THE THYROID GLAND

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

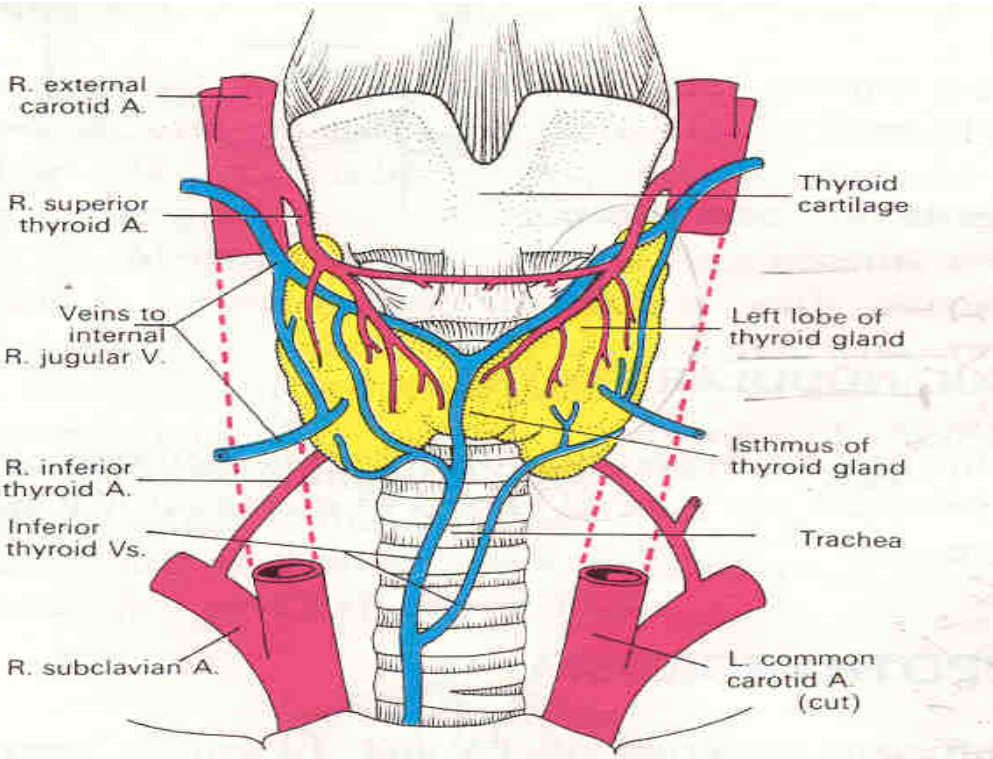


Figure 14:8 Position of thyroid gland and associated structures.

HORMONES

- T3 Triiodothyronine 10%.
- T4 thyroxine (tetraiodothyronine) 90%.
- Reverse T3
- Calcitonin.

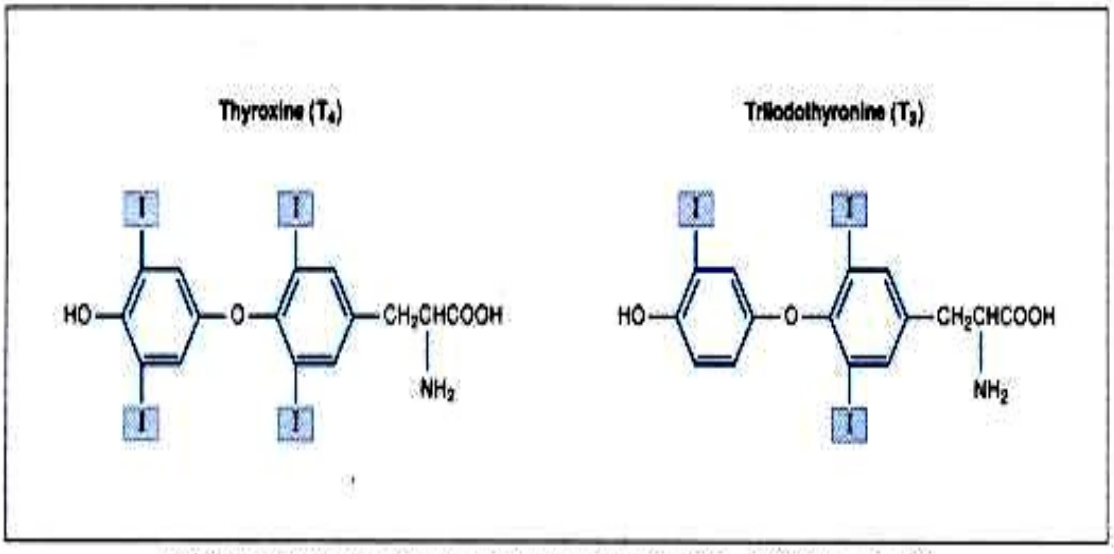
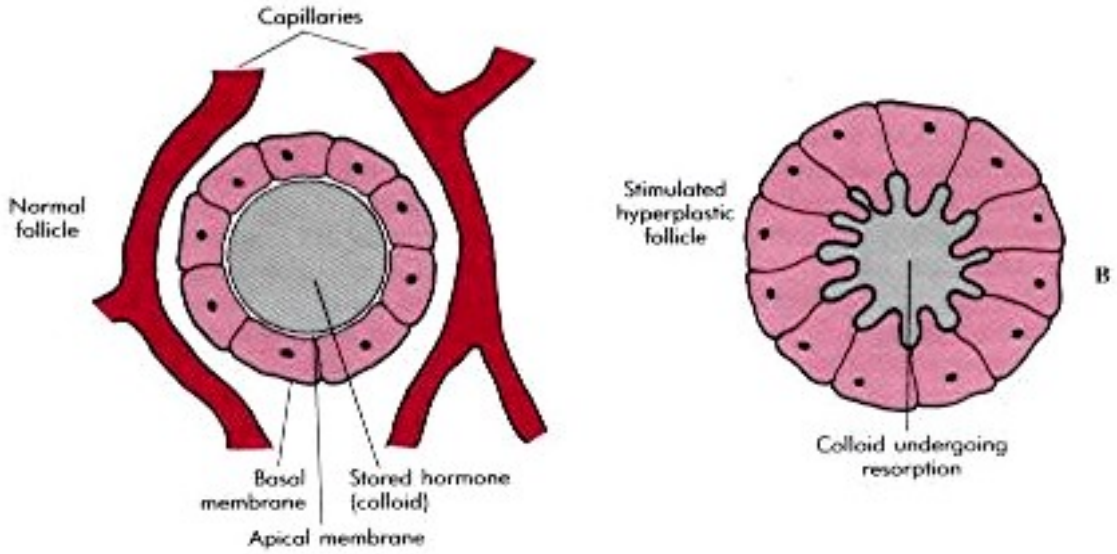
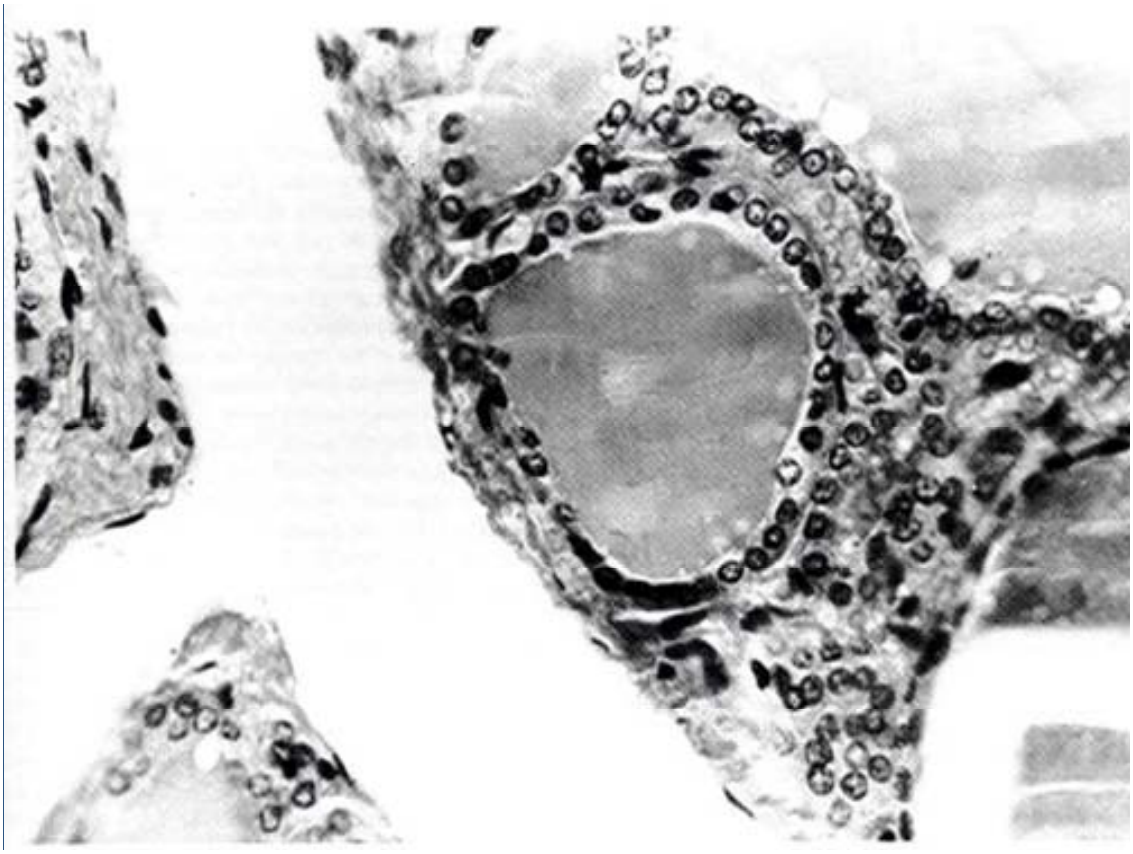


FIGURE 9–14. Structures of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3).

SYNTHESIS



■ Fig. 49-1 **A,** Photomicrograph of thyroid gland follicle. **B,** Schematic drawing of normal thyroid gland follicle and a follicle stimulated by thyrotropin. Note change in shapes from cuboidal to columnar, relocation of nuclei to base of cells, and scalloped appearance of follicle lumen.



THREE UNIQUE FEATURES

1- Contains a large amount of iodine.

- supplied in diet.

- 1mg/week.

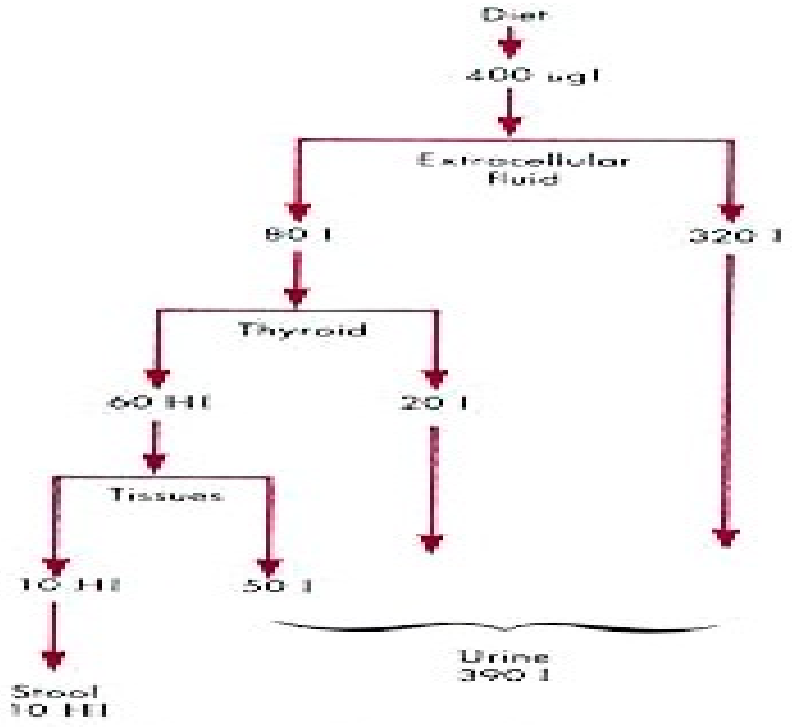


Fig. 49-2 Average daily iodide turnover in humans (United States). Note that 20% of the intake is taken up by the thyroid gland and 15% turns over in hormone synthesis and disposal. The unneeded excess is excreted in the urine. *I*, Iodide; *HI*, hormonal iodide.

2- Synthesis is partially intracellular and partially extracellular.

3- T4 is the major product.

STEPS IN BIOSYNTHESIS

1- THYROGLOBULIN FORMATION AND TRANSPORT:

- 140 tyrosine.
- Rough endoplasmic reticulum and Golgi apparatus.

2- IODIDE PUMP OR IODIDE TRAP:

- Active transport
- Wolff-chaikoff effect.
- Ratio of concentration from 30-250 times.
- It is stimulated by TSH.

3- OXIDATION OF IODIDE TO IODINE:

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

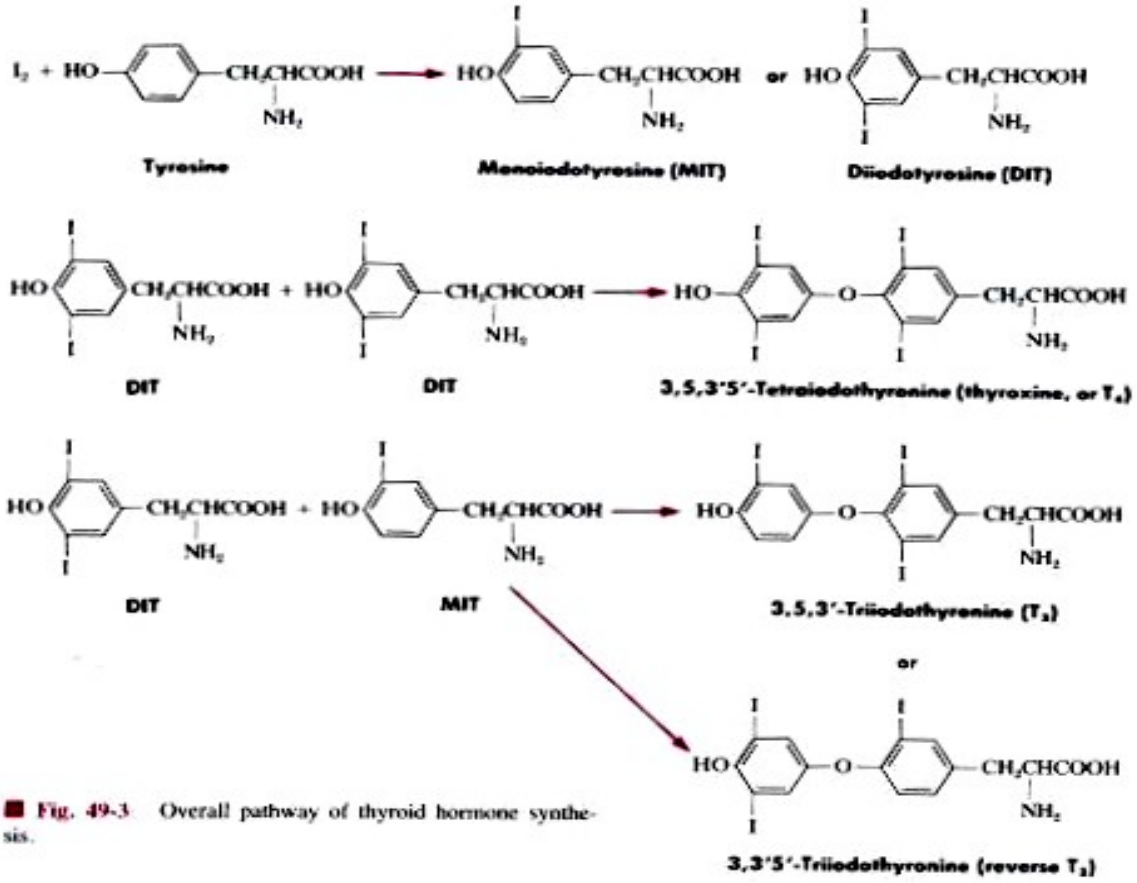
4- ORGANIFICATION OF THYROGLOBULIN

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

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.



■ Fig. 49-3 Overall pathway of thyroid hormone synthesis.

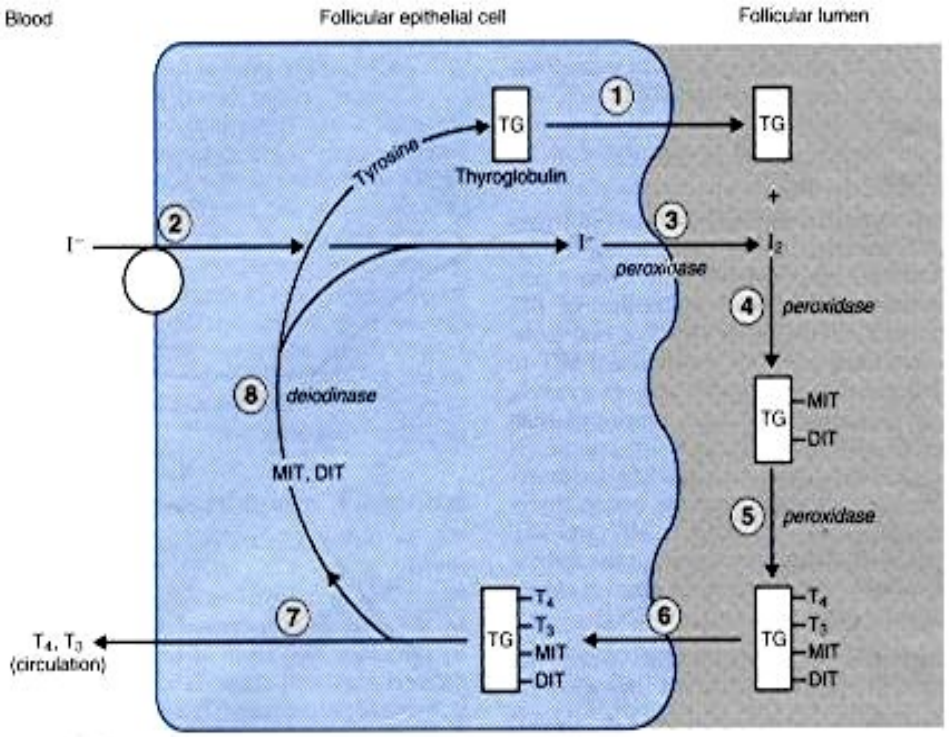
6- Endocytosis of thyroglobulin.

7- Fusion of lysosomes immediately with the vesicles.

8- Hydrolysis of the peptide bond to release *DIT*+*MIT*+*T4*+*T*3 from the thyroglobulin.

9- Delivery of T4 and T3 to the systemic circulation.

10- Deiodination of DIT and MIT by thyroid deiodinase.



Event	Site	Enzyme	Inhibitor
1 Synthesis of TG; extrusion into follicular lumen	Rough ER, Golgi apparatus		
2 I^- pump	Basal membrane		Perchlorate, thiocynate
3 Oxidation of $I^- \rightarrow I_2$	Apical (luminal) membrane	Peroxidase	Propylthiouracil (PTU)
4 Organification of I_2 into MIT and DIT	Apical membrane	Peroxidase	Propylthiouracil
5 Coupling reaction of MIT and DIT into T_3 and T_4	Apical membrane	Peroxidase	Propylthiouracil
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	

FIGURE 9–16. Steps involved in the synthesis of thyroid hormones in thyroid follicular cells. Circled numbers correspond to steps discussed in the text. DIT, diiodotyrosine; ER, endoplasmic reticulum; MIT, monoiodotyrosine; PTU, propylthiouracil; TG, thyroglobulin; T_3, triiodothyronine; T_4, thyroxine.

THYROID HORMONES IN THE CIRCULATION

120 ng/dl T3 8 µg/dl T4

1- Unbound:
0.03% of T4 and 0.3% of T3.

2- Bound:
- 70- 80% bound to thyroxine-binding globulin (TBG) synthesised in the liver.

- The reminder is bound to albumine.

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

In pregnancy:
↑ estrogen → ↑ TBG → ↓ T3 + T4 free level → stimulation of thyroid secretion.

RELEASE OF T4 AND 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- Stored in the targeted tissues.

3- Enzyme 5- iodinase.

REGULATION OF HORMONES SECRETION

- It is regulated by the hypothalamic-pituitary axis.

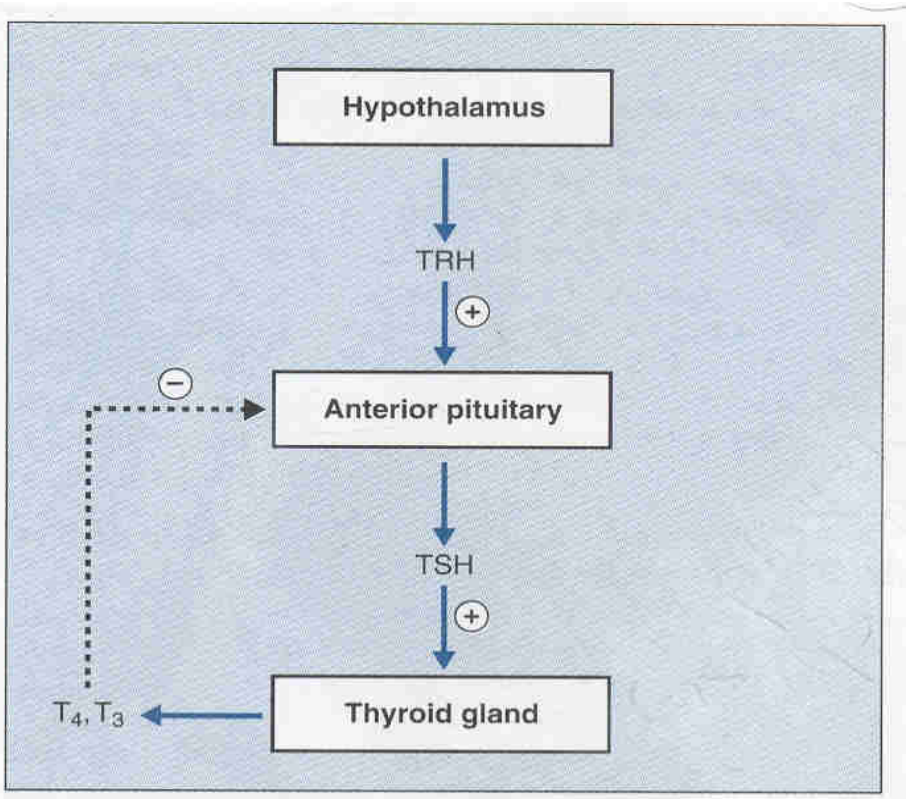


FIGURE 9–17. Regulation of thyroid hormone secretion. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine.

1- Thyrotropin-releasing hormone (TRH):

- Tripeptide.
- from the hypothalamus.
- Act on the thyrotrophs of the anterior pituitary
- Transcription and secretion of TSH.
- Phospholipase second messenger system.

2- Thyroid-stimulating hormone (TSH):

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

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.

- 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.

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 I^- pump)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

ACTION OF THYROID HORMONES

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

T3 + nuclear receptor → T3-receptor complex → activation of thyroid regulating element on DNA → ↑DNA transcription → formation of mRNA → translation of mRNA → specific protein synthesis (target tissue specific).

1- Basal metabolic rate (BMR):

- Is the energy requirement under basal condition (stat of mental and physical rest 12-18 hours after a meal).

- Complete lake of thyroid hormones → 40% ↓ in BMR.

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

2- Metabolism

A)- Effect on carbohydrate metabolism:

1- increase glucose uptake by the cells.
2- increase glycogenolysis.
3- increase gluconeogenesis.
4- increase absorption from the gastrointestinal tract.

B)- Effects on fat metabolism:

1- increase lipolysis.
2- decrease plasma cholesterol by increase loss in feces.
3- increase oxidation of free fatty acids.

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

3- Effects on the cardiovascular system:

- increase heart rate. → Cardiac out put up to 60%
- increase stroke volume. →
- decrease peripheral resistance.

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

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.

6- Effects on the CNS:

A)- perinatal period:
Thyroid hormones are essential for maturation of the CNS.
perinatal decrease of hormones secretion
↓
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- mental capacity.

7- 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.

8- Effects on bone:

a)- promote bone formation.
b)- promote ossification.
c)- promote fusion of bone plate.
d)- promote bone maturation.

9- Effects on respiration:

1- increase ventilation rate.
2- increase dissociation of oxygen from Hb

10- Effects on the G.I tract:

1- increase appetite and food intake.
2- increase of digestive juices secretion.
3- increase of G.I tract motility.

excess secretion → diarrhea.
lake of secretion → constipation.

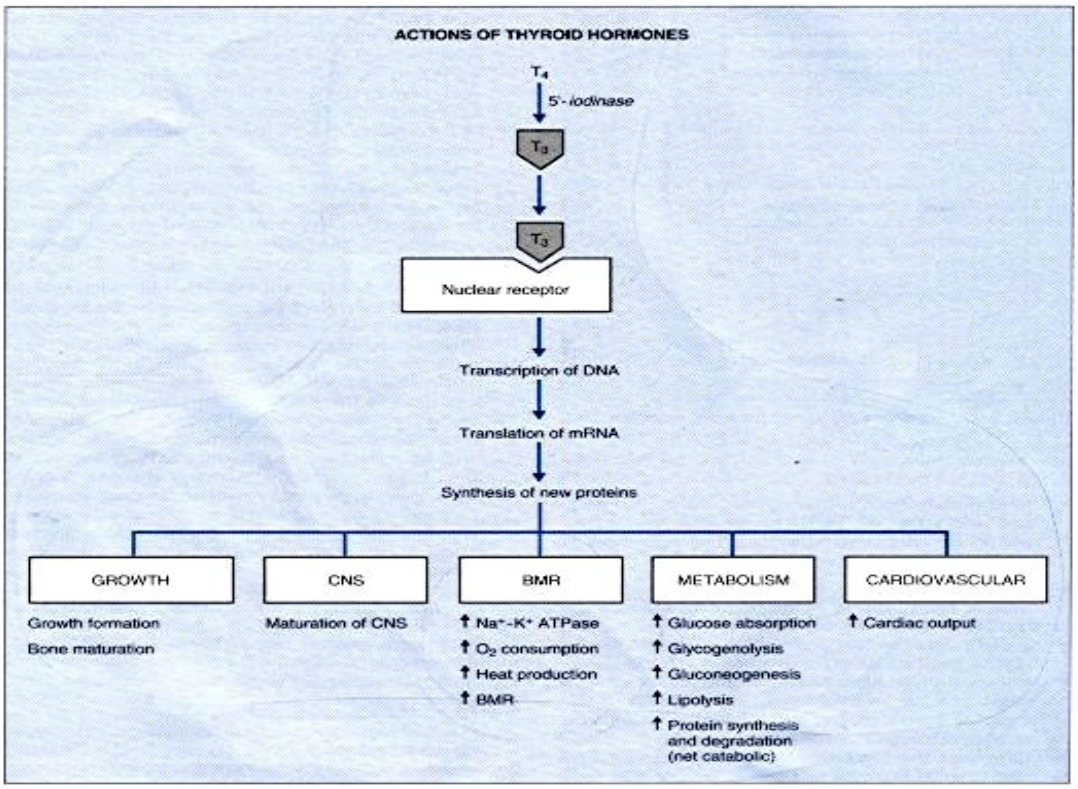


FIGURE 9–18. Mechanism of action of thyroid hormones. Thyroxine (T_4) is converted to triiodothyronine (T_3) in target tissues. The actions of T_3 on several organ systems are shown. BMR, basal metabolic rate; CNS, central nervous system; DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid.