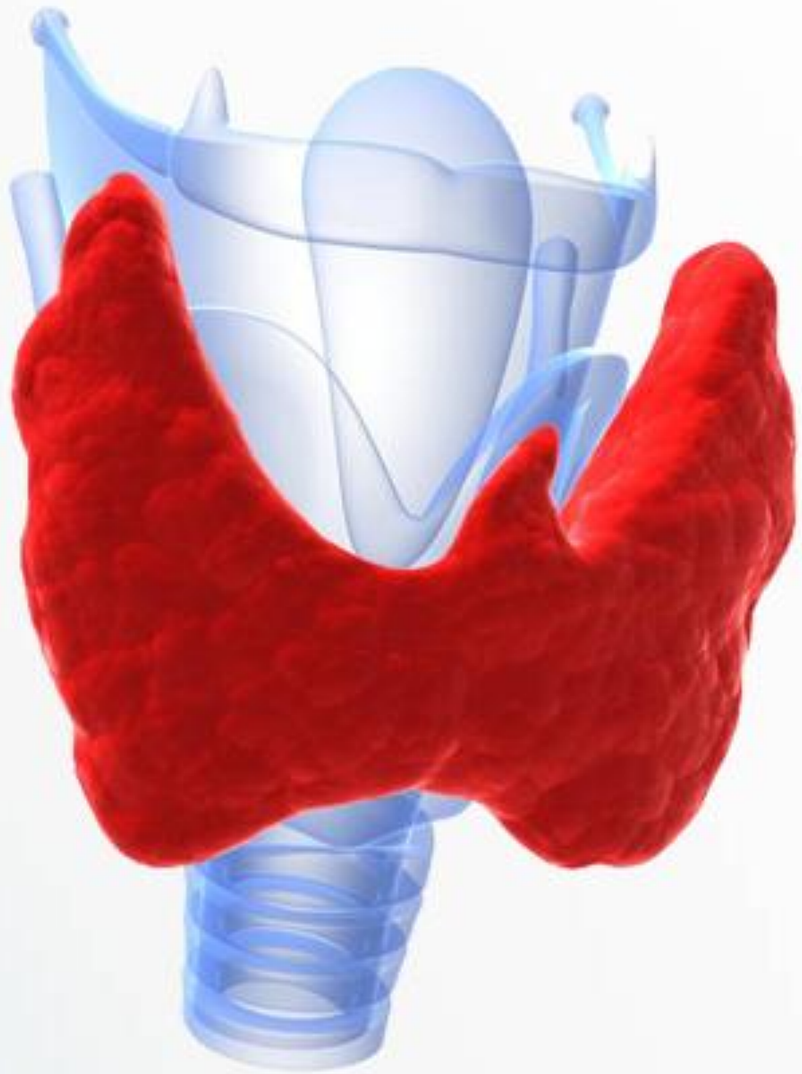
Physiology team



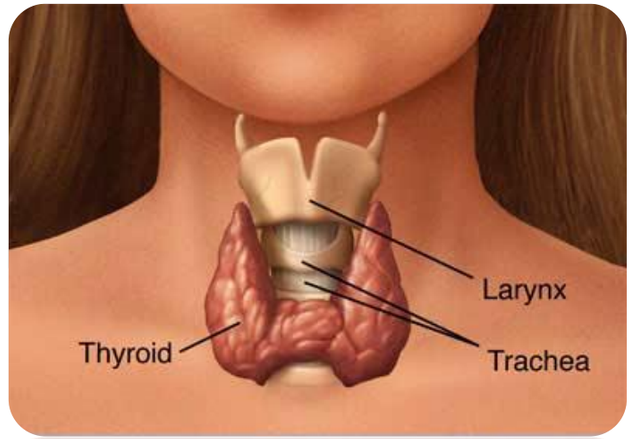
6 Thyroid Gland

Sources:
Female slides
BRS physiology

MED 433 Teams

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 :

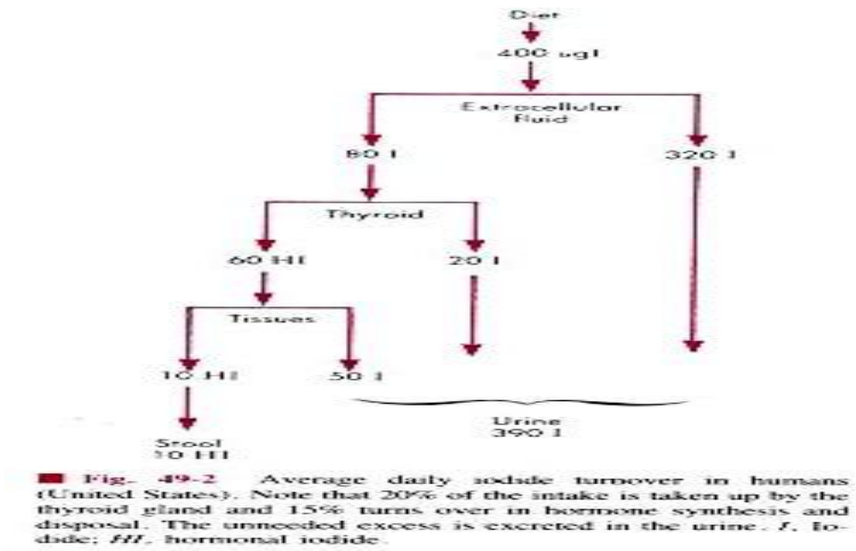
- **T4 (tetraiodothyronine) (thyroxine) 90%.**
- **T3 (Triiodothyronine)10%.**
- **Reverse T3.** (inactive form of T3 that produced as by product)
- **Calcitonin.**

Synthesis :

Follicular cells =T3 & T4 .
Para follicular cells = calcitonin .

Three unique features :-

1- Contains a large amount of iodine. (1mg/week - supplied in diet).
2- Synthesis is partially intracellular and partially extracellular.
3- T4 is the major product.
4- T3 is the most active form.



■ Fig. 49-2 Average daily iodide turnover in humans (United States). Note that 20% of the intake is taken up by the thyroid gland and 15% turns over in hormone synthesis and disposal. The unneeded excess is excreted in the urine. *I*, Iodide; *HI*, hormonal iodide.

Iodide intake equal to iodide excreted

Thyroid Hormones [T3 - T4]

Biosynthesis: by the follicular cells .

1- Thyroglobulin synthesis.

2-Iodide pump.

3- Oxidation of iodide to iodine.

4- Iodination of tyrosine, to form mono-iodotyrosine (MIT)

& di-iodotyrosine (DIT).

5- Coupling;

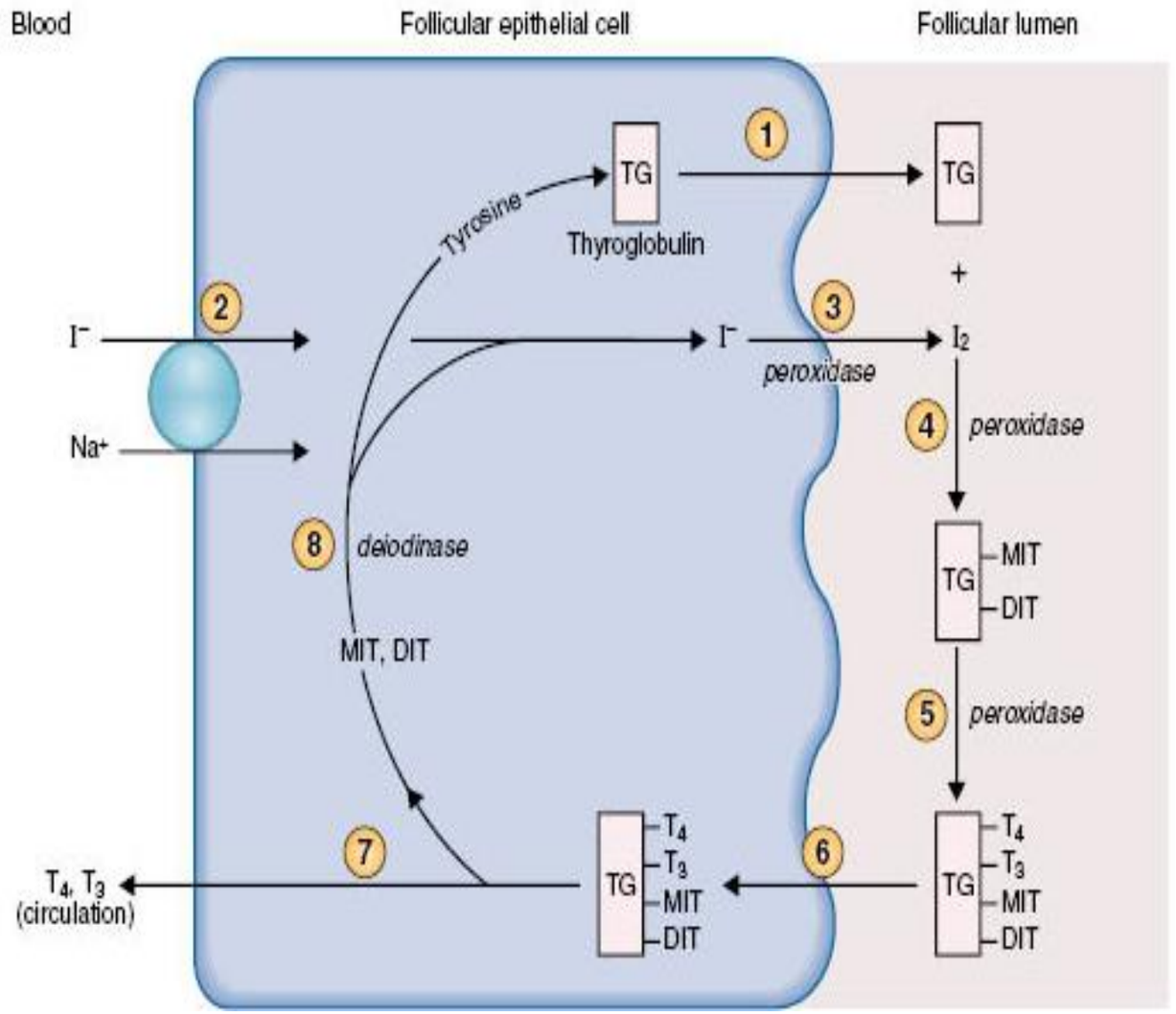
MIT + DIT = Tri-iodothyronine, (T3).

DIT + DIT = Tetra-iodothyronine, (T4)/ Thyroxine.

6- Endocytosis of thyroglobulin.

7- Hydrolysis, Release of T3 and T4

8-Recycling of MIT and DIT



Steps in biosynthesis :-

1- Thyroglobulin formation and transport:

- Glycoprotein.
- Combined of 140 Tyrosine that happened in Rough endoplasmic reticulum and Golgi apparatus.

2- Iodide pump or iodide trap:

- Active transport (because the concentration in thyroid is more than in blood)
- It is stimulated by TSH.
- Wolff-chaikoff effect
  - Reduction in thyroid hormone levels caused by administration of a large amount of iodine
  - Increase in thyroid hormone levels caused by administration of a low amount of iodine
- Ratio of concentration from 30-250 times in thyroid gland than blood

3- Oxidation of iodide to iodine : :

BY Thyroid peroxidase.

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

4- Organification (iodination) of thyroglobulin :

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

*MIT: mono iodo tyrosine

*DIT: di iodo tyrosine

5- COUPLING REACTION:

DIT + DIT ⟶ T4 (faster)

DIT + MIT ⟶ T3

- Catalyzed by thyroid peroxidase.

- It is stored as colloid in lumen.

- Is sufficient for 2-3 months.

6- Endocytosis of thyroglobulin to intracellular.

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	

Propylthiouracil (PTU): A drug that blocks the production of thyroid hormone By the thyroid gland. PTU is used to treat hyperthyroidism

Thyroid hormones in the circulation :-

1- Bound: Inactive

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

2- Unbound (Free): Active

0.03% of T4

0.3% of T3.

In hepatic failure:

TBG ↓, free T3/T4 ↑

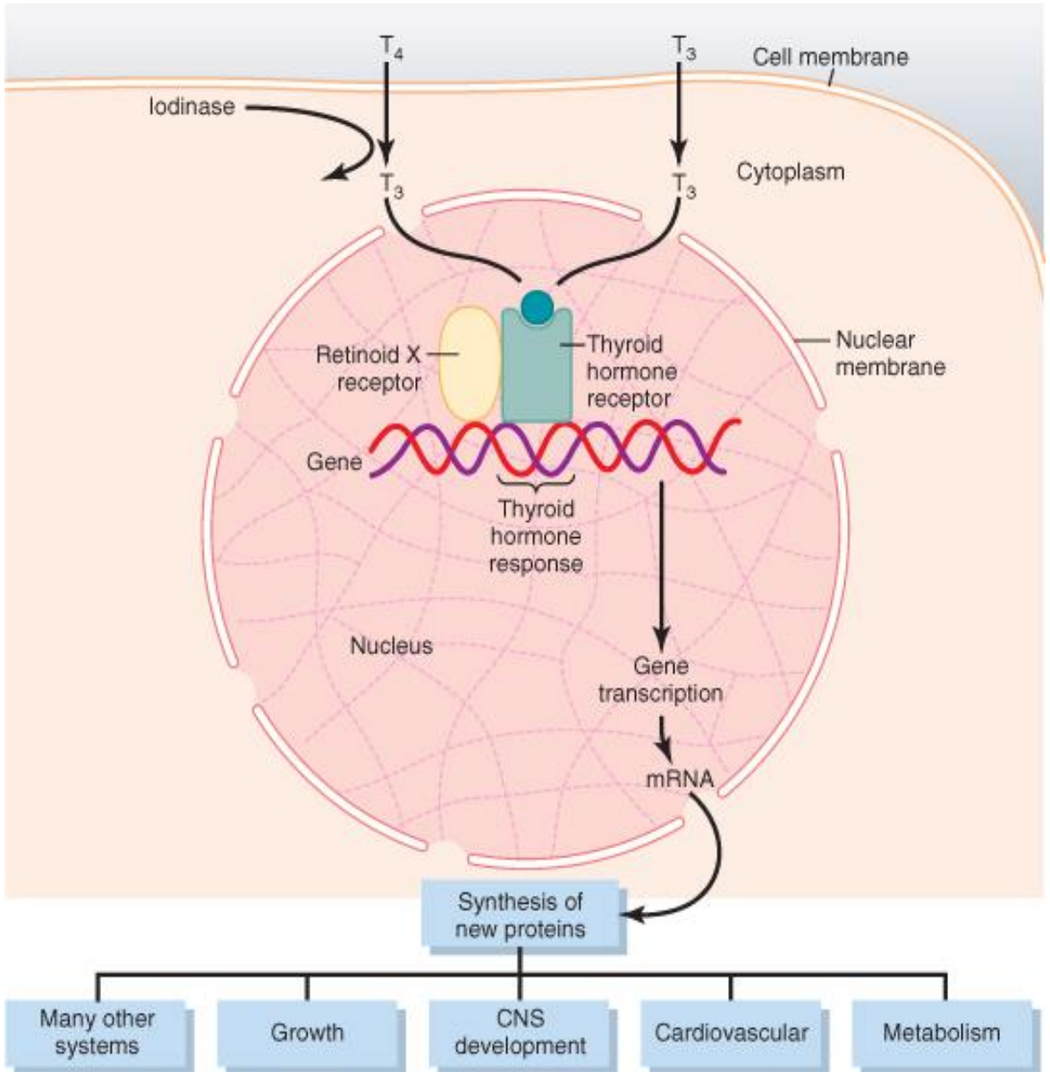
⟶ inhibition of thyroid secretion.

In pregnancy:

estrogen ↑, TBG ↑, freeT3/T4 ↓

⟶ stimulation of thyroid secretion.

Release of t4 and t3 to the tissues:-



RELEASE OF T4&T3 TO THE TISSUES

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. T3 is in blood is much smaller amounts but, is 4 times as potent as T4.

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.

T3 + nuclear receptor

↓

activation of thyroid regulating element on DNA

↓

↑DNA transcription formation of mRNA

↓

translation of mRNA specific *protein synthesis*

↓

target tissue specific

ACTION OF THYROID HORMONES

Metabolism

A) Effect on carbohydrate:

Increase:

-Glucose uptake by the cells.

-Glycogenolysis.

-Gluconeogenesis.

-Absorption from the GIT.

B) Effects on fat metabolism:

-Increase lipolysis & oxidation of free fatty acids.

-Decrease cholesterol by increase loss in feces.

C) Effect on protein metabolism:

overall effect is catabolic leading to decrease in muscle mass.

The metabolic effects are due to the induction of metabolic enzymes:

1-Cytochrome oxidase.

2-NAPDH cytochrome C reductase.

3- Alpha glycerophosphate dehydrogenase.

4- malic enzymes.

5- several proteolytic enzymes.

CVS

-Increase heart rate & stroke volume (increase cardiac output up to 60%).

-Decrease peripheral resistance.

= The end result is increase delivery of oxygenated blood to the tissues.

CVS effects are due to:

1- Thyroid hormones potentiate the effect of *catecholamine* in the circulation ⟶ activation of β-adrenergic receptors.

2- Direct induction of:

a) myocardial β-adrenergic receptors.

b) sarcoplasmic reticulum.

c) Ca+2 ATPase.

d) myosine.

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% in BMR.

- Extreme increase of thyroid hormones ↑ 60-100% in BMR.

Bone

promote:

- Bone formation.
- Ossification.
- Fusion of bone plate.
- Bone maturation.

ACTION OF THYROID HORMONES cont.

CNS

A) Peri-natal period:

-Thyroid hormones are essential for maturation of the CNS.

-decrease of hormones secretion lead to irreversible mental retardation.

-Screening is necessary to introduce hormone replacement.

B) In adult:

Increase in thyroid hormone secretion:

1-hyperexcitability.

2- irritability.

Decrease in thyroid hormones secretion:

1- slow movement.

2- impaired memory.

3- decreased mental capacity.

Autonomic nervous system

- Produce 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.

GIT

1- increase appetite and food intake.

2- increase of digestive juices secretion.

3- increase of G.I tract motility:

- excess secretion lead to diarrhea.

- lack of secretion lead to constipation.

Respiration

1- increase ventilation rate.

2- increase dissociation of oxygen from Hb by increasing RBC 2,3-DPG (2,3 diphosphoglycerate).

REGULATION OF HORMONES SECRETION:

It is regulated by the hypothalamic-pituitary axis.

1- Thyrotropin-releasing hormone (TRH):

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

2- Thyroid-stimulating hormone (TSH):

- Glycoprotein.
- Anterior pituitary.
- Regulate secretion and growth of thyroid gland (trophic effect).

Action of TSH: (- TSH secretion started at 11-13 of gestational weeks.)

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

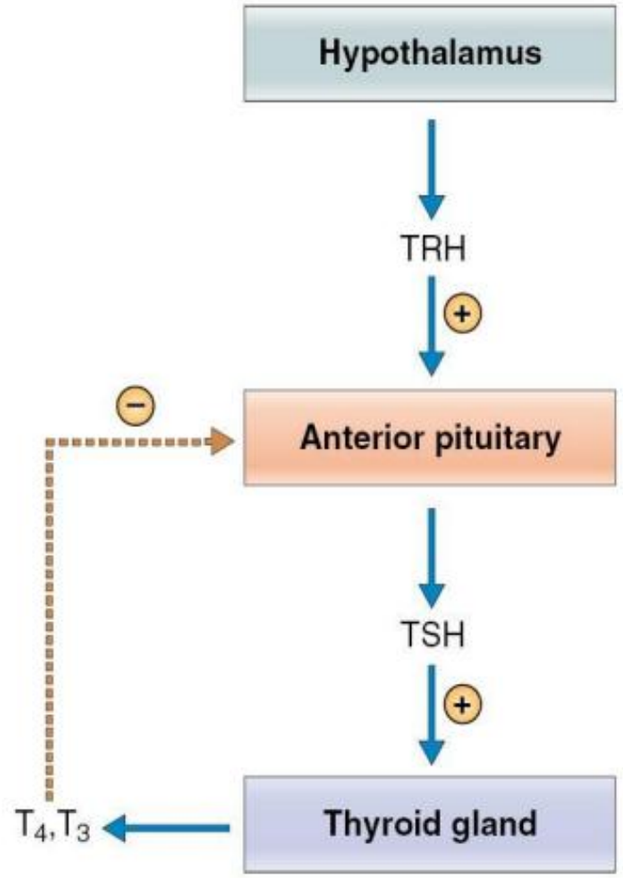
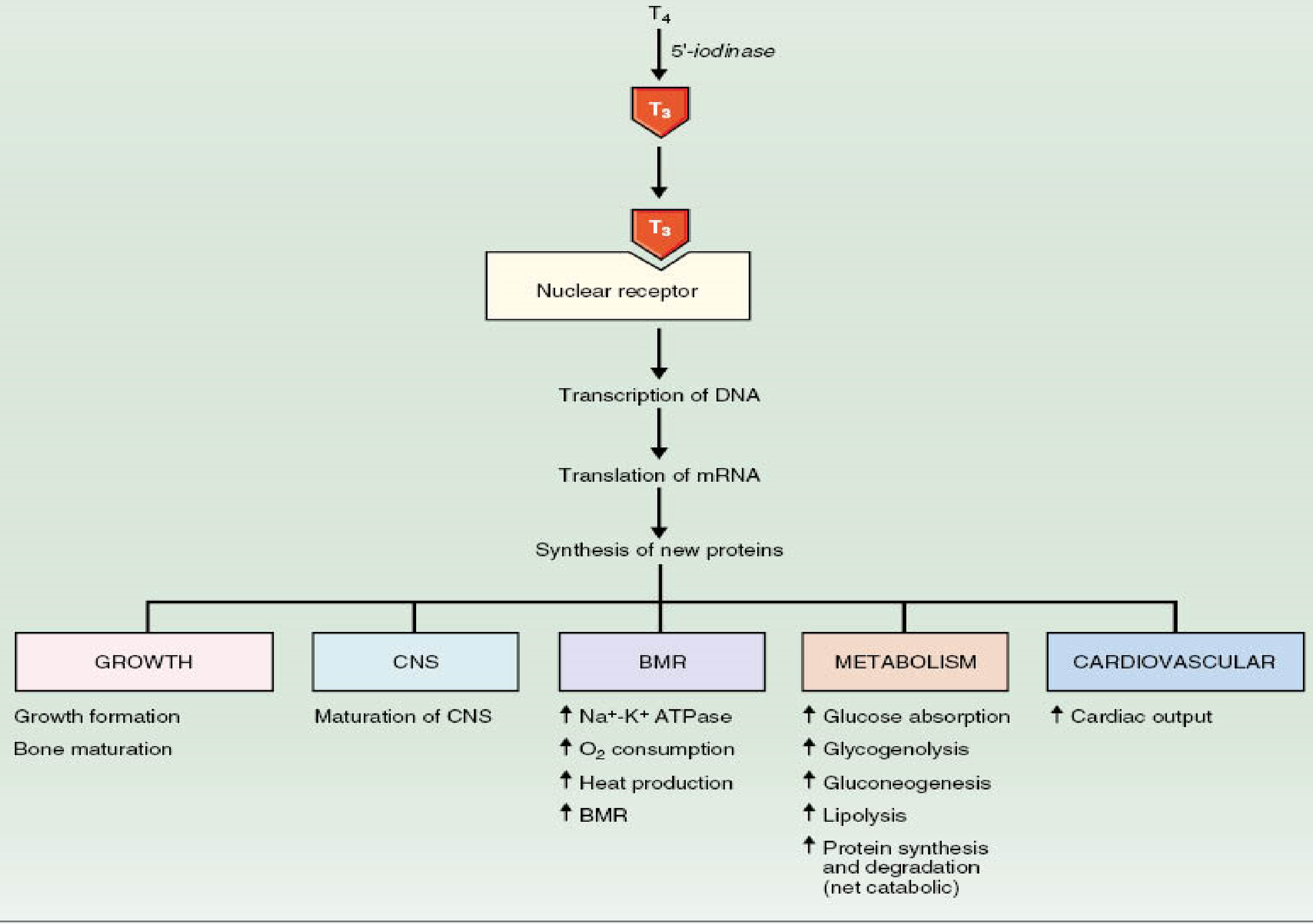


Table 9-8 Factors Affecting Thyroid Hormone Secretion

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)

-TSH + receptor ⟶ activation of adenylyl cyclase via Gs protein ⟶ ↑ cAMP ⟶ activation of protein kinase ⟶ multiple phosphorylation ⟶ ↑ secretion and thyroid growth.

ACTIONS OF THYROID HORMONES



Summery

- Thyroid hormones: T3 + T4 + Calcitonin.
- Thyroid hormones synthesis is both

Intracellular: Thyroglobulin synthesis + Oxidation of iodide to iodine.

Extracellular: iodination + coupling.

- In hepatic failure: TBG decreases = inhibition of thyroid secretions.
- In pregnancy : TBG increases = stimulation of thyroid hormones.
- T4 is deionized to T3 by Iodinase enzyme.
- Thyroid hormone receptor is a nuclear receptor.
- Action of thyroid hormones: BMR, Metabolism (carbohydrate + fat + protein), CVS, CNS, respiratory, GIT and bone effects.
- Thyroid hormones secretion is regulated by hypothalamic-pituitary axis: TRH + TSH.

A. Synthesis of thyroid hormones (Figure 7-8)

- Each step in synthesis is **stimulated by TSH**.

1. **Thyroglobulin** is synthesized from tyrosine in the thyroid follicular cells, packaged in secretory vesicles, and extruded into the follicular lumen (step 1).
2. **The iodide (I^-) pump, or Na^+–I^- cotransport**
   - is present in the thyroid follicular epithelial cells.
   - actively transports I^- into the thyroid follicular cells for subsequent incorporation into thyroid hormones (step 2).
   - is **inhibited by thiocyanate and perchlorate anions**.
3. **Oxidation of I^- to I_2**
   - is catalyzed by a **peroxidase enzyme** in the follicular cell membrane (step 3).
   - **I_2** is the reactive form, which will be "organified" by combination with tyrosine on thyroglobulin.
   - The peroxidase enzyme is **inhibited by propylthiouracil,** which is used therapeutically to reduce thyroid hormone synthesis for the treatment of hyperthyroidism.
   - The same peroxidase enzyme catalyzes the remaining organification and coupling reactions involved in the synthesis of thyroid hormones.

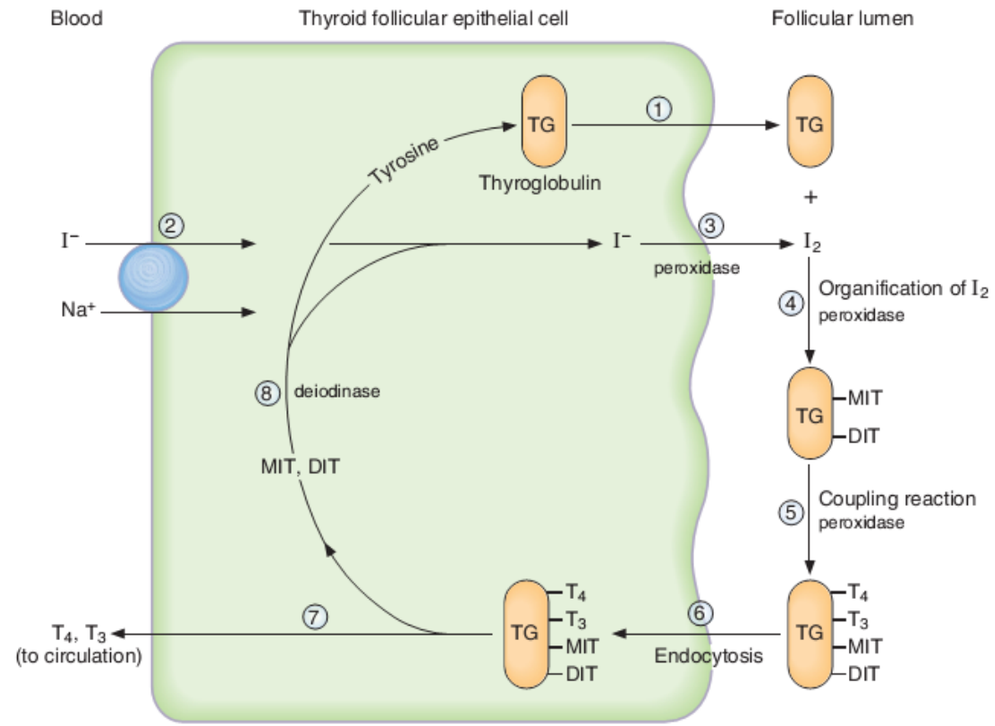


FIGURE 7-8 Steps in the synthesis of thyroid hormones. Each step is stimulated by thyroid-stimulating hormone. DIT = diiodotyrosine; I^- = iodide; MIT = monoiodotyrosine; T_3 = triiodothyronine; T_4 = thyroxine; TG = thyroglobulin.

4. **Organification of I_2**
   - At the junction of the follicular cells and the follicular lumen, tyrosine residues of thyroglobulin react with I_2 to form **monoiodotyrosine (MIT) and diiodotyrosine (DIT)** (step 4).
   - High levels of I^- inhibit organification and, therefore, inhibit synthesis of thyroid hormone **(Wolff–Chaikoff effect)**.
5. **Coupling of MIT and DIT**
   - While MIT and DIT are attached to thyroglobulin, two coupling reactions occur (step 5).

   a. When two molecules of DIT combine, **thyroxine (T_4)** is formed.
   b. When one molecule of DIT combines with one molecule of MIT, **triiodothyronine (T_3)** is formed.
      - More T_4 than T_3 is synthesized, although T_3 is more active.
   c. Iodinated thyroglobulin is stored in the follicular lumen until the thyroid gland is stimulated to secrete thyroid hormones.
6. **Stimulation of thyroid cells by TSH**
   - When the thyroid cells are stimulated, iodinated thyroglobulin is taken back into the follicular cells by endocytosis (step 6). Lysosomal enzymes then digest thyroglobulin, releasing T_4 and T_3 into the circulation (step 7).
   - Leftover MIT and DIT are deiodinated by **thyroid deiodinase** (step 8). The I_2 that is released is reutilized to synthesize more thyroid hormones. Therefore, deficiency of thyroid deiodinase mimics I_2 deficiency.
7. **Binding of T_3 and T_4**
   - In the circulation, most of the T_3 and T_4 is bound to thyroxine-binding globulin **(TBG)**.

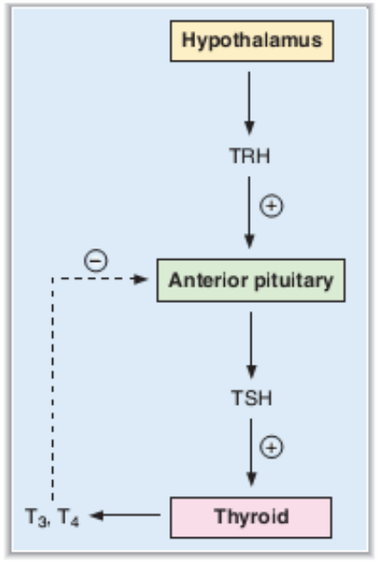


FIGURE 7-9 Control of thyroid hormone secretion. T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

   a. In **hepatic failure,** TBG levels decrease, leading to a decrease in total thyroid hormone levels, but normal levels of free hormone.
   b. In **pregnancy,** TBG levels increase, leading to an increase in total thyroid hormone levels, but normal levels of free hormone (i.e., clinically, euthyroid).
8. **Conversion of T_4 to T_3 and reverse T_3 (rT_3)**
   - In the peripheral tissues, T_4 is converted to T_3 by **5′-iodinase** (or to rT_3).
   - **T_3 is more biologically active than T_4.**
   - rT_3 is inactive.

B. Regulation of thyroid hormone secretion (Figure 7-9)

1. **Hypothalamic–pituitary control—TRH and TSH**
   - a. **TRH** is secreted by the hypothalamus and stimulates the secretion of TSH by the anterior pituitary.
   - b. **TSH** increases both the synthesis and the secretion of thyroid hormones by the follicular cells via an **adenylate cyclase–cAMP** mechanism.
     - Chronic elevation of TSH causes **hypertrophy** of the thyroid gland.
   - c. **T_3 down-regulates TRH receptors** in the anterior pituitary and thereby inhibits TSH secretion.
2. **Thyroid-stimulating immunoglobulins**
   - are components of the immunoglobulin G (IgG) fraction of plasma proteins and are **antibodies to TSH receptors** on the thyroid gland.
   - bind to TSH receptors and, like TSH, **stimulate the thyroid gland to secrete T_3 and T_4.**
   - circulate in high concentrations in patients with **Graves' disease,** which is characterized by high circulating levels of thyroid hormones and, accordingly, low concentrations of TSH (caused by feedback inhibition of thyroid hormones on the anterior pituitary).

C. Actions of thyroid hormone

- **T_3 is three to four times more potent than T_4.** The target tissues convert T_4 to T_3 (see IV A 8).

1. **Growth**
   - Attainment of adult stature requires thyroid hormone.
   - Thyroid hormones act synergistically with growth hormone and somatomedins to promote **bone formation**.
   - Thyroid hormones stimulate **bone maturation** as a result of ossification and fusion of the growth plates. **In thyroid hormone deficiency, bone age is less than chronologic age**.
2. **Central nervous system (CNS)**
   - a. **Perinatal period**
     - Maturation of the CNS **requires thyroid hormone in the perinatal period.**
     - Thyroid hormone deficiency causes irreversible mental retardation. Because there is only a brief perinatal period when thyroid hormone replacement therapy is helpful, **screening for neonatal hypothyroidism is mandatory.**
   - b. **Adulthood**
     - **Hyperthyroidism** causes hyperexcitability and irritability.
     - **Hypothyroidism** causes listlessness, slowed speech, somnolence, impaired memory, and decreased mental capacity.
3. **Autonomic nervous system**
   - Thyroid hormone has many of the same actions as the sympathetic nervous system because it **up-regulates β_1-adrenergic receptors in the heart**. Therefore, a useful adjunct therapy for hyperthyroidism is treatment with a β-adrenergic blocking agent, such as propranolol.
4. **Basal metabolic rate (BMR)**
   - **O_2 consumption and BMR are increased** by thyroid hormone in all tissues except the brain, gonads, and spleen. The resulting increase in heat production underlies the role of thyroid hormone in temperature regulation.
   - Thyroid hormone **increases the synthesis of Na^+,K^+-ATPase** and consequently increases O_2 consumption related to Na^+–K^+ pump activity.
5. **Cardiovascular and respiratory systems**
   - Effects of thyroid hormone on cardiac output and ventilation rate combine to ensure that more O_2 is delivered to the tissues.
   - a. Heart rate and stroke volume are increased. These effects combine to produce **increased cardiac output**.
   - b. Ventilation rate is increased.
6. **Metabolic effects**
   - Overall, metabolism is increased to meet the demand for substrate associated with the increased rate of O_2 consumption.
   - a. Glucose absorption from the gastrointestinal tract is increased.
   - b. **Glycogenolysis, gluconeogenesis,** and **glucose oxidation** (driven by demand for ATP) are increased.
   - c. Lipolysis is increased.
   - d. Protein synthesis and degradation are increased. The overall effect of thyroid hormone is **catabolic**.

MCQs

1- Thyroid hormones belong to which class of hormone?
a) steroids
b) proteins
c) polypeptides
d) amino acid derivatives

2- C-cells are present in :
a) thyroid gland
b) adrenal cortex
c) parathyroid gland
d) pituitary gland

3- Thyroid gland secretes approximately ___% T4 and ___%T3 :
a) 20,80
b) 10,90
c) 80,20
d) 90,10

4- Not an action of thyroid hormone :
a) raises BMR
b) increases cardiac output
c) decreases cholesterol
d) loss of libido

5- Calcitonin is responsible for :
a) Increasing the plasma calcium level
b) decreasing the plasma calcium level
c) increasing parathyroid hormone level
d) decreasing thyroxine level

1- d 2- a 3- d 4- d 5- b

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