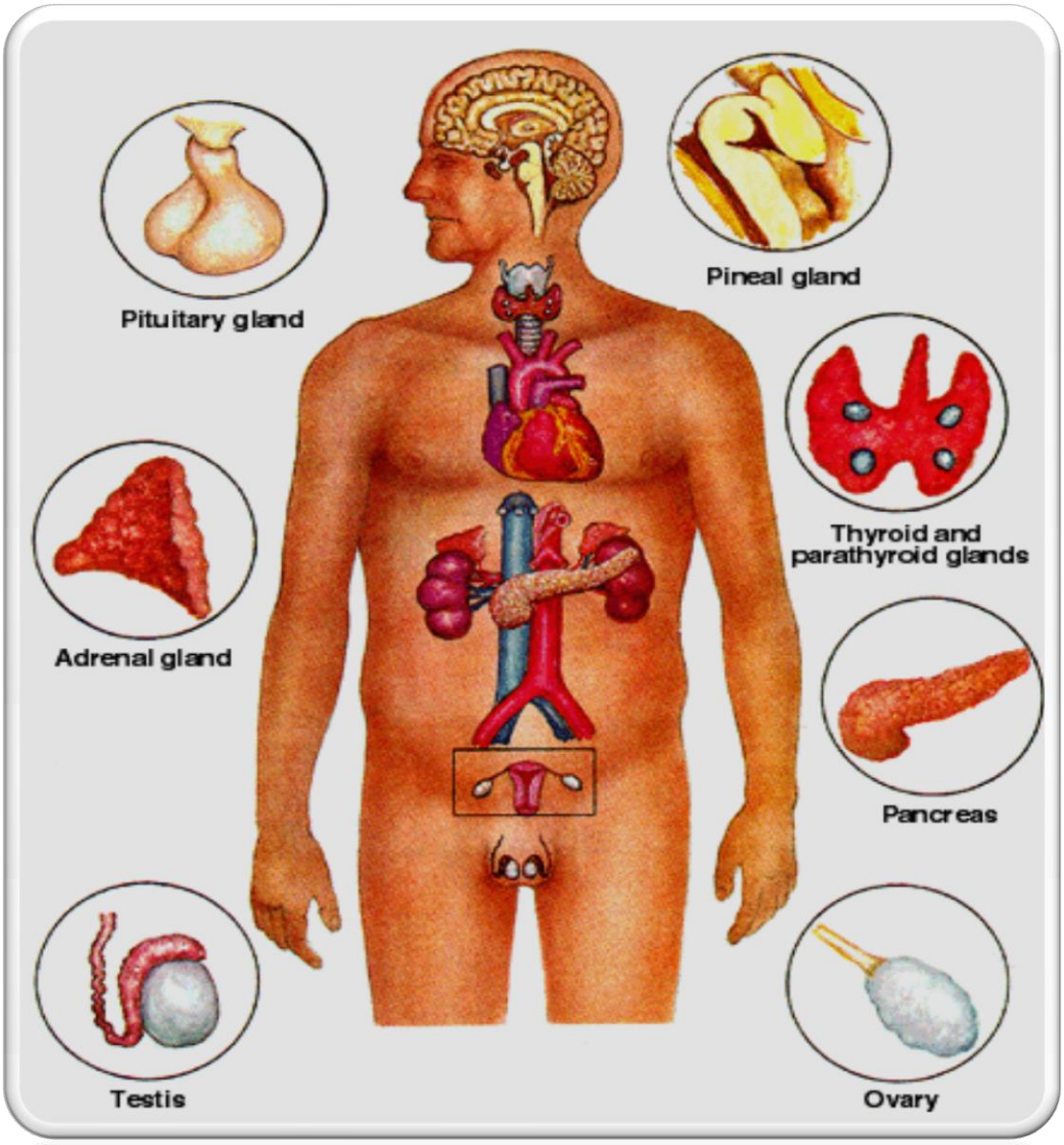
ENDOCRINE BLOCK
PHYSIOLOGY TEAM 431



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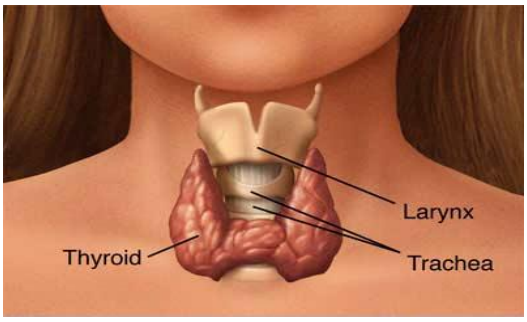
THE THYROID GLAND

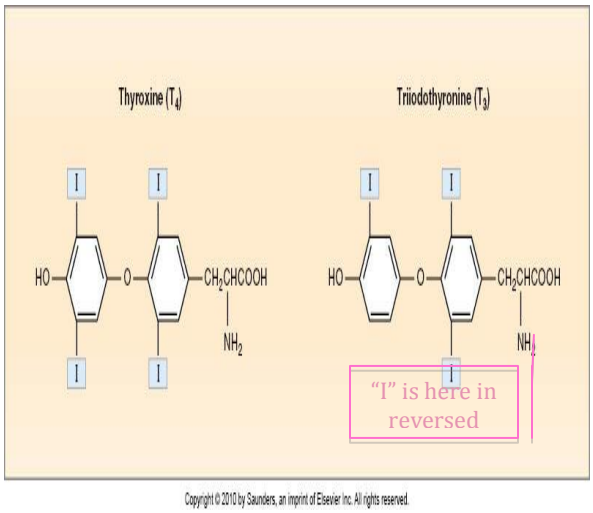
Red=important
Blue=explanation
Green=male notes
Pink=female notes

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

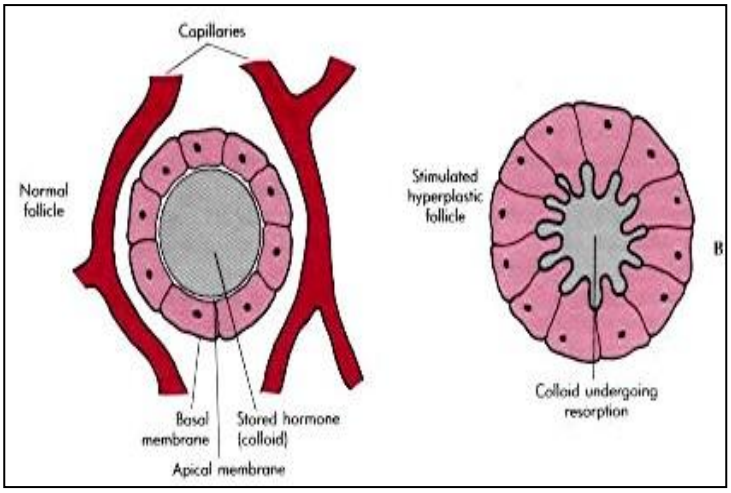


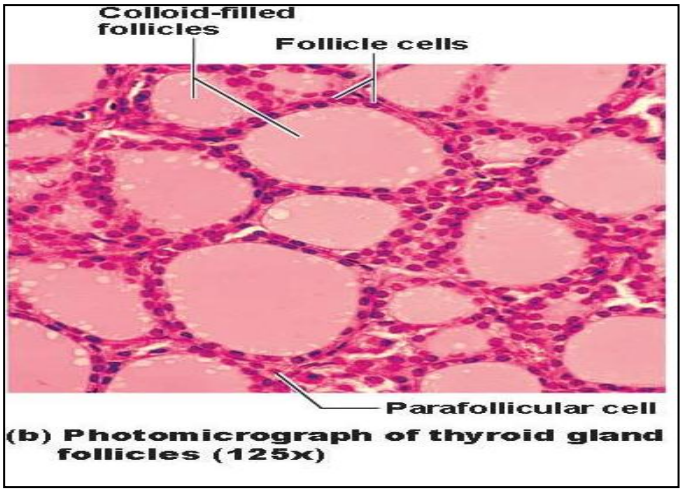
HORMONES;;

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



SYNTHESIS





- Follicular cells synthesize T3 & T4
- Colloid stores T3 & T4
- Parafollicular cells synthesize calcitonin

THREE UNIQUE FEATURES

1- Contains a large amount of iodine. (90% of iodine)

- supplied in diet.
- 1mg/week.

- 20% goes to thyroid, part gives the hormone which is delivered to tissues or recycled then excreted in stool and part is excreted in urine.
- 80% is directly excreted in urine (the major excretory pathway)

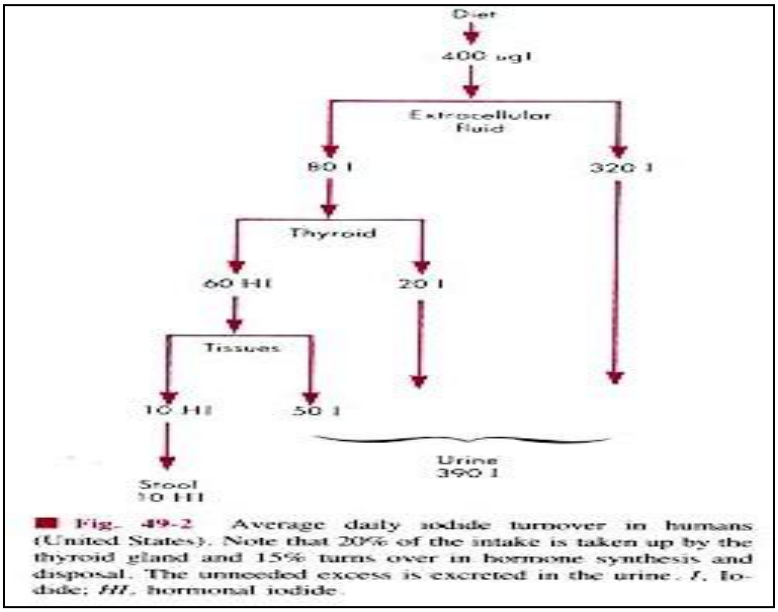


Fig. 49-2 Average daily iodide turnover in humans (United States). Note that 20% of the intake is taken up by the thyroid gland and 15% turns over in hormone synthesis and disposal. The unneeded excess is excreted in the urine. *I*, Iodide; *HI*, hormonal iodide.

2- Synthesis is partially intracellular and partially extracellular (in colloid).

3- T4 is the major product.

Thyroid Hormones [T3 - T4]

Biosynthesis: *by the follicular cells*

1- **Iodide pump**. (active (needs energy))

2- **Thyroglobulin synthesis**.

3- **Oxidation** of iodide to iodine.

4- **Iodination** of tyrosine, to form

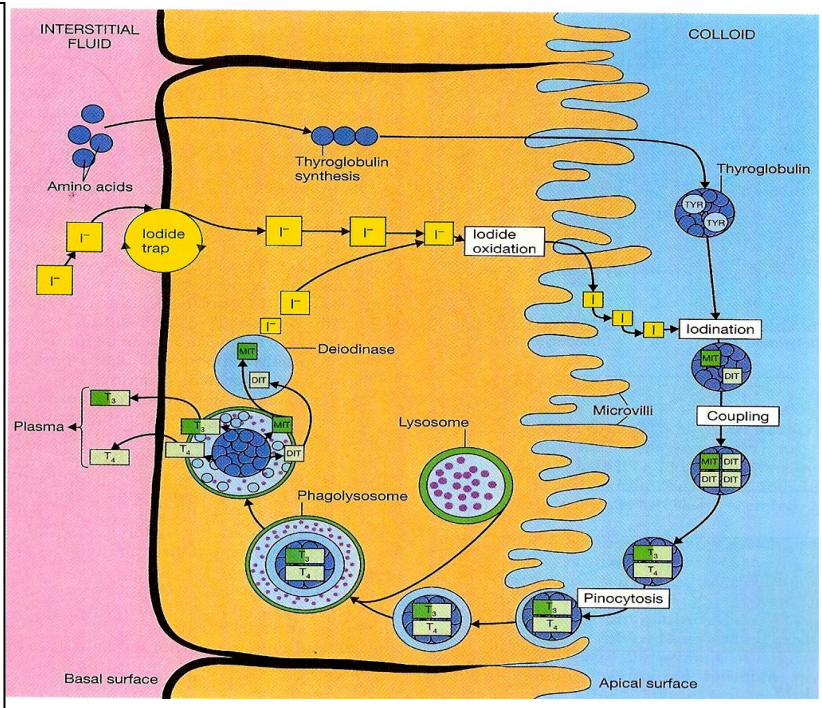
mono-iodotyrosine (MIT) & Di-iodotyrosine (DIT).

5- **Coupling**;

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

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

6- **Release**.



Against concentration gradient

STEPS IN BIOSYNTHESIS

1- THYROGLOBULIN FORMATION AND TRANSPORT:

- thyroglobulin is a Glycoprotein.
- it has Tyrosine.
- synthesized in Rough endoplasmic reticulum and Golgi apparatus.

2- IODIDE PUMP OR IODIDE TRAP:

- Active transport. (Na and I cotransport)
- It is stimulated by TSH (thyroid stimulating hormone)

- Wolff-chaikoff effect

(A reduction in thyroid hormone levels caused by administration of a large amount of iodine). (negative feedback)

Ratio of concentration from 30-250 times. (concentration of iodide)

3- OXIDATION OF IODIDE TO IODINE:

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

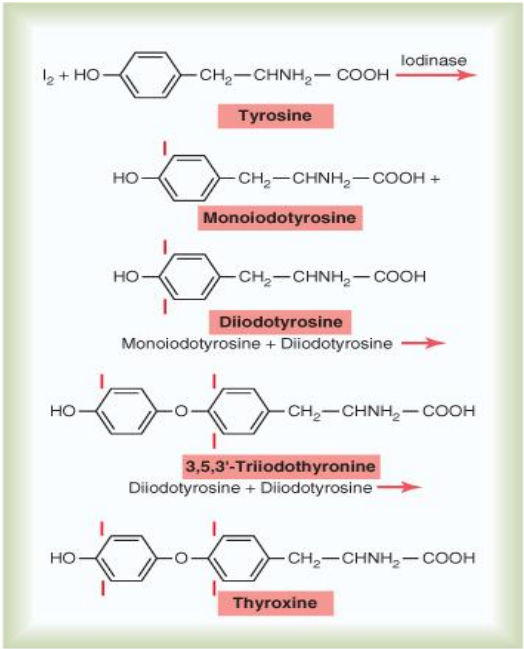
4- ORGANIFICATION OF THYROGLOBULIN

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



6- ENDOCYTOSIS (PINOCYTOSIS) OF THYROGLOBULIN.

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

2- Unbound (Free): (active form)
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.

pregnant women need thyroid for her body and for the fetus → so there will be stimulation of gland to release more thyroid hormone by increasing the level of estrogen which lead to increase level of TBG → decrease T3 and T4 to the minimum level of normal range →stimulate gland to secrete more

Release Of T4 & T3 To The Tissues

1- The release is slow because of the high affinity of the plasma binding proteins.

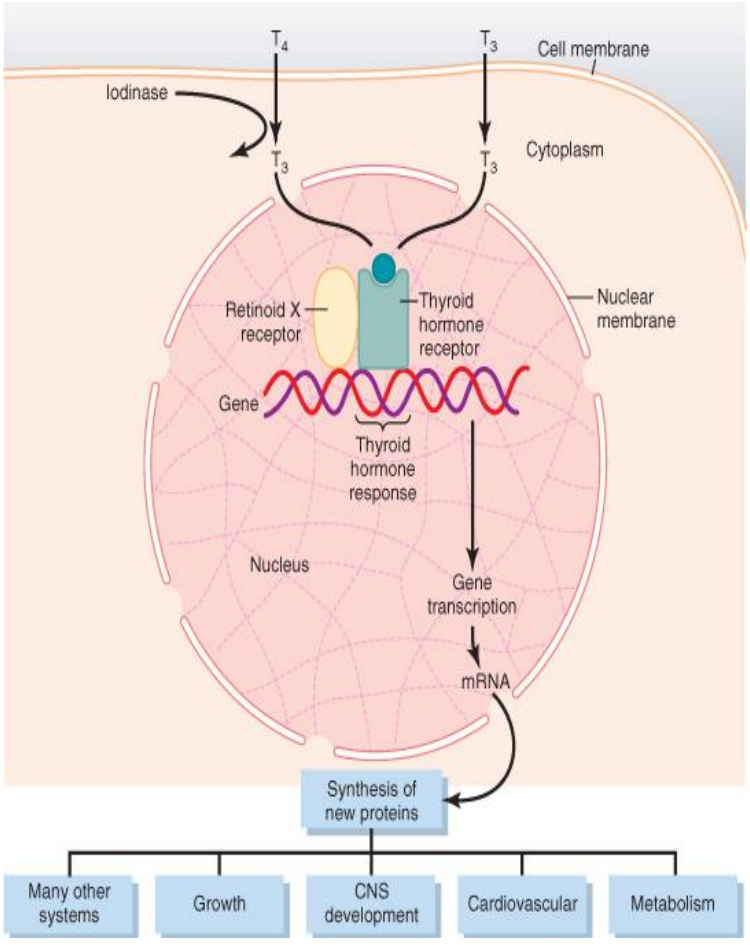
- ½ of T4 in the blood is released every 6 days.
- ½ of T3 in the blood is released every one day.

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

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

5- Most of T4 is deionized to T3 by iodinase enzyme.

6- In the nucleus, T3 mainly binds to "thyroid hormone receptor" and influence transcription of genes.
(So proteins are synthesized)



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)]

1- Basal Metabolic Rate (BMR):

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

- Complete lake of thyroid hormones → 40-50% ↓ 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. (decrease glycogenesis)
3- Increase gluconeogenesis.
4- Increase absorption from the GIT.

} Increase glucose for energy

B) Effects on fat metabolism:

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

C) Effect on protein metabolism:

overall effect is *catabolic* leading to decrease in muscle mass.
(Thyroid hormones will synthesize and catabolize proteins but the catabolism is more ,so the net result is catabolism)

- **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

} Not important

3- Effects on the Cardiovascular system:

- increaseheart rate.
- increase stroke volume. } Cardiac output up to 60%
- decrease peripheral resistance. (because the heat produced from metabolism will cause vasodilatation)

*end result is increase delivery of oxygenated blood to the tissues. (because of metabolism)

The CVS effects are due to:

1- Thyroid hormones potentiate the effect of *catecholamine* in the circulation → activation of β-adrenergic receptors. (Adrenaline, noradrenaline)

Catecholamine increase heart rate

2- Direct induction of:
a) myocardial β-adrenergic receptors.
b) sarcoplasmic reticulum.
c) Ca^{+2} ATPase.
d) myosine.

4- Effects on the CNS:

A) Peri-natal period:

Thyroid hormones are essential for ***maturation*** of the CNS.

decrease of hormones secretion

↓

irreversible mental retardation

Thyroid hormone secretion begins in the 3rd month of the intra-uterine life, we can treat the hormone deficiency within the first 6 months but after that mental retardation is irreversible even if we use drugs

- 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- decrease mental capacity.

5- Effects on bone

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

2,3 Diphosphoglycerate
A highly anionic organic phosphate which is present in human red blood cells at about the same molar ratio as hemoglobin. It binds to deoxyhemoglobin but not the oxygenated form, therefore diminishing the oxygen **affinity of hemoglobin.**

6- Effects on respiration

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

7-Effects on GIT

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

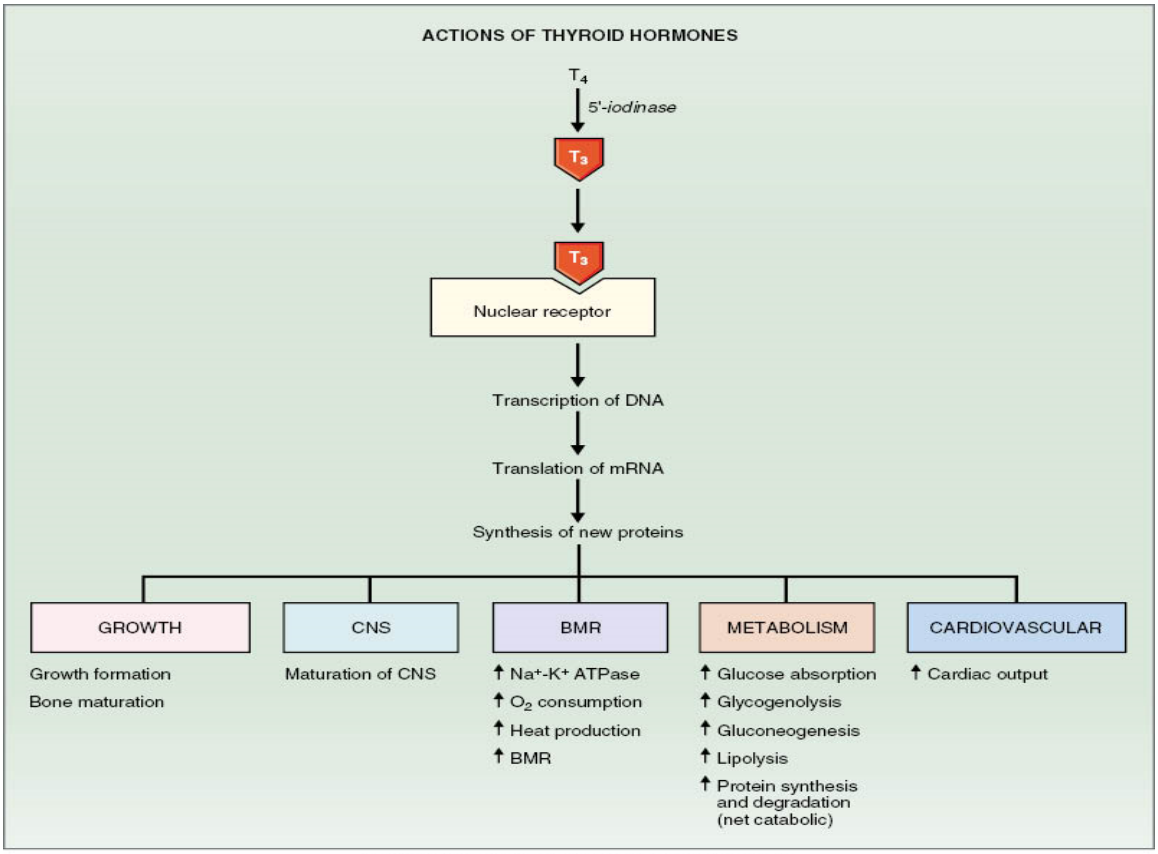
excess secretion → diarrhea.
Lack of secretion → constipation

8- Effects on the autonomic nervous system

Produced the same action as *catecholamines* via β-adrenergic receptors including:

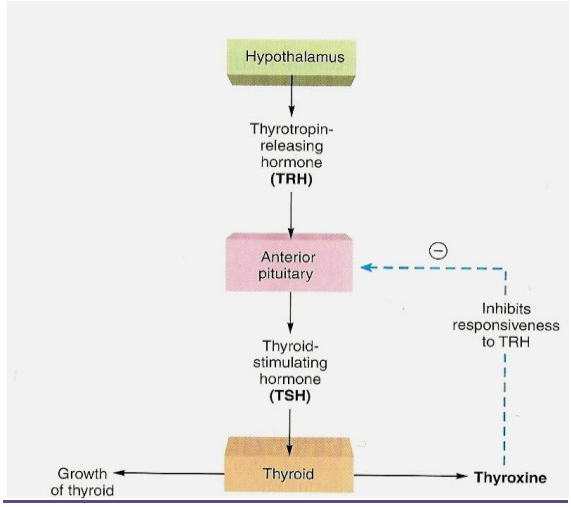
a) increase BMR.
b) increase heat production.
c) increase heart rate.
d) increase stroke volume.

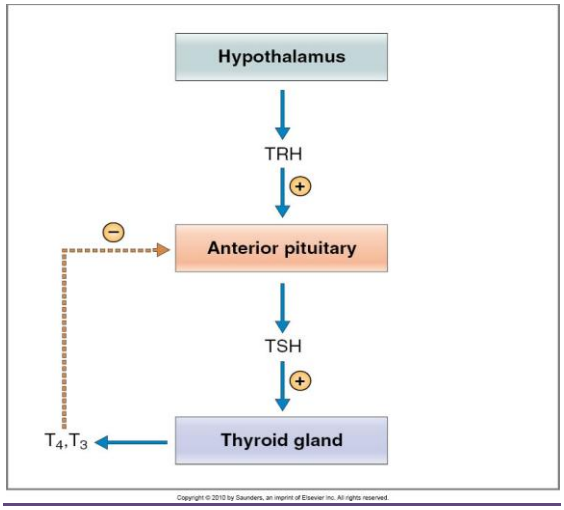
i.e. β-blocker (propranolol) is used in treatment of hyperthyroidism.



REGULATION OF HORMONES SECRETION

- It is regulated by the hypothalamic-pituitary axis.





1- Thyrotropin-releasing hormone (TRH):

-Tripeptide.

- released from 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.

In patient with under activity of gland → increase TBG → decrease free T3 and T4 → TSH will stimulate gland to secrete but there is no secretion → increase growth of gland → goiter

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

- **Action of TSH**
  1- Increase proteolysis of the thyroglobulin.
  2- Increase pump activity (for Na and I cotransport)
  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.

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)

TSI has same structure and function as TSH → when it binds to receptor → stimulate gland to secrete more thyroid → no feedback mechanism to inhibit secretion of TSI → hyperthyroidism (grave's disease)

SUMMARY

T4 is the main product of the thyroid.
T3 enters the nuclei of cells and do its actions.
Iodine enters to colloid against concentration gradient by active transport.
Thyroglobulin is the protein carrying T3 & T4 in the colloid.
In liver failure there is inhibition of thyroid secretion unlike pregnancy.
Thyroid hormones affect all systems of the body.

QUESTIONS

1-what is the major product of the thyroid gland?

A-T3
B- T4
C- Calcitonin
D- Iodine

2-how are thyroid hormones excreted mainly?

A - Urine
B - Sweat
C - Stool
D - Saliva

3-regarding thyroid hormone, which answer of the following is correct?

A- TH decreases GIT motility
B- TH decreases lipolysis
C- TH increases glycogenesis
D- TH increases amino acid production

Answers 1-B , 2-A , 3-D