Physiology Team

ENDOCRINE BLOCK

LECTURE 6

THE THYROID GLAND

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OBJECTIVES

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Not Given :|

MIND MAP

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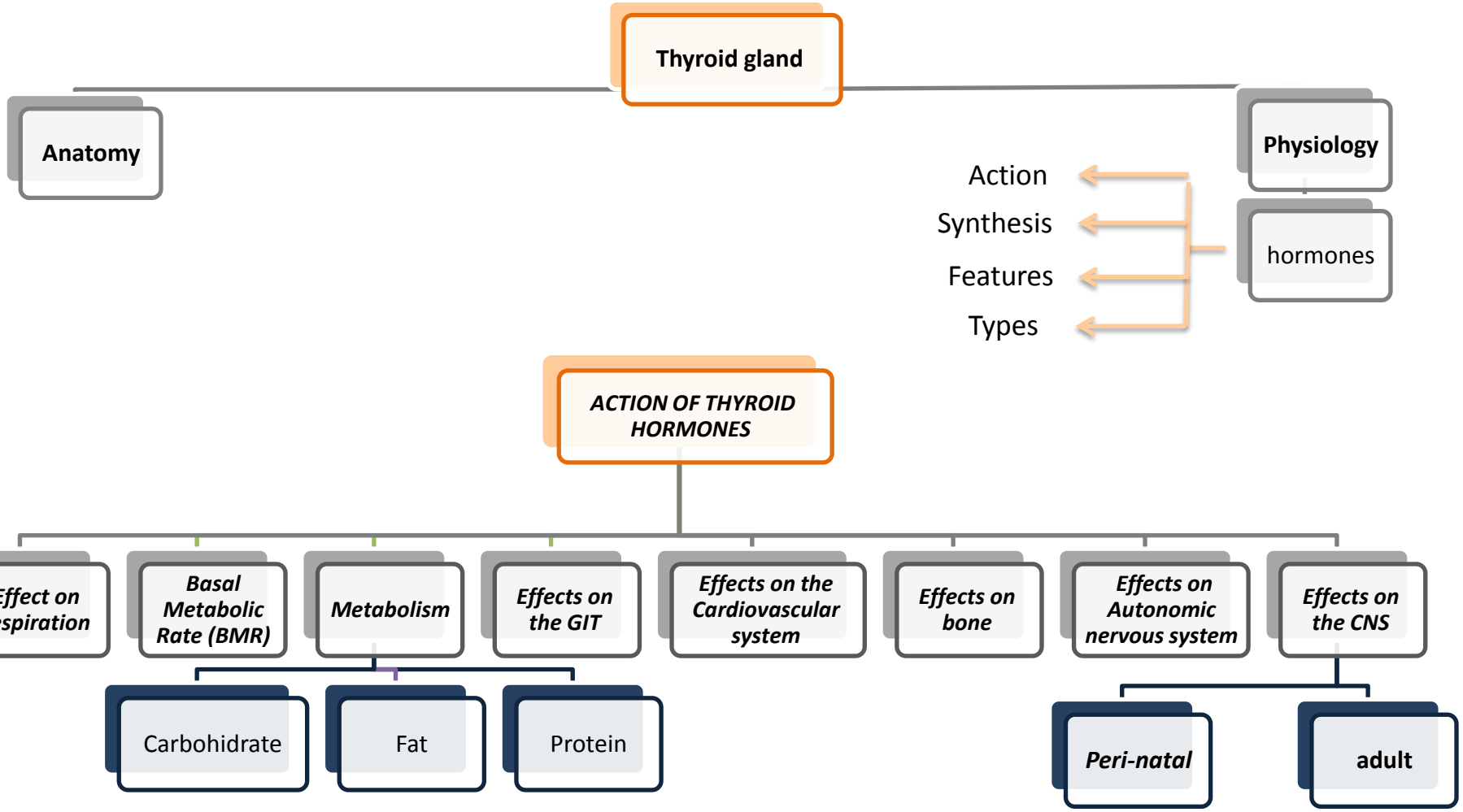
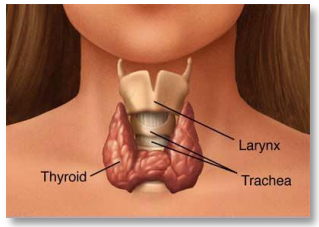
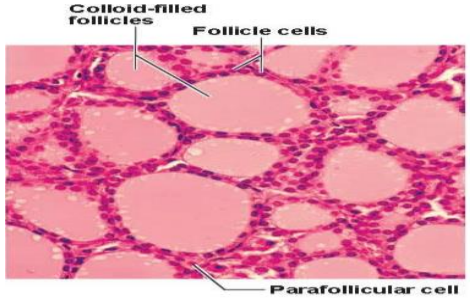


Anatomy:

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





Hormones:

- **T4 :** (**Tetra**iodothyronine)=(thyroxine)→ **90%.**
- **T3** : (**Tri**iodothyronine)→ **10%.**
- **Reverse T3**: (same as T3 but (I) is attached to the other circle) **inactive form of T3.**
- **Calcitonin** → function is calcium homeostasis.

Three unique features of synthesis of thyroid hormones:

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

2- Synthesis of hormone is partially **intracellular** (by the follicular cells) and partially extracellular.

3- **T4** is the **major product** even though it's less active than T3.

Biosynthesis of Thyroid Hormones: (summary)

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1. Iodide pump.
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.

Please watch this for better understanding

STEPS in details:

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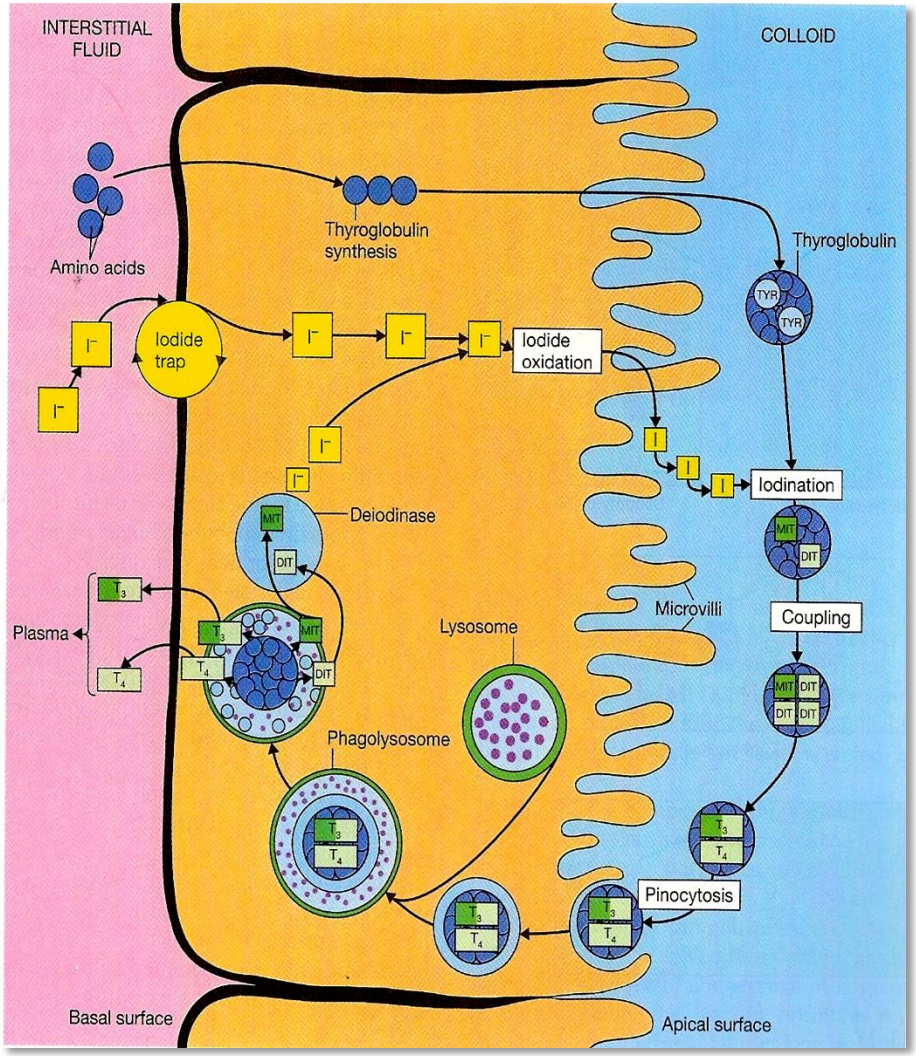
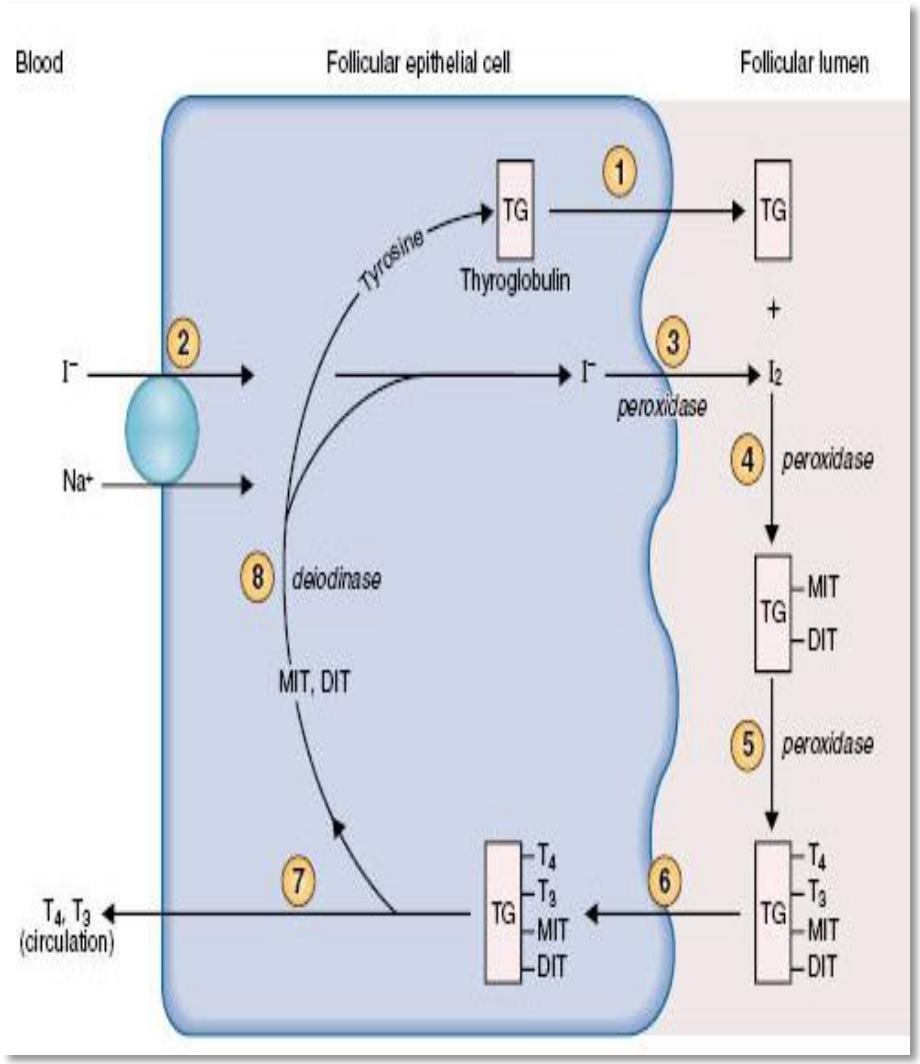
Step	Notes
1- thyroglobulin formation and transport	**Structure:-** Glycoprotein. **Building Block:-** 140 Tyrosine. **Location:-** Rough endoplasmic reticulum and Golgi apparatus.
2-iodide trap by iodide pump	• **Type**:- Active transport. • **Regulation**:- - It is stimulated by TSH -It is inhibited by 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.
3- oxidation of iodide to iodine	• **Enzyme**:- Thyroid peroxidase. • **Location**:- It is located in or attached to the apical membrane
4- organification of thyroglobulin (Iodination)	- 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 • DIT+MIT **Catalyzed by thyroid peroxidase** → T4 **(faster)** → that's why It's the major one T3 • It is stored as colloid. • Is sufficient for 2-3 months. Even without iodine supplementation
6- Endocytosis 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).	

Illustrations





■ Slides ■ Important ■ Females' Notes ■ Explanation ■ Males' Notes

Summary

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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	

Thyroid Hormones In The Circulation:

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1- Bound:

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

2- Unbound (Free):

- A) **0.03% of T4**
- B) **0.3% of T3**

Affecting on binding of thyroid hormones:-

In hepatic failure		
↓ TBG	↑ Free T3/T4	*Inhibition* of thyroid secretion.
In pregnancy		
↑ estrogen → ↑ TBG	↓ Free T3/T4	*stimulation* of thyroid secretion.

RELEASE OF T4 AND T3 TO THE TISSUES:

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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- In tissue Most of T4 (90%) is deionized to T3 by iodinase enzyme.

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

ACTION OF THYROID HORMONES:

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- 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

↓

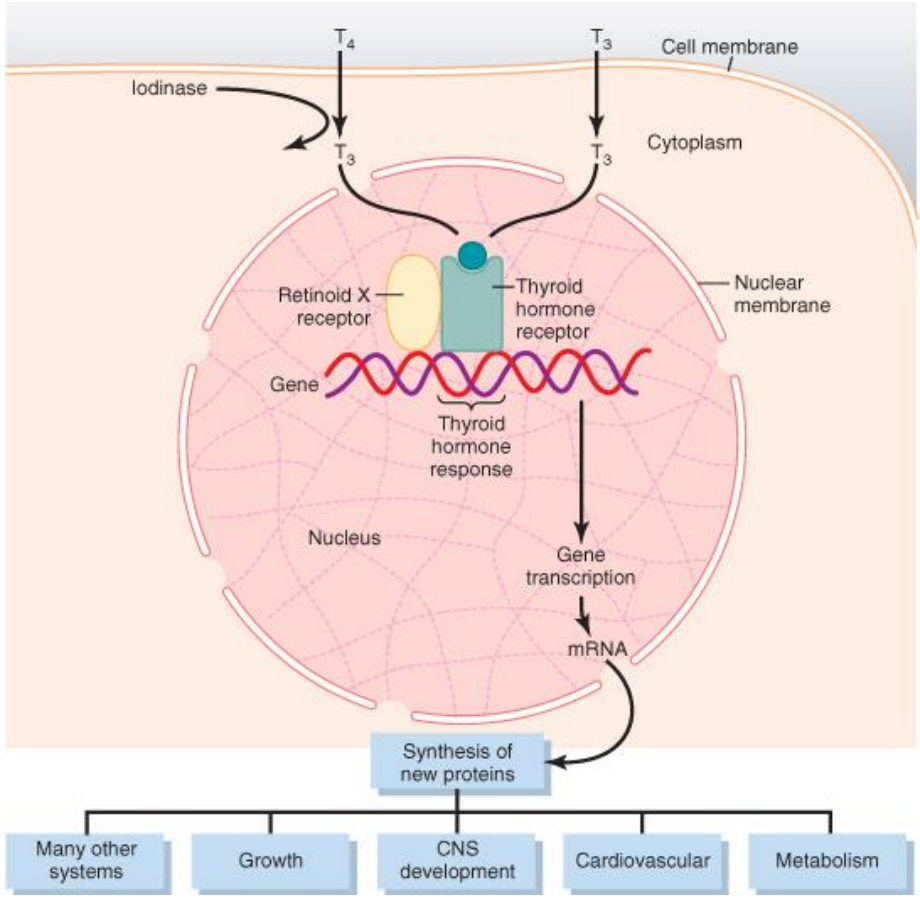
formation of mRNA

↓

translation of mRNA

↓

Specific ***protein synthesis*** (target tissue specific)]



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ACTION OF THYROID HORMONES:

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1- Basal Metabolic Rate (BMR)

Definition: 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

2- Metabolism

A) carbohydrate metabolism:	B) fat metabolism:	C) protein metabolism:
1. increase glucose uptake by the cells. 2. increase glycogenolysis. 3. increase gluconeogenesis. 4. increase absorption from the GIT.	1. increase lipolysis. 2. decrease plasma cholesterol by increase loss in feces. 3. increase oxidation of free fatty acids.	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 enzyme

3- Effects on the Cardiovascular system

- increase heart rate & increase stroke volume → **Cardiac output up to 60%**
- decrease peripheral resistance.

end result is increase delivery of oxygenated blood to the tissues. / The blood pressure **increase** due to **increase** Cardiac output up to 60%

The cardiovascular effects are due to:

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

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.

If there is **decrease** of hormones secretion lead to **irreversible mental retardation** → so 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

ACTION OF THYROID HORMONES:

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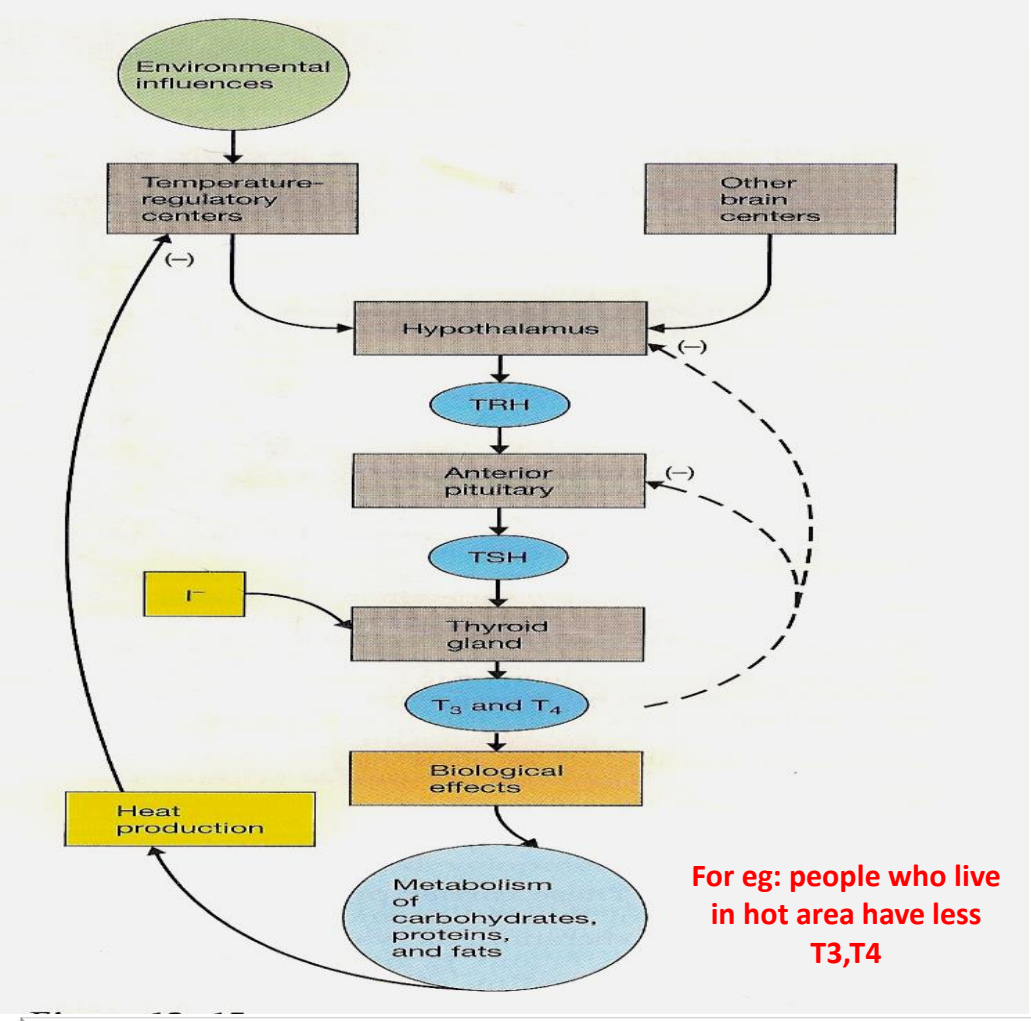
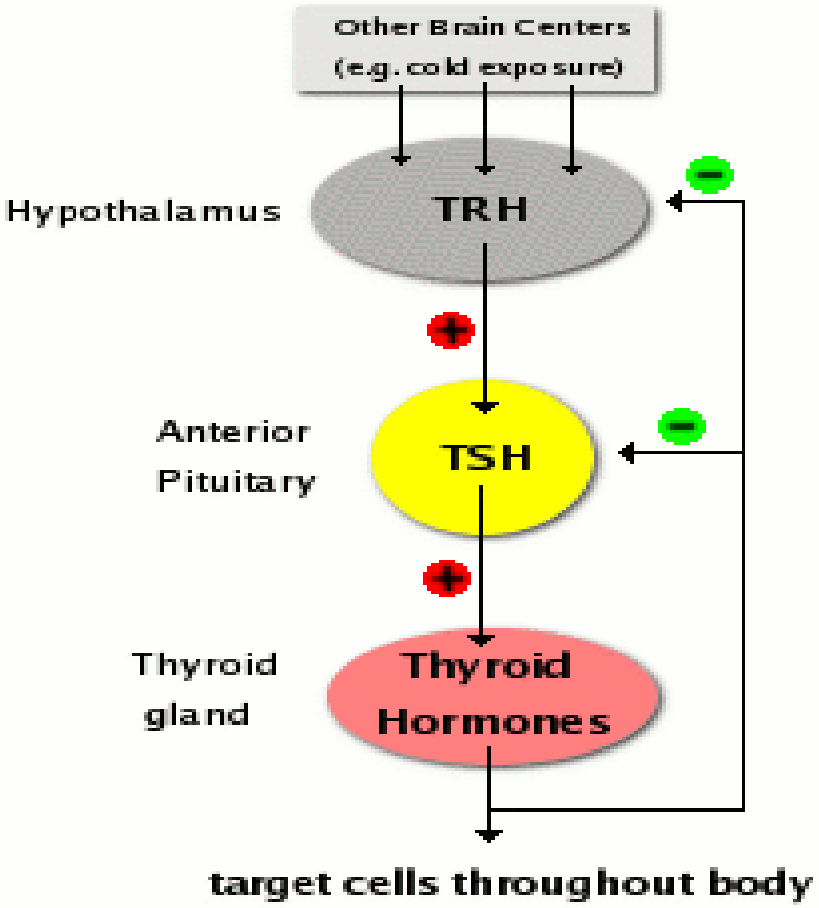
5- Effects on bone	**1.**promote bone formation **2.**promote ossification **3.**promote fusion of bone plate 4. promote bone maturation.
6- Effects on Respiration	1- increase ventilation rate. 2- increase dissociation of oxygen from Hb by increasing RBC 2,3-DPG (2,3 diphosphoglycerate). **2,3 Diphosphoglycerate**: 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.
7- Effects on the GIT	1- increase *appetite* and food intake. ياكل ما يسمن 2- increase of digestive juices *secretion*. 3- increase of G.I tract *motility*. - excess secretion → diarrhea. - lake of secretion → constipation 
8- Effects on Autonomic nervous system	**Produced the same action as *catecholamines* via β-adrenergic receptors including:** 1. increase BMR. 2. increase heat production. 3. increase heart rate. 4. 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.
- Mainly By negative feedback



For eg: people who live in hot area have less T3,T4



Factors affecting thyroids hormone secretion:

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Stimulatory factors	Inhibitory factors
• TSH • Thyroid-stimulating Immunoglobulins • Increasing TBG levels (e.g, pregnancy)	• Iodide deficiency • Deiodinase deficiency • Excessive **I** intake (Wolff-Chaikoff effect) • Perchlorate; thiocynate (inhibits Na/I co-transport) • Propylthiouracil (inhibits peroxidase enzyme) • Decrease TBG levels (e.g., liver disease)

1- Thyrotropin-releasing hormone (TRH):

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

2- Thyroid-stimulating hormone (TSH):

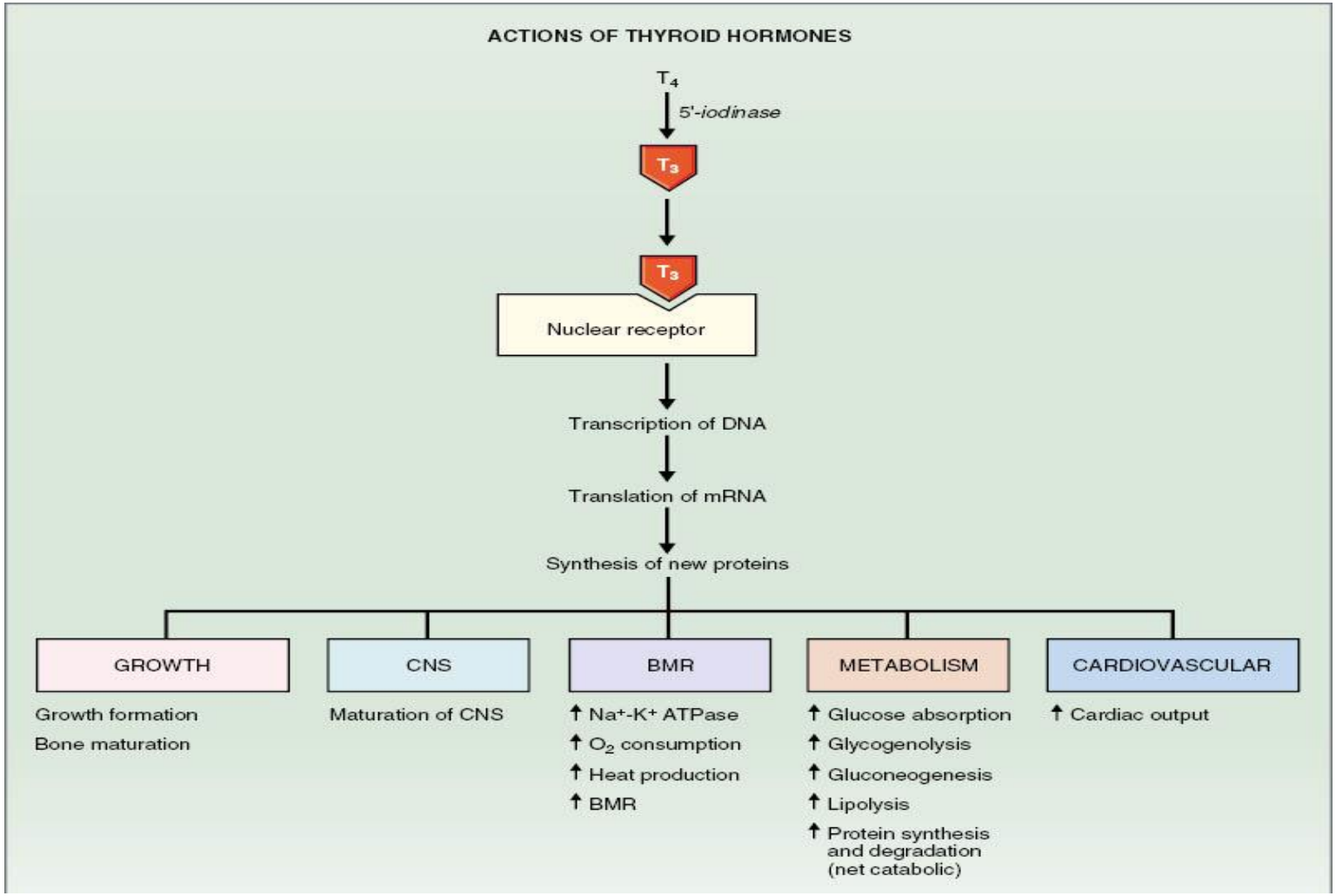
- Glycoprotein.
- Secreted from Anterior pituitary.
- Regulate metabolism
- Stimulate secretion and growth of thyroid gland (trophic effect).

*** 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


ACTIONS OF THYROID HORMONES
T_4
5'-iodinase
T_3
T_3
Nuclear receptor
Transcription of DNA
Translation of mRNA
Synthesis of new proteins
GROWTH
CNS
BMR
METABOLISM
CARDIOVASCULAR
Growth formation
Bone maturation
Maturation of CNS
↑ Na^+-K^+ ATPase
↑ O_2 consumption
↑ Heat production
↑ BMR
↑ Glucose absorption
↑ Glycogenolysis
↑ Gluconeogenesis
↑ Lipolysis
↑ Protein synthesis and degradation (net catabolic)
↑ Cardiac output

SUMMARY

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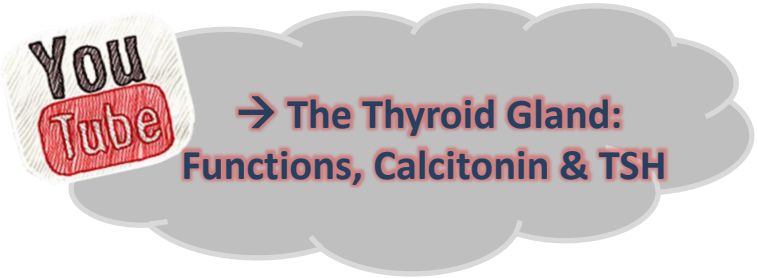
- our **thyroid gland** is an endocrine gland found at the base of your neck. The **thyroid follicles** found inside the gland contain a protein-rich fluid, from which we get the thyroid hormones: T3 and T4.
- Your diet must include iodine, which is easily obtained from iodized salt, in order to form the thyroid hormones. If there are three iodine atoms attached to the hormone, we call it **T3, or triiodothyronine**. If there are four iodine atoms attached, we call it **T4, or thyroxine**.
- T3 and T4 work together to control processes in the body including metabolism, body temperature, growth and development, and heart rate.
- Before these hormones can be formed, your anterior pituitary gland must secrete **thyroid-stimulating hormone (TSH)**, which is a hormone that stimulates the thyroid gland to produce T3 and T4.
- Besides influencing your metabolism, your thyroid gland also plays a role in regulating blood calcium levels through another hormone called **calcitonin**. Calcitonin has the effect of lowering blood calcium.



QUESTIONS

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1-Which hormone has the effect of lowering blood calcium by moving calcium into your bones?

A. Calcitonin
B. Thyroxine
C. TSH
D. T3

2. Which of the following trace minerals must be taken in through your diet for a healthy thyroid gland?

A. Magnesium
B. Iodine
C. Potassium
D. Calcium

3. Which hormone is the antagonist of Calcitonin?
gland?

A. T4
B. Thyroxine
C. Parathyroid Hormone
D. TSH

4-Which of the following statements concerning thyroid function are correct?
Please select all that apply.

A. T3 and T4 stimulate the secretion of TSH by the anterior pituitary
B. People who have an under-active thyroid gland have a low BMR
C. A resting pulse rate of 65 beats per minute would suggest a diagnosis of thyrotoxicosis
D. Most of the iodide in the body is present in the thyroid gland
E. Thyroid hormones are essential for the early development and maturation of the central nervous system

1	A
2	B
3	C
4	B,D,E

THE END

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If there are any Problems or Suggestions,
Feel free to contact us:

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THANK YOU

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