues (liver, kidney, etc.)

deiodinate "remove of one of the iodine by an enzyme" 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

Thyroglobulin-bound (70%)

Albumin-bound (25%)

Transthyretin-bound (5%)

The unbound (free) form of T4 and T3 are biologically active

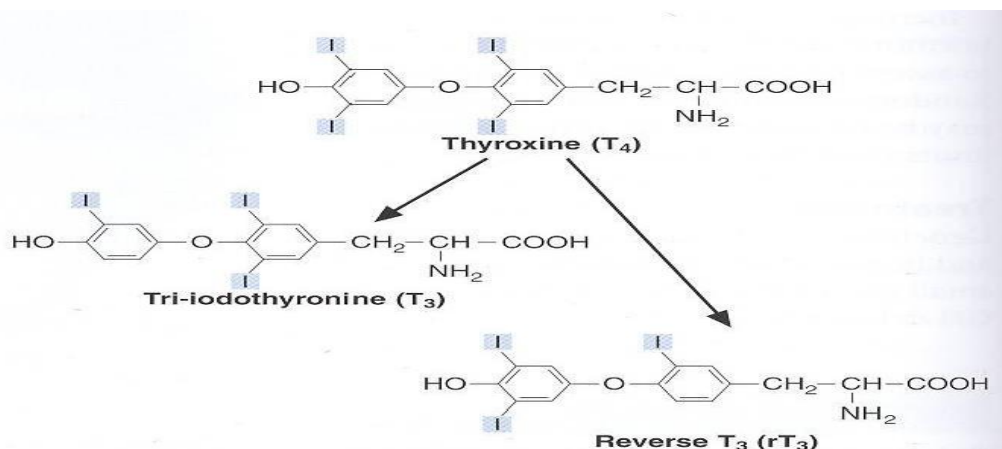


Fig. 1 The chemical structures of T₄, T₃ and rT₃.

Thyroid hormone action

- Essential for normal maturation and metabolism of all body tissues
- Affects the rate of protein, carbohydrate and lipid metabolism
- Thermogenesis (**genesis of Heat**)
- Hypothyroid children have delayed skeletal maturation, short stature, delayed puberty
- Untreated congenital hypothyroidism causes permanent brain damage
- 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

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)

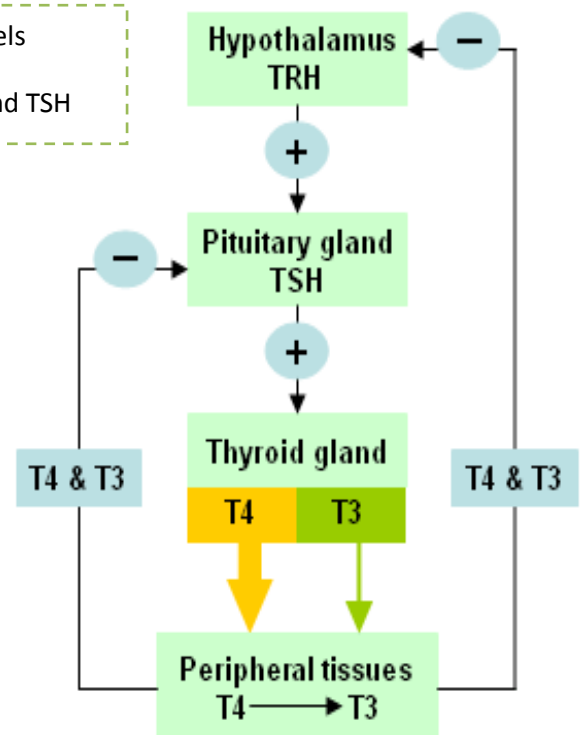
TSH stimulates the thyroid to produce T3/T4 until levels return to normal

T3/T4 exert **negative feed back** control on the hypothalamus and pituitary

Controlling the release of **both TRH and TSH**

High thyroid levels suppress TRH And TSH

Low thyroid levels stimulate TRH and TSH to produce more hormone



Team Notes:

- LDL receptors → take the LDL from circulation (↓LDL in blood), so when down regulation LDL ↑ in blood

Thyroid function tests

1. TSH measurement:

Indicates thyroid status

Sensitive, first-line test

2. Total T4 or free T4:

-Indicates thyroid status

-Monitors anti-thyroid treatment

-Monitors thyroid supplement treatment

-TSH may take upto 8 weeks to adjust to new level during treatment (that's why T4 used as monitor but TSH not)

3. Total T3 or free T3:

Rise in T3 is independent of T4

In some patients only T3 rises (T4 is normal)*"see the notes below"

For earlier identification of thyrotoxicosis

4. Antibodies:

Diagnosis and monitoring of autoimmune thyroid disease (Hashimoto's thyroiditis)

Goitre

Enlarged thyroid gland

May be associated with:

Hypofunction

Hyperfunction

Normal function of thyroid gland

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

Secondary hypothyroidism:

Failure of the pituitary to secrete TSH (rare)

Failure of the hypothalamic-pituitary-thyroid axis

Team Notes:

- *T3 rises could be due to non-thyroidal disease , peripheral tissue disturbed function convert more than what should –more than normal-

Notes from Abdullah alaqeel:

- TSH :
- $\uparrow \rightarrow$ hypothyroidism
- $\downarrow \rightarrow$ hyperthyroidism

Hypothyroidism

Causes:

Hashimoto's disease (antibodies produced → block the secretion of thyroid)

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

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

Non-thyroidal illness (problem in hypothalamus, pituitary or peripheral tissue)

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

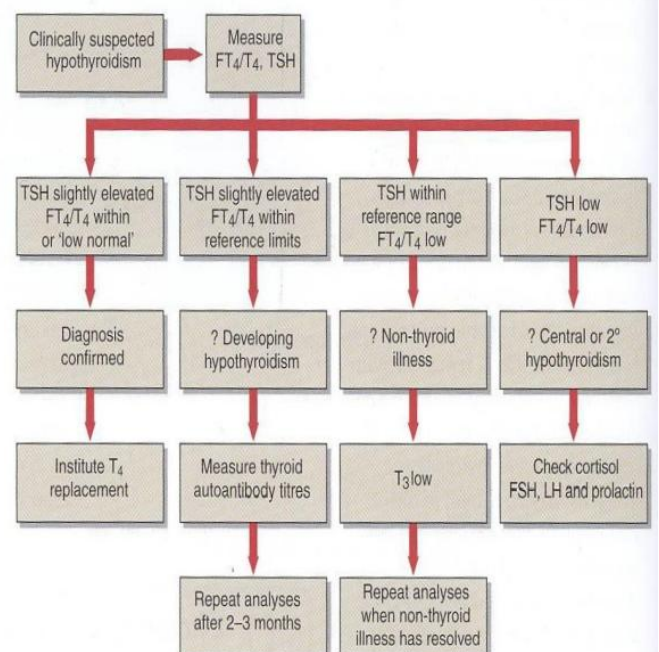


Fig. 1 Strategy for the biochemical investigation of suspected hypothyroidism.

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

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 (b/c of excess motility)

Eyelid retraction and lid lag (exophthalmos)

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

Diagnosis

Suppressed TSH level

Raised thyroid hormone level

Confirms primary hyperthyroidism

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 ^{131}I inhibits T4/T3 synthesis

Surgery: thyroidectomy

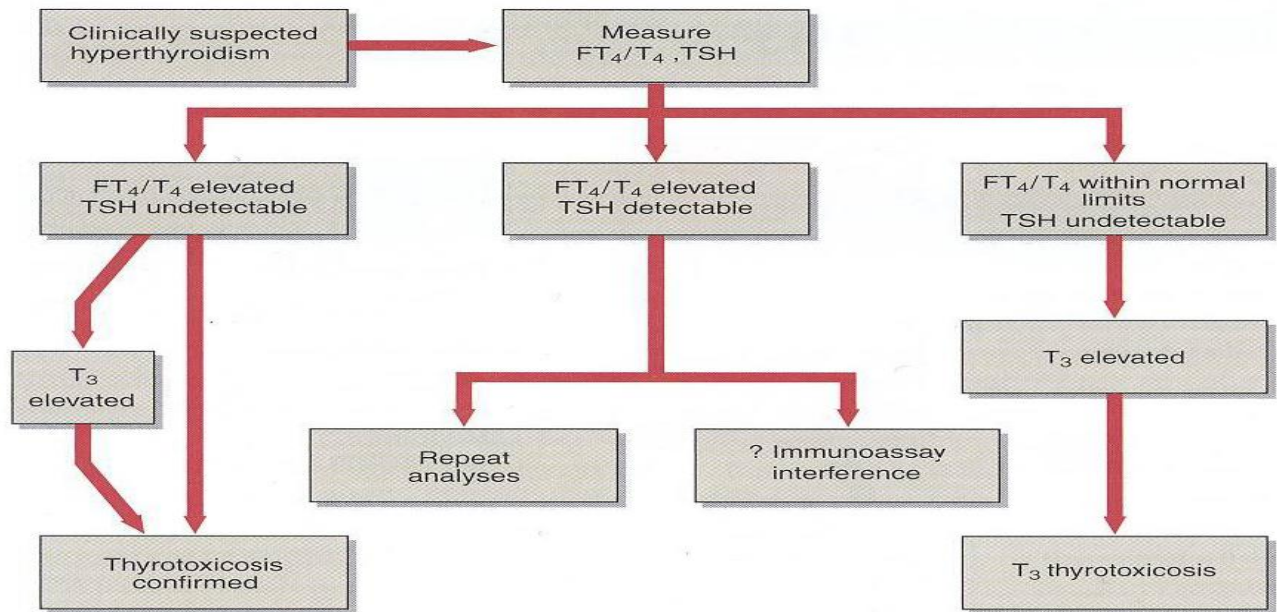


Fig. 2 Strategy for the biochemical investigation of suspected hyperthyroidism.

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

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 by increasing metabolism (more nutrient transport in the cell)

This increases the demand for ATP to maintain the gradient

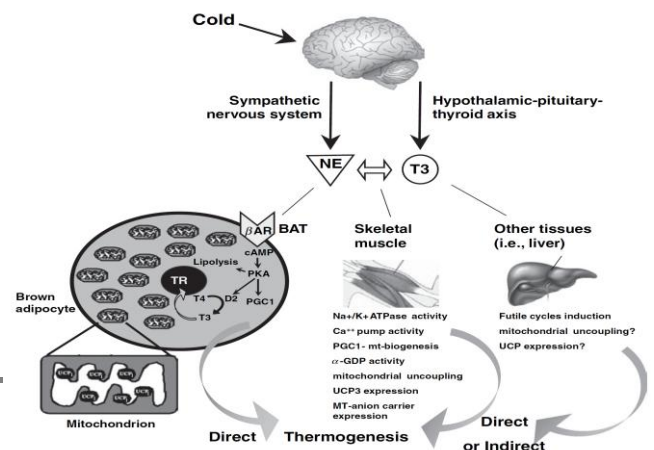
ATP synthesis and consumption is increased that produce heat

Team note :

(gradient means the difference .. when we say reduce the gradients means ..reduce the difference .. so more nutrients are needed → more nutrient will enter the cell → more ATPs are consumed .. heat will be produced)

Team Notes:

- Thyroid disease could be manifested by disturbance in thermogenesis



Revision Questions :

- 1. Most of the thyroid hormones in the plasma are bound to?**
 - a. Thyroglobulin : almost 70%
 - b. Then albumin : almost 25% of hormones
- 2. Most of the thyroid hormones secreted by the thyroid gland is in which form?**
 - a. T4 (thyroxine)
 - b. In the peripheral tissue the T₄ is converted into T₃
 - c. But don't forget the thyroid also secretes T₃ , but the most is T₄
- 3. What is the most biologically active form of thyroid hormones? And why?**
 - a. T₃ (tri-iodothyronine)
 - b. Because it binds less to plasma proteins , making it free and more active
- 4. Congenital hypothyroidism is dangerous mainly because of its effect on?**
 - a. The brain : causes mental retardation
- 5. Why do hypothyroidism patients have low serum cholesterol?**
 - a. LDL :
 - i. thyroid hormones increases the uptake of LDL into the liver via up-regulation of the receptors
 - ii. so when there are low thyroid hormones > down regulation of receptors > LDL stays in the blood
 - b. the gut fails to excrete sterol
- 6. Low levels of T₃ and T₄ will most probably do what on the pituitary-hypothalamic axis?**
 - a. increase the secretion of TSH & TRH leading to more T₃ and T₄ synthesis
- 7. What is the first line thyroid function test?**
 - a. measurement of TSH
- 8. what is the first line test for thyroid dysfunction ?**
 - a. free T₄ and TSH
- 9. What is the thyroid function test used for monitoring treatment?**
 - a. T₄ : because its faster than T₃
- 10. When is the measurement of T₃ indicated?**
 - a. Early detection of thyrotoxicosis
 - i. Extra: Because when large amounts of thyroid hormones are in the blood and they reach the target tissue , the majority will be transformed to T₃ at the target tissue and thus higher than normal levels of T₃ can indicate thyrotoxicosis very early
- 11. Can goitres (enlarged thyroid gland) be associated with hypothyroidism?**
 - a. Yes

12. What is the test for diagnoses of hypothyroidism?

- a. Elevated TSH
 - i. Because there is no T3 and T4, so no negative feedback... so high levels of TSH will be secreted

13. How do you check for neonatal hypothyroidism?

- a. TSH screening

14. What is the difference between the autoimmune diseases graves and Hashimoto's thyroiditis in the clinical symptoms?

- a. Graves disease causes **hyper**thyroidism
- b. Hashimoto's thyroiditis causes **hypo**thyroidism

15. How do you diagnose hyperthyroidism?

- a. Suppressed TSH levels : due to the high amounts of T4 & T3
- b. High thyroid hormone levels

16. What will happen to serum levels of T4 in pregnancy?

- a. In pregnancy we have more synthesis of TBG : thyroglobulin binding protein
- b. So the total level of T4 will be high , but the free T4 will be normal

17. How do thyroid hormones maintain heat (thermogenesis)?

- a. By increasing the demand of ATP to maintain the gradient across the NA/K pump
- b. And how does it increase demand? by increasing metabolism thus lowering the gradient level