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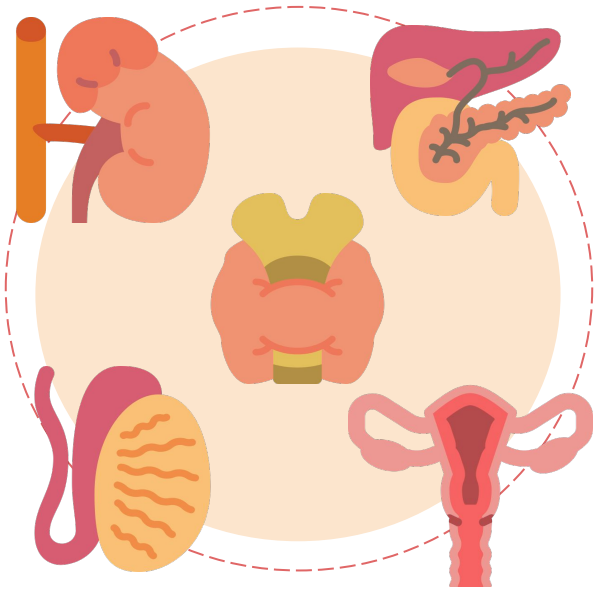

Thyroid
Hyperthyroidism & Hypothyroidism

Objectives:

- Describe the synthesis of thyroid hormones.
- Diagram the control over the thyroid gland.
- Compare between the hormones released by the thyroid gland.
- Discuss the actions of the thyroid hormones.
- Identify the terms goiter, hypo and hyperthyroidism.
- List the causes and types of goiter, hypo and hyperthyroidism.
- Discusses the clinical picture of hypo and hyperthyroidism.
- Explain the laboratory tests to diagnose hypo and hyperthyroidism.
- Outline management regimen for hypo and hyperthyroidism.

Done by :

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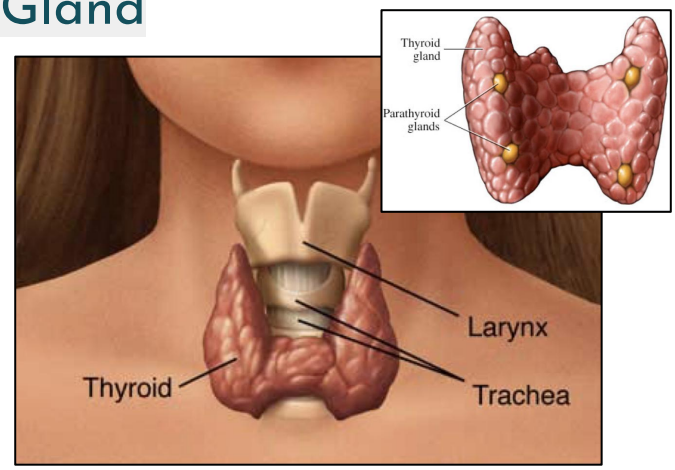
Colour index:
- Important
- Numbers
- Extra

وَأَن لَّيْسَ لِلْإِنسَانِ إِلَّا مَا سَعَىٰ

Thyroid Gland

- It is located below the larynx on either sides and anterior to the trachea.
- The first recognized endocrine gland.
- 20g in adult.



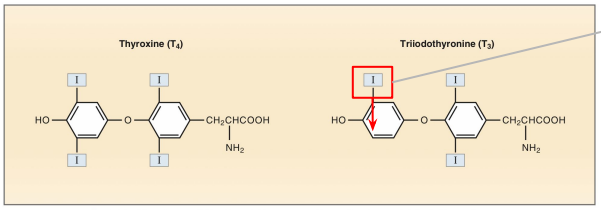
Hormones

T4
tetraiodothyronine (thyroxine)
90%.

T3
(Triiodothyronine)
10%.
"but it's more active than T4"

Reverse T3
Inactive

Calcitonin



If we move iodine ion to the other side, we will get reverse T3 which is inactive.
Why don't we have reverse T4?
Because the rings are fully occupied by iodine ions.

Synthesis

*Colloid stores the hormone.
*Parafollicular cells secretes calcitonin.
Follicular cells synthesize T3 and T4.

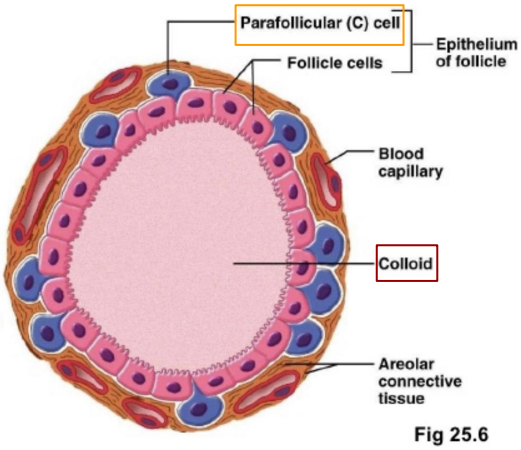
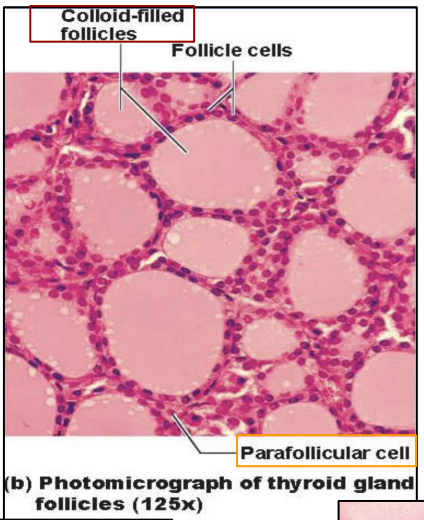
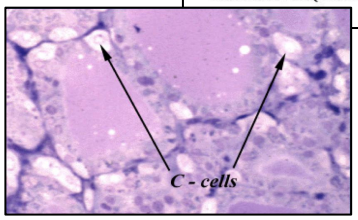


Fig 25.6

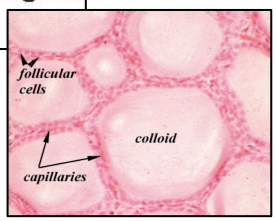


(b) Photomicrograph of thyroid gland follicles (125x)

Calcitonin



T3 , T4



* In = out

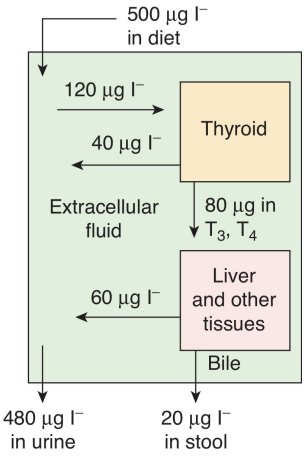


FIGURE 19–5 Iodine metabolism. The figure shows the movement of iodide amongst various body compartments on a daily basis.

Three unique features

1- Contains a large amount of iodine.*
- supplied in diet, 1mg/week.

No iodine, no thyroid hormones.

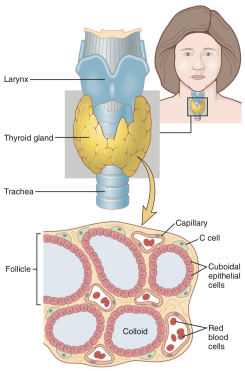
2- Synthesis is partially intracellular *inside the follicular cells* **and partially extracellular***inside the colloid***.**

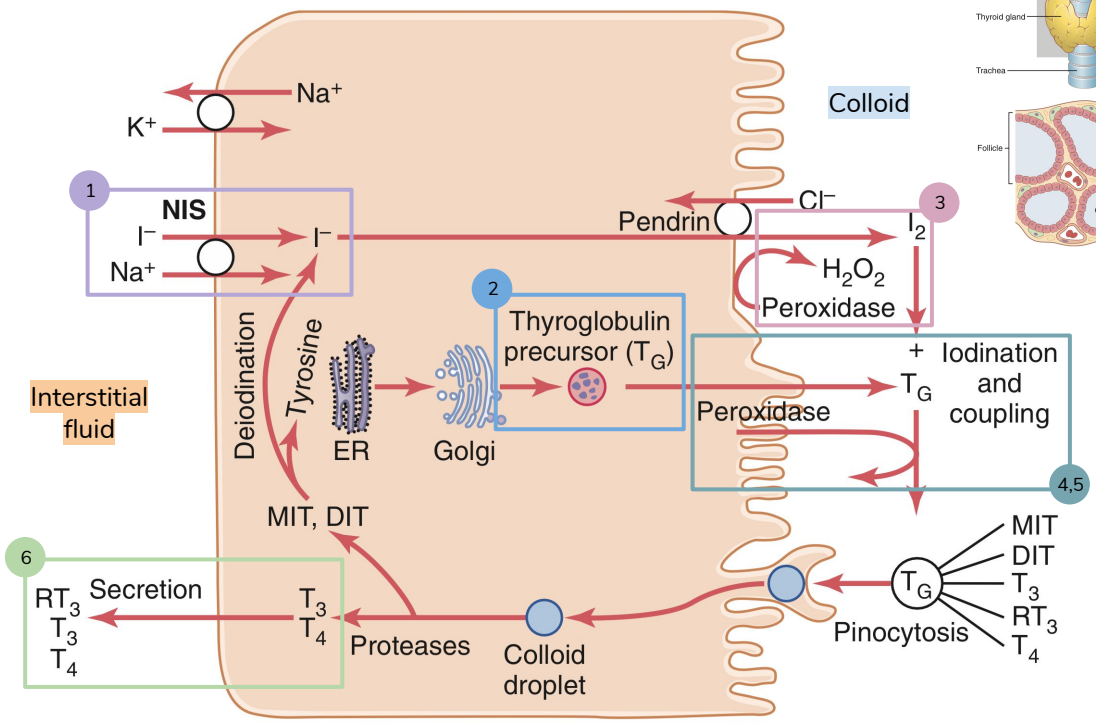
3- T4 is the major product.

Thyroid Hormones [T3 - T4]

Biosynthesis (by the follicular cells):

1. **Iodide pump/ trap** (NIS)
2. **Thyroglobulin synthesis**.
3. **Oxidation** of iodide to iodine.
4. **Iodination** of tyrosine, to form
   - **Mono-iodotyrosine (MIT)**
   - **Di-iodotyrosine (DIT)**
5. **Coupling**;
   - MIT + DIT = Tri-iodothyronine, (T3).
   - DIT + DIT = Tetra-iodothyronine, (T4)/ Thyroxine.
6. **Release**.





Steps in Biosynthesis:

1 Thyroglobulin formation and transport:

- Glycoprotein.
- Tyrosine.
- Rough endoplasmic reticulum and Golgi apparatus.

2 Iodide pump or iodide trap:

It is active transport because the concentration of iodine in the thyroid is greater than in blood vessels.
Wolff-chaikoff effect:
Briefly, if iodine conc. in the blood is low, the body will increase the uptake of iodine by increasing effect of iodine pump and vice versa.

- Active transport. "Na/I cotransporter"
- It is stimulated by TSH.
- Wolff-chaikoff effect
  - (A reduction in thyroid hormone levels caused by administration of a large amount of iodine).
- Ratio of concentration from 30-250 times.

¥ decrease
^ increase

Wolff-chaikoff effect
^ iodine conc. > ¥ effect of iodine pump > ¥ iodine uptake
¥ iodine conc. > ^ effect of iodine pump > ^ iodine uptake

3 Oxidation of iodide to iodine:

- Thyroid peroxidase.
  - It is located in or attached to the apical membrane.

4 Organification of thyroglobulin:

- Binding of iodine with thyroglobulin.
- Catalyzed by thyroid peroxidase, to form MIT/DIT
- Remain attached to thyroglobulin until the gland stimulated to secrete.

5 Coupling reaction:

DIT + DIT → T4 (faster)
DIT + MIT → T3

- Catalyzed by thyroid peroxidase.
- It is stored as colloid.
- Is sufficient for 2-3 months. So, if the patient has any problem the symptoms won't appears immediately, it takes time.

6 Endocytosis of thyroglobulin.

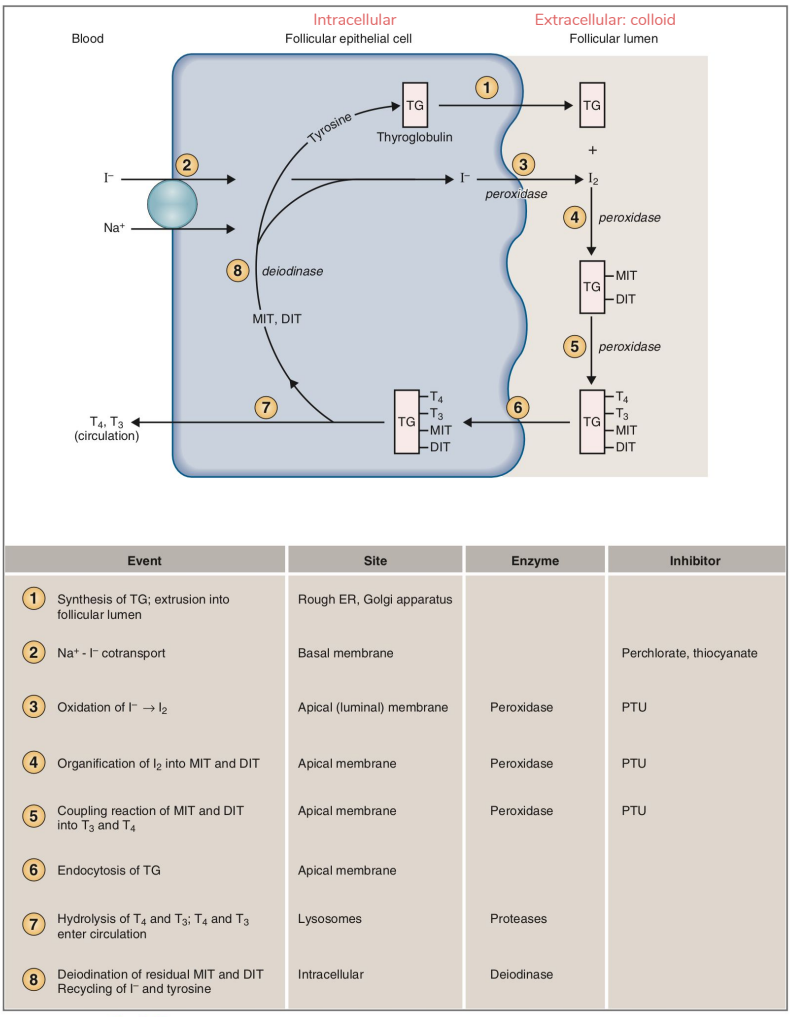
By taking them from colloid to inside the follicular cells.

7 Fusion of lysosomes immediately with the vesicles.

8 Hydrolysis of the peptide bond to release DIT+MIT+T4+T3 from the thyroglobulin.

9 Delivery of T4 and T3 to the systemic circulation.

10 Deiodination of DIT and MIT by thyroid deiodinase (recycling).



Event	Site	Enzyme	Inhibitor
1 Synthesis of TG; extrusion into follicular lumen	Rough ER, Golgi apparatus		
2 Na^+ - I^- cotransport	Basal membrane		Perchlorate, thiocyanate
3 Oxidation of $I^- \rightarrow I_2$	Apical (luminal) membrane	Peroxidase	PTU
4 Organification of I_2 into MIT and DIT	Apical membrane	Peroxidase	PTU
5 Coupling reaction of MIT and DIT into T_3 and T_4	Apical membrane	Peroxidase	PTU
6 Endocytosis of TG	Apical membrane		
7 Hydrolysis of T_4 and T_3; T_4 and T_3 enter circulation	Lysosomes	Proteases	
8 Deiodination of residual MIT and DIT Recycling of I^- and tyrosine	Intracellular	Deiodinase	

Fig. 9.18 **Steps involved in the synthesis of thyroid hormones in thyroid follicular cells.** Also see the text for an explanation of the circled numbers. *DIT,* Diiodotyrosine; *ER,* endoplasmic reticulum; *MIT,* monoiodotyrosine; *PTU,* propylthiouracil; T_3, triiodothyronine; T_4, thyroxine; *TG,* thyroglobulin.

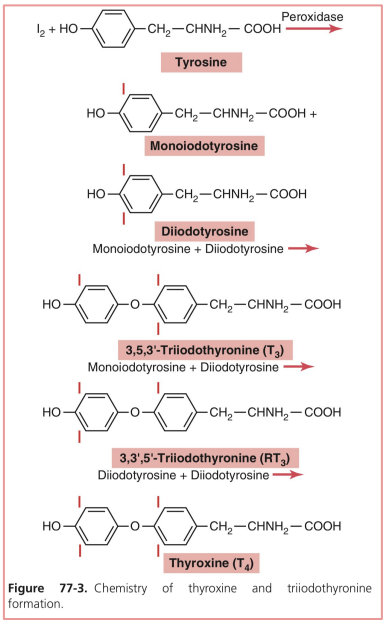


Figure 77-3. Chemistry of thyroxine and triiodothyronine formation.

Thyroid Hormones in The Circulation:

Bound

- 70- 80% bound to thyroxine-binding globulin (TBG) synthesized in the liver.
- The reminder is bound to albumin.

Unbound

"Free" "active form"

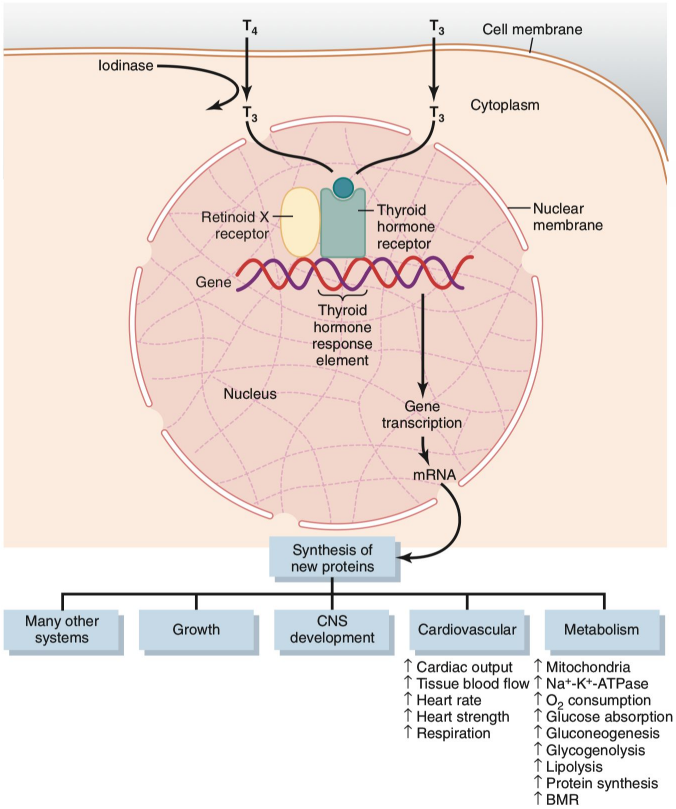
- 0.03% of T4
- 0.3% of T3

In hepatic failure:
↓TBG → ↑free T3/T4 → inhibition of thyroid secretion.

Feedback mechanism

In pregnancy:
↑Estrogen → ↑TBG → ↓free T3/T4 → stimulation of thyroid secretion.

Release of T4 and T3 to The Tissue



1. **The release is slow because of the high affinity of the plasma binding proteins.**
   - **½** of T4 in the blood is released every **6** days.
   - **½** of T3 in the blood is released every **one** day.

2. **T4 & T3 readily diffuse through the cell membrane.**

3. **Stored in the targeted tissues (days to weeks).**

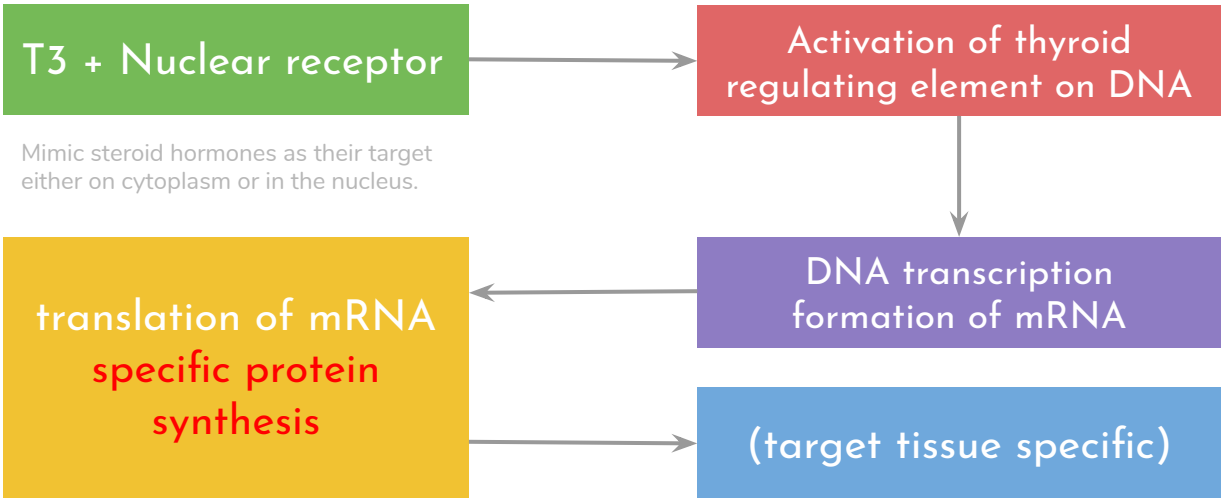
4. **Most of T4 is deionized to T3 by iodinase enzyme.** At tissue level

5. **In the nucleus, T3 mainly binds to "thyroid hormone receptor" and influence transcription of genes.**

Action of Thyroid Hormones

- Before binding to the nuclear receptors 90% of T4 is converted to T3.

How ? Doctor nervana said read it



Action of Thyroid Hormones

Basal Metabolic Rate (BMR):		• Is the energy requirement under basal condition. (mental and physical rest 12-18 hours after a meal). • Complete lack of thyroid hormones. (40-50% decrease in BMR). • Extreme increase of thyroid hormones. (60-100% increase in BMR).
Metabolism (The aim is to increase expression of glucose to the cells, so that it can be utilized and used in energy production)	**Effects on <u>carbohydrate</u> metabolism**	**1-** increase glucose uptake by the cells. **2-** increase glycogenolysis. **3-** increase gluconeogenesis. **4-** increase absorption from the GIT.
	Effects on <u>fat</u> metabolism	**1-** Increase lipolysis. **2-** decrease plasma cholesterol by increase loss in feces. Because GI motility increases. Lead to diarrhea and steatorrhea. **3-** Increase oxidation of free fatty acids.
	Effect on <u>protein</u> metabolism	overall effect is catabolic leading to decrease in muscle mass. Thin patients.
	The metabolic effects are due to induction of metabolic enzymes: Dr nervana said read it	**1-** Cytochrome oxidase. **2-** NADPH cytochrome C reductase. **3-** Alpha- glycerophosphate dehydrogenase. **4-** Malic enzymes. **5-** Several proteolytic enzymes

Action of Thyroid Hormones

CNS

Perinatal period

- Thyroid hormones are essential for maturation of the CNS.
- decrease of hormones secretion
  ↓
- Irreversible mental retardation
- Screening is necessary to introduce hormone replacement.

In adult

- **Increase in thyroid hormone secretion:**

1-hyperexcitability.
2- irritability.

- **Decrease in thyroid hormones secretion:**

1- slow movement.
2- impaired memory.
3- decrease mental capacity.

Cardiovascular system

Because of increasing demand by the cells, the body compensate by increasing cardiac output to deliver more oxygenated blood.

- Increase heart rate & stroke volume. → Cardiac output up to 60%
- Decrease peripheral resistance. *peripheral vasodilation*
- End result is **increase** delivery of oxygenated blood to the tissues.

The cardiovascular effects are due to:
1- Thyroid hormones potentiate the effect of catecholamine in the circulation leads to activation of β-adrenergic receptors.
2- Direct induction of:
a) myocardial β-adrenergic receptors.
b) sarcoplasmic reticulum. To increase calcium source.
c) Ca+2 ATPase. That return Calcium to sarcoplasmic reticulum.
d) myosine.

Action of Thyroid Hormones

Effects on bone:

Potentiate effect of growth hormone."Permissiveness"

a) promote bone formation.

b) promote ossification.

c) promote fusion of boneplate.

d) promote bone maturation.

Effects on Respiration:

1- increase ventilation rate.

2- increase dissociation of oxygen from Hb by increasing RBC 2,3-DPG (2,3 diphosphoglycerate)."Increasing unloading of oxygen by shifting the curve to the right"

Effects on the GIT:

1- increase appetite and food intake.

2- increase of digestive juices secretion.

3- increase of G.I tract motility.

excess secretion ⟶ diarrhea.

Lack of secretion ⟶ constipation.

Effects on Autonomic nervous system:

Produced the same action as catecholamines via

β-adrenergic receptors including:

a) increase BMR.

b) increase heat production.

c) increase heart rate.

d) increase stroke volume.

i.e. β-blocker (propranolol) is used in treatment of hyperthyroidism.

Summary

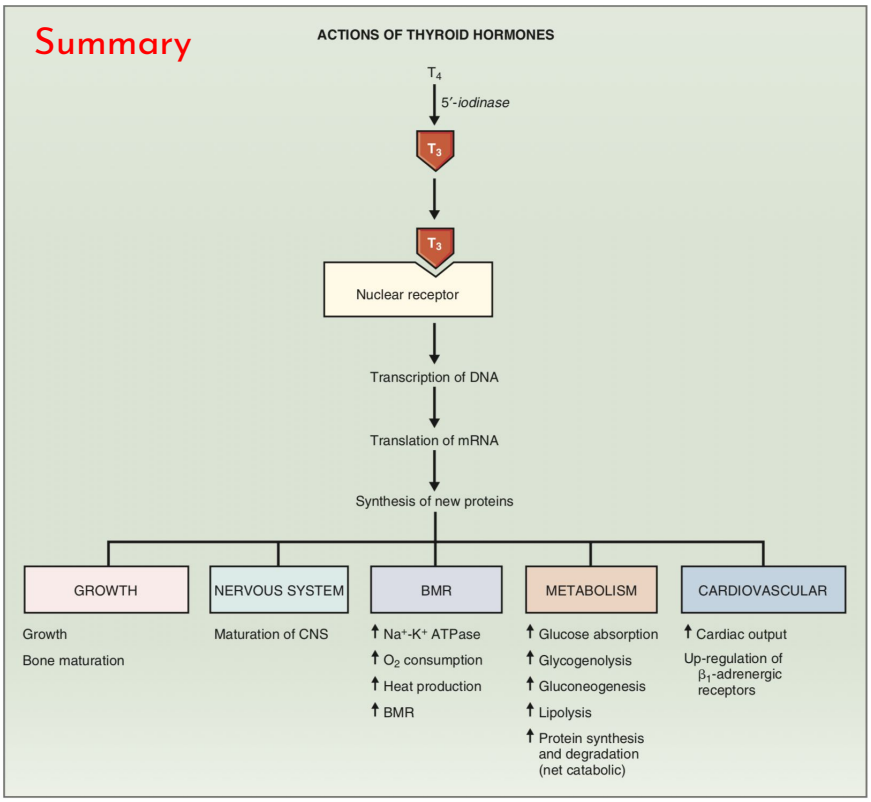
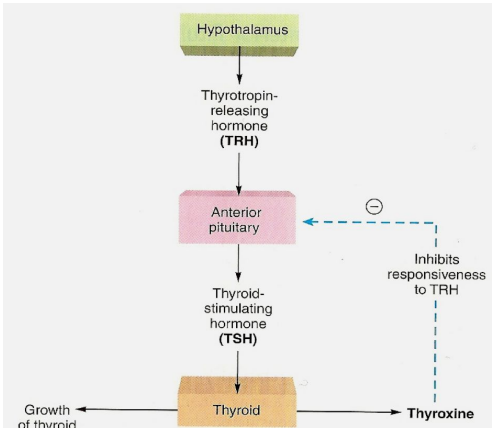


Fig. 9.20 **Mechanism of action of thyroid hormones.** Thyroxine (T_4) is converted to triiodothyronine (T_3) in target tissues. The actions of T_3 on several organ systems are shown. *BMR*, Basal metabolic rate; *CNS*, central nervous system; *DNA*, deoxyribonucleic acid; *mRNA*, messenger ribonucleic acid.

REGULATION OF HORMONES SECRETION

It is regulated by the hypothalamic-pituitary axis.



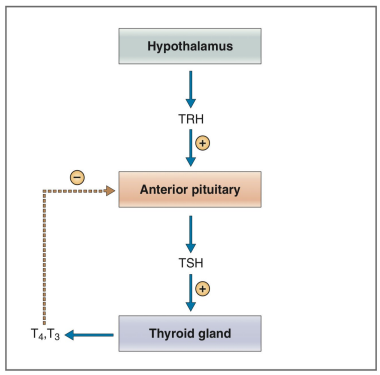


Fig. 9.19 Regulation of thyroid hormone secretion. T_3, Triiodothyronine; T_4, thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone.

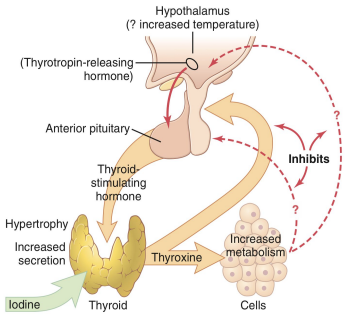
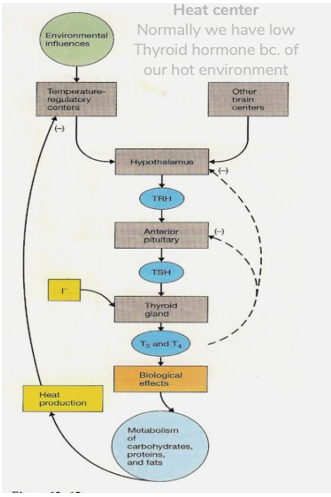


Figure 77-7. Regulation of thyroid secretion.



1- Thyrotropin-releasing hormone (TRH):

- Tripeptide.
- Paraventricular nuclei of the hypothalamus.
- Act on the thyrotrophs of the anterior pituitary.
- Transcription and secretion of TSH.
- Phospholipid second messenger system.

2- Thyroid-stimulating hormone (TSH):

- Glycoprotein.
- Anterior pituitary.
- Regulate metabolism , secretion and growth of thyroid gland (trophic effect)
- TSH secretion started at 11-12 of gestational weeks.
- **TSH + receptor** ⟶ activation of adenylyl cyclase via Gs protein ⟶ cAMP activation of protein kinase ⟶ multiple phosphorylation ⟶ **secretion and thyroid growth.** Dr nervana said just read its involved in biochem

Action of TSH:

1. Increase proteolysis of the thyroglobulin.
2. Increase pump activity.
3. Increase iodination of tyrosine.
4. Increase coupling reaction.
5. **Trophic effect.**

TABLE 9.8 Factors Affecting Thyroid Hormone Secretion

Stimulatory Factors	Inhibitory Factors
TSH	I^- deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I^- intake (Wolff-Chaikoff effect)
	Perchlorate, thiocyanate (inhibit Na^+-I^- cotransport)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

TBG, Thyroxine-binding globulin; *TSH*, thyroid-stimulating hormone.

Increase apetite

تيمونك الدكتور: تجيك وحدة مخففه ملابسها جالسه على طاولة الأكل ورايحة وجايه على دورة المياة

diarrhea

Heat intolerance + weight loss

Common in female

Hyperthyroidism

Thyroid Diseases can be described in terms of function (Euthyroid, hypothyroid & hyperthyroid), size (enlarged = goiter). Goiter can be Eu,hypo or hyper.

Overactivity of the thyroid gland.

Female : Male ratio **8 : 1**.

Activity of the gland:

- **5-10 times** increase in **secretion**.
- **2-3 times** increase in **size**.

Causes

Graves' Disease:

- **Autoimmune** disorder
- Increased circulating level of **T**hyroid **S**timulating **I**mmunoglobulins **(TSI)**
- 95%
- 4-8 times more common in female than male

Thyroid gland tumor:

- 95% is benign
- History of head and neck irradiation.
- Family history
- Common in breast cancer patients who had radiation therapy

Exogenous T3 & T4:

- Rare cause
- Ingestion of excessive amount of thyroid hormone

Excess TSH secretion:

- Disease of the **Hypothalamus (TRH)**
- Disease of the **Pituitary (TSH)**

Diagnosis

Goiter in 95%

Skin:

- Smooth, warm and moist.
- Heat intolerance, night sweating

Musculoskeletal:

- Muscle atrophy.

Neurological:

- Tremors.
- Enhanced reflexes.
- Irritability.

Cardiovascular:

- Increase heart rate.
- Increase stroke volume.
- Arrhythmias.
- Hypertension.

G.I tract:

- Weight loss.
- Diarrhea. -Increased appetite

Exophthalmos:

- Anxious staring expression.
- Protrusion of eyeballs.

Exophthalmos

Others:

- Menstrual cycle disturbance.
- Increased glomerular filtration rate.

Investigations

Serum T3, T4 ,TSH measurement.

Serum T3, T4 are High

- TSH is Low in **primary** hyperthyroidism
- TSH is Elevated in **secondary** hyperthyroidism

Treatment

Medical therapy:

- With 3-4 monthly monitoring

Surgery:

- Subtotal thyroidectomy

Indication for surgery:

A) Relapse after medical treatment.
B) Drug intolerance.
C) Cosmetic.
D) Suspected malignancy.

Hypothyroidism

Loss of apetite — Mimic depression

نيمونك الدكتور: تجيك وحدة سمينة لابسه كل ملابس الدولاب منسدحه على الكنب والاكل قدامها ما انوكل

- **Under activity** of the thyroid gland.
- More common in females (30-60 years old)

Cold intolerance — Weight gain — Common in female

Causes

Inherited abnormalities of thyroid hormone synthesis:

- Peroxidase defect.
- Iodide trapping defect.
- Thyroglobulin defect.

Endemic Colloid Goiter: (Before table salt)

↓Iodide →↓Hormone formation→ ↑TSH→↑Thyroglobulin→↑Size (>10 times)

Idiopathic Nontoxic Colloid Goiter:

- Iodine intake is normal

Inflammation →↑Cell damage →↓Hormone secretion→↑TSH→↑Activity of normal cells→↑Size

Gland Destruction (Surgery).

Pituitary diseases or tumors.

Hypothalamus diseases or tumors.

Diagnosis

Skin:

- Dry skin.
- Cold intolerance.

Musculoskeletal:

- ↑Muscle bulk.
- ↓Skeletal growth.
- Muscle sluggishness. - hyporeflexia - stiffness All over

Neurological:

- Slow movement.
- Impaired memory.
- Decrease mental capacity. - dull

Cardiovascular:

- ↓Heart rate.
- ↓Stroke volume.

- Miniature ECG (small amputated)

G.I Tract:

- Constipation
- Increased weight

- Decreased appetite

Myxoedema:
An edematous appearance throughout the body

Others:

- Loss of libido
- Menstrual cycle disturbance
- Decrease glomerular filtration rate.

Investigations

Serum T3, T4 are low

- TSH is elevated in **primary** hypothyroidism
- TSH is low in **secondary** hypothyroidism

Treatment

L-Thyroxine

- Starting dose is 25-50µg
- 2-4 weeks period.

First response seen is weight loss.

- gradual increase in dose is important

TABLE 9.9 Pathophysiology of Thyroid Hormones

	Hyperthyroidism	Hypothyroidism
Symptoms	Increased basal metabolic rate Weight loss Negative nitrogen balance Increased heat production Sweating Increased cardiac output Dyspnea (shortness of breath) Tremor, muscle weakness Exophthalmos Goiter	Decreased basal metabolic rate Weight gain Positive nitrogen balance Decreased heat production Cold sensitivity Decreased cardiac output Hypoventilation Lethargy, mental slowness Drooping eyelids Myxedema Growth retardation Mental retardation (perinatal) Goiter
Causes	Graves disease (increased thyroid-stimulating immunoglobulins) Thyroid neoplasm Excess TSH secretion Exogenous T_3 or T_4 (factitious)	Thyroiditis (autoimmune or Hashimoto thyroiditis) Surgery for hyperthyroidism I^- deficiency Congenital (cretinism) Decreased TRH or TSH
TSH Levels	Decreased (feedback inhibition of T_3 on the anterior lobe) Increased (if defect is in anterior pituitary)	Increased (by negative feedback if primary defect is in thyroid gland) Decreased (if defect is in hypothalamus or anterior pituitary)
Treatment	Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis) Thyroidectomy $^{131}I^-$ (destroys thyroid) β-Adrenergic blocking agents (adjunct therapy)	Thyroid hormone replacement therapy

TRH, Thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone.

Cretinism

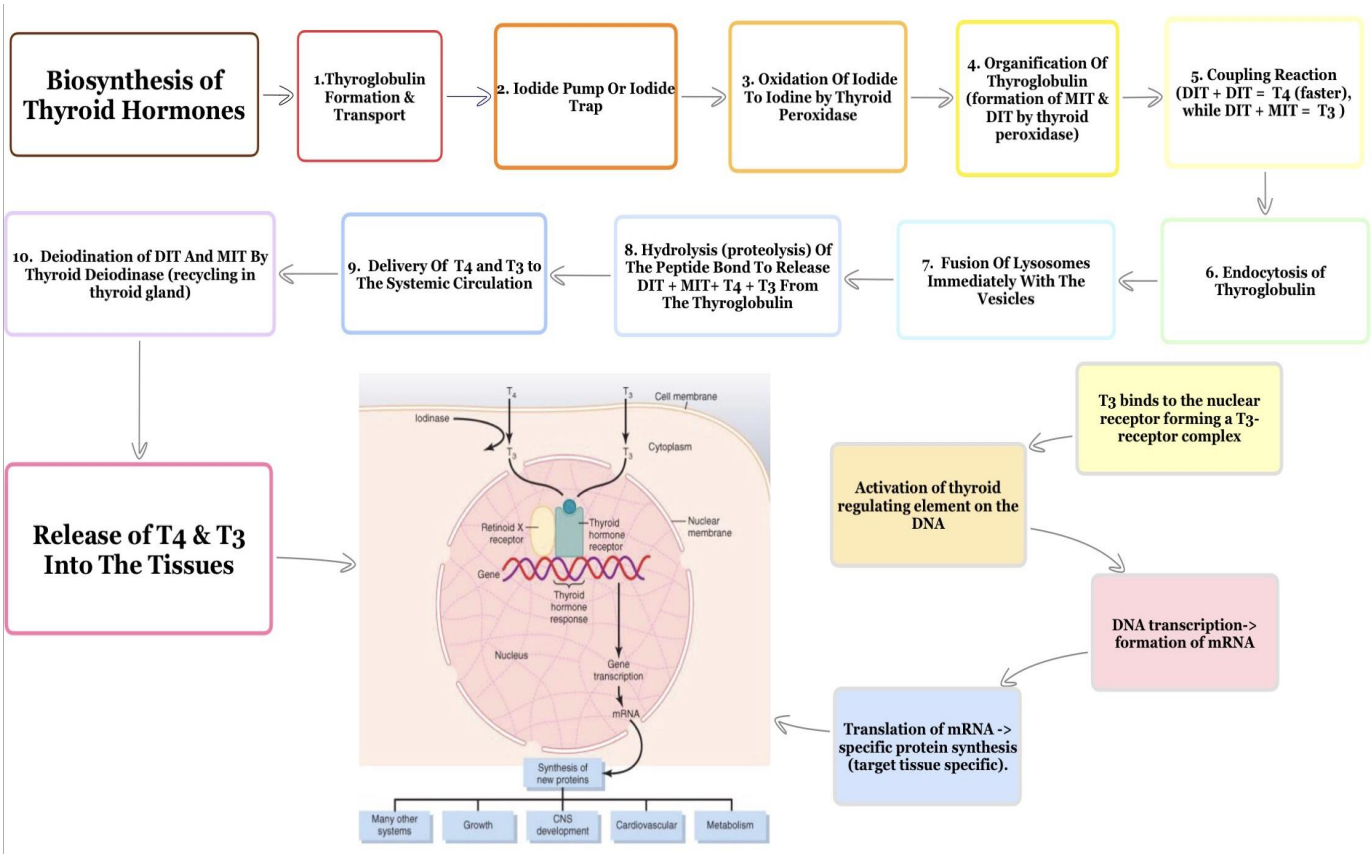
- Extreme hypothyroidism during infancy and childhood **(failure of growth)**.

Causes	1) Congenital lack of thyroid gland (Congenital Cretinism). 2) Genetic deficiency leading to failure to produce hormone. 3) Lack of Iodine in the diet (Endemic Cretinism)
Symptoms	1. Infant is normal at birth but abnormality appears within weeks. 2. Protruding tongue. 3. Dwarf with short limbs. 4. Mental retardation. 5. Often presents with umbilical hernia. 6. Delayed eruption of teeth.  
Treatment	• Changes are **irreversible** unless treatment is given early.

Summary

Hormones	TH in circulation	TH Actions
★ T_4 + T_3 (by follicular cells) ★ rT3 ★ Calcitonin (by parafollicular cells)	• Unbound (small amount, activated) • Bound(high amount, bound to TGB)	★ **Increase** in: ANS , Respiration , carbohydrate anabolism , lipid and protein catabolism , cardiac output , GIT appetite and digestion , bone growth ★ **CNS**: Decrease in fetal life cause mental retardation, in adults it causes slow movement and memory ★ **BMR**: Loss of TH-> low BMR High TH -> high BMR

Enzymes and stimulation	Liver and pregnancy
• **TSH** - active transport of iodide • **Thyroid peroxidase** - oxidation of iodide to iodine, iodination thyroglobulin and coupling of DIT and MIT • **Thyroid deiodinase**- deiodination of DIT and MIT • **5-Iodinase enzyme**- deionization of T4 to T3	• Decrease TBG-> increase of free T3 and T4 -> Inhibition of thyroid secretion. • Increase in estrogen levels-> Increase in TGB ->Decrease in free levels of T3 & T4 -> stimulation of thyroid secretions



MCQs

Q1: Which of the following physiological responses is greater for triiodothyronine (T3) than for thyroxine (T4)?

A) Secretion rate from the thyroid
B) Plasma concentration
C) Plasma half-life
D) Affinity for nuclear receptors in target tissues

Q2: A patient is administered sufficient thyroxine (T4) to increase plasma levels of the hormone several-fold. Which of the following sets of changes is most likely in this patient after several weeks of T4 administration?

A) Increased respiratory rate, heart rate and plasma cholesterol conc.
B) Increased respiratory rate, heart rate and decreased plasma cholesterol conc.
C) Increased respiratory rate, plasma cholesterol conc and decreased heart rate.
D) Decreased respiratory rate, heart rate and increased plasma cholesterol conc.

Q3: the effect of liver disease on thyroid hormones is:

A) Decreased free hormones, stimulated thyroid secretion.
B) Increased free hormones, stimulated thyroid secretion
C) Increased free hormones, inhibited thyroid secretion.
D) Increased bound hormones, inhibited thyroid secretion.

Q4: The enzyme Thyroid Peroxidase contributes in which step in thyroid hormones synthesis:

A) Deiodination of DIT and MIT
B) Coupling reaction
C) Iodide pump
D) Thyroglobulin formation

Q5) Perchlorate mechanism is:

A) Inhibition of Na/I cotransport
B) Inhibition of peroxidase enzyme
C) Stimulates thyroid secretion
D) Decrease TBG levels

Answers
Q1: D
Q2: B
Q3: C
Q4: B
Q5: A

MCQs

1/ Inhibition of the iodide pump would be expected to cause which change?

A) Increased synthesis of T4
B) Increased synthesis of thyroglobulin
C) Increased metabolic rate
D) Decreased TSH secretion

2/ A patient has a goiter associated with high plasma levels of both TRH and TSH. Her heart rate is elevated. this patient most likely has which condition?

A) An endemic goiter
B) A hypothalamic tumor secreting large amounts of TRH
C) A pituitary tumor secreting large amounts of TSH
D) Graves' disease

3/ A 46-year-old man has "puffy" skin and is lethargic. His plasma TSH concentration is low and increases markedly when he is given TRH. What is the most likely diagnosis?

A) Hypothyroidism due to an abnormality in the hypothalamus
B) Hyperthyroidism due to an abnormality in the hypothalamus
C) Hyperthyroidism due to a thyroid tumor
D) Hypothyroidism due to an abnormality in the pituitary

4/ Which symptom would least likely be associated with thyrotoxicosis?

A) Tachycardia
B) Increased appetite
C) Somnolence
D) Increased sweating

5/ A patient presents with tachycardia and heat intolerance. You suspect Graves' disease. Which of the following is not consistent with your diagnosis?

A) Increased total and free T4
B) Suppressed plasma [TSH]
C) Exophthalmos
D) Decreased thyroid radioactive iodine uptake

6/ A 37-year-old woman presents to her physician with an enlarged thyroid gland and high plasma levels of T4 and T3. Which of the following is likely to be decreased?

A) Heart rate
B) Cardiac output
C) Peripheral vascular resistance
D) Metabolic rate

Answers

1- B.
2- B.
3- A.
4- C.
5- D.
6- C.