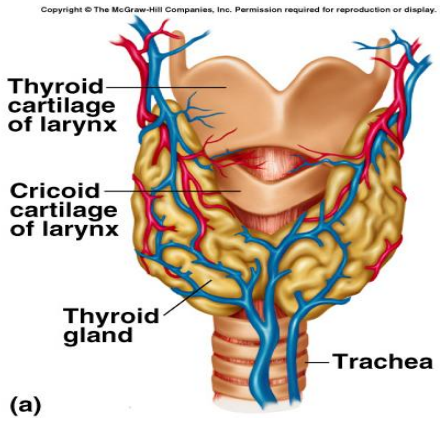
THE THYROID GLAND

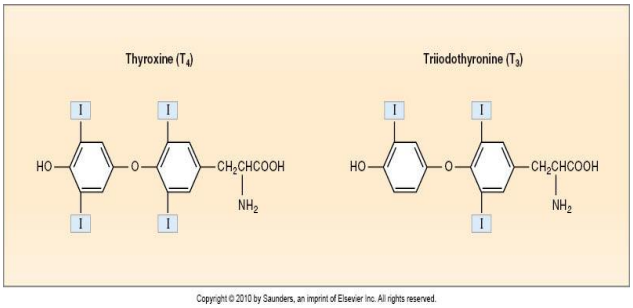
Location :

- **It is located below the larynx on either sides and anterior to the trachea.**
- **The first recognized endocrine gland.** بسبب تضخمها الملحوظ في كثير من الحالات ومكانها البارز
- **Weigh : 20g in adult.**
- **It has 2 or 3 lobes and has rich blood supply**



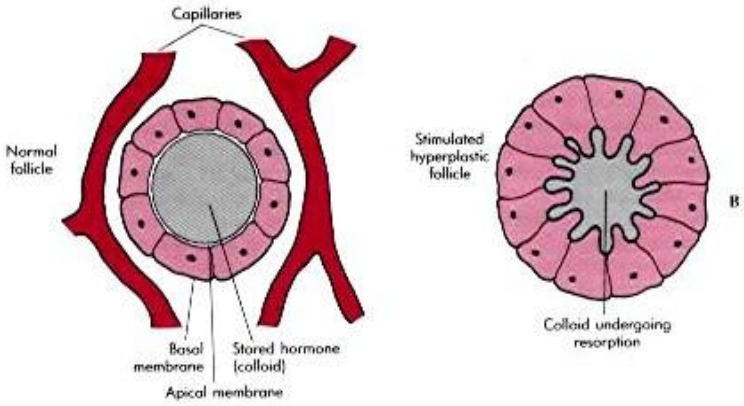
HORMONES WICH SECRETED BY THYROID GLAND :

- **1- T3 Triiodothyronine 10%.** (IT consist of 3 I atoms) – (it form only 10% of the hormonal secretion of the gland but it is very active)
- **2- T4 thyroxine (tetraiodothyronine) 90%.** (IT consist of 4 I atoms) – (it form 90% (most of) the hormonal secretion of the gland but it activity is lower than T3)
- **3- Reverse T3** (it is inactive form help in regulation of thyroid hormons in the body تفصل لاحقا وفي البايو ايضا)
- **4- Calcitonin.**

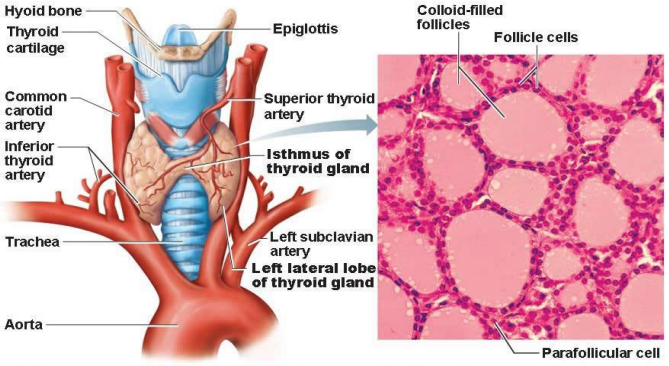


SYNTHESIS:

- **T3 , T4 and rT3 are synthesized by follicular cells**
- **Calcitonine is synthesized by Parafollicular cells**



■ 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.



(a) Gross anatomy of the thyroid gland, anterior view

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

THREE UNIQUE FEATURES OF THYROID HORMONS :

1- Contains a large amount of iodine. **WHICH COME FROM :**

- supplied in diet.

- 1mg/week.

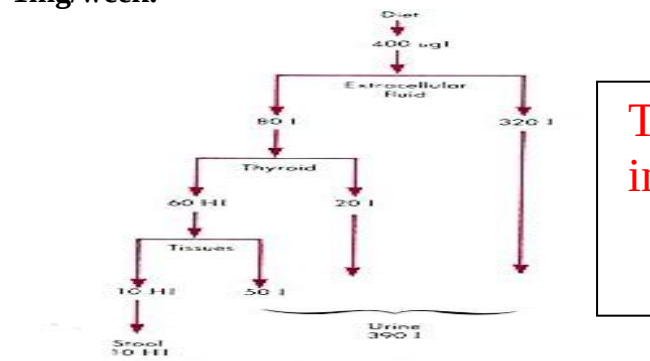


Fig. 49-2. Average daily iodide turnover in humans (United States). Note that 20% of the intake is taken up by the thyroid gland and 15% turns over in hormone synthesis and disposal. The unneeded excess is excreted in the urine. *I*, Iodide; *HI*, hormonal iodide.

THE amount of Iodine which get inside the body equal the amount which execrated outside

2- Synthesis is partially intracellular and partially extracellular. مهمه جدا

وسوف تتوضح في عمليه التصنيع لاحقا

With the completed hormones stored extracellular in the follicular lumen .

3- T4 is the major product . (because it form 90 % of the whole hormonal production but it has low activity so the target tissues converted it to active T3 تفصل لاحقا)

STEPS IN BIOSYNTHESIS: هذي الجزئيه : يقول الدكتور غير داخله في المقرر ولكن مهم جدا جدا قرائتها لفهم جميع المواد الاخرى التي تتحدث عن هذا الموضوع

The recipe الطريقه for making thyroid hormones calls for تتطلب وجود two principle raw خام materials:

- *1- Tyrosines* (single Amino Acid) are provided from a large glycoprotein scaffold called *thyroglobulin*
- 2- *Iodine*

تفاصيل التصنيع ودمج المركبان الخام:

1-THYROGLOBULIN FORMATION AND TRANSPORT:

- THYROGLOBULIN synthesized by thyroid epithelial cells (in Rough endoplasmic reticulum and Golgi apparatus) and secreted into the lumen of the follicle to form – colloid is essentially a pool of thyroglobulin - .

-. A molecule of thyroglobulin contains 140 tyrosine.

- Rough endoplasmic reticulum and Golgi apparatus are the main Factories to made the THYROGLOBULIN . .

2- IODIDE PUMP OR IODIDE TRAP (NA – I cotransport) :

iodide (I-) يكون اليود بشكل ايوني في الدم, is actively taken up from blood by thyroid epithelial cells (basal membrane), which have on their outer plasma membrane a sodium-iodide symporter or "iodine trap" وهذا عباره عن مضخه.

. So the Iodide is :

- Active transport to the inside of the cell (follicular cell)

- and the the pumping is affected by Wolff-chaikoff effect وفكره هذا انه اذا كان اليود عالى بالدم نشاطيه الغده تقل والعكس صحيح.

Note : the activity of the pump is regulated by I- levels in the body , so low level will stimulate the pump . when there is dietary deficiency of I- , the NA I pump increases it's activity , attempting to compensate for the deficiency . if the dietary deficiency is sever , however , even the NA I pump cannot compensate , and the synthesis of thyroid hormones will be decreased (High level will inhibit , very low " severe " inhibit , slightly low will stimulate)

- and the Ratio of concentration from 30-250 times.
- and the Pump is stimulated by TSH.

3- OXIDATION OF IODIDE TO IODINE:

Once inside the cell (at the apical membrane) , iodide is oxidized to I2 الشكل غير المتأين and transported into the lumen of the follicle along with thyroglobulin .
The oxidation process is done by Thyroid peroxidase Enzyme .
مهمه جدا جدا

4- ORGANIFICATION OF THYROGLOBULIN

Organification means : Binding of iodine with Thyroglobulin.

It Catalyzed by thyroid peroxidase. To form :

1. **MIT : Mono iodone thyroxine (T1)**
2. **DIT : Di iodine thyroxcine (T2)**

These (MIT and DIT) Remain attached to thyroglobulin until the thyroid gland is stimulated to secrete it's hormones .

Note : High levels of I- inhibit the organification and synthesis of thyroid hormones which known as the Wolff-Chaikoff effect .

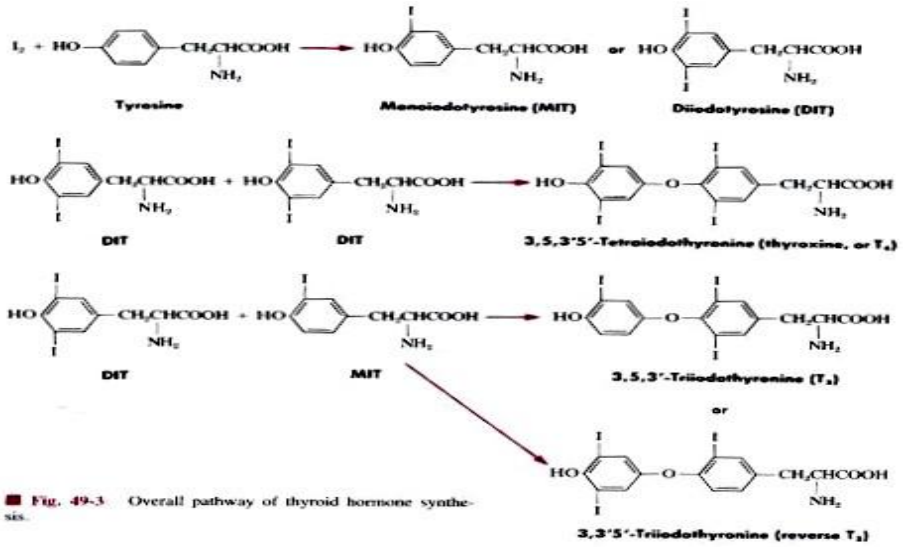
5- COUPLING REACTION :

The thyroglobine's attached (MIT and DIT) undergoes coupling reaction to form T3 and T4 as following :
DIT + DIT → T4
DIT + MIT → T3

These (MIT , DIT , T3 and T4) Remain attached to thyroglobulin until the gland stimulated to secret

It is located in or attached to the apical membrane (the side of the cell (follicular cell) which face the Follecular lumen). انظر الرسمه تحت اخر شي

Rember : the basal Membrene : is the side of the cell which face the blood stream



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

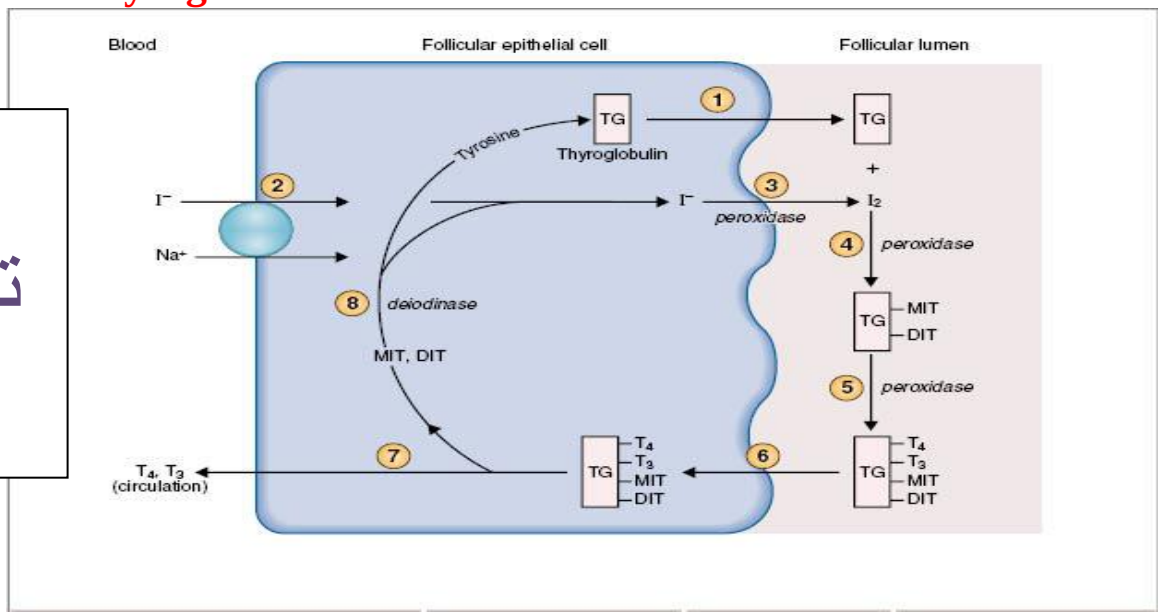
6- Endocytosis of thyroglobulin (and its attachments) to inside the cell

7- HYDROLYSIS OF T3 and T4 from THYROGLOBULIN BY LYSOSOMAL ENZYMES " after fusion of thyroglobulin with lysosomal membranes "

8- Delivery of T4 and T3 to the systemic circulation through the basal membrane.

رسمه تلخص ما سبق

9- Deiodination of DIT and MIT by thyroid deiodinase : After this step it will go back to it's precursor (I- and tyrosine) the I- will recycled and added to I- transported by the pump . tyrosine is incorporated into synthesis of new thyroglobulin .



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: (T3 and T4 are found in the blood either :

1- Unbound (free) عملها وتؤدي نشطه تكون الشكل بهذا:
0.03% of T4 and 0.3% of T3.
The free form lead to negative feedback on its own secretion from the Thyroid gland

2- Bound نشطه غير بحاله وتكون ببروتين مرتبطه تكون:
- 70- 80% bound to thyroxine-binding globulin (TBG) synthesised in the liver مهمه جدا يصنع هذا البروتين في الكبد.
- The reminder is bound to albumine.
The bounded form do not lead to negative feedback

So In hepatic failure:

TBG (decrease) → increase T3 + T4 free level (Active) → inhibition of thyroid secretion.

And In pregnancy:
estrogen → (increase) TBG → decrease T3 + T4 free level → stimulation of thyroid secretion.

RELEASE OF T4 AND T3 TO THE TISSUES:

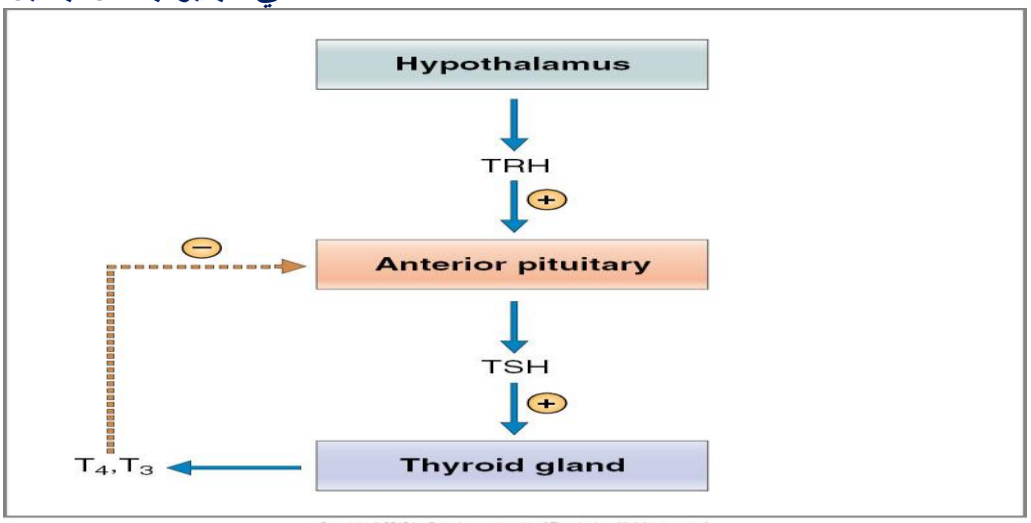
1-The release is slow because of the high affinity of the plasma binding protein
- **½ of T4 in the blood is released every 6 days.**
- **½ of T3 in the blood is released every one day.**

2- T3 and T4 Stored in the targeted tissues .

3-the Enzyme 5- iodinase transform the T4 to more active form (T3) مهمه جدا

Note : in starvation the tissue 5'-iodinase is inhibited (such as skeletal muscle) lead to lowering O2 consumption and basal metabolic rate , while the brain 5'-iodinase is not inhibited during caloric deprivation .

REGULATION OF HORMONES SECRETION: مشروحه في البايو بشكل جميل



By :

1- Thyrotropin-releasing hormone (TRH):

-it chemical structure : Tripeptide.

- it secreted from : Paraventricular nuclei of the hypothalamus.

- it Act on the thyrotrophs of the anterior pituitary

It activate Transcription and secretion of TSH from Pitutary. (recall the other action of TRH is stimulate the secretion of prolactin by anterior pituitary) .

2- Thyroid-stimulating hormone (TSH):

- it chemical structure: Glycoprotein.

- - it secreted from : Anterior pituitary.

- **It Regulate metabolism , secretion of thyroid hormones and growth of thyroid gland (trophic effect زياده حجم الغده).**

Note : the secretion of TSH begin at approximately gestational week 13 , the same time that fetal thyroid gland begins secreting thyroid hormones .

Action of TSH: (it stimulates each step in biosynthetic pathway)

- 1- Increase proteolysis of the thyroglobulin. (more I- and tyrosine)
- 2- Increase pump activity and oxidation .
- 3- Increase iodination of tyrosine.(organification)
- 4- Increase coupling reaction.
- 5- increase endocytosis
- 6- Trophic effect. زياده حجم الغده

- TSH secretion started at 11-13 of gestational weeks. مهمه جدا جدا
- TSH + receptor = activation of adenylyl cyclase via Gs protein cAMP (second messenger) activation of protein kinase multiple phosphorylation , secretion and thyroid growth.

مهمه حفظ

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)

Thyroid-stimulating immunoglobulins : antibodies to TSH receptor , they are components of IgG and when these antibodies binds to TSH receptors they produce the same action of TSH on thyroid cells → stimulation of synthesis and secretion of thyroid hormones and hypertrophy and hyperplasia of the gland (Graves' disease)

ACTION OF THYROID HORMONES:

- Before binding to the nuclear receptors 90% of T4 is converted to T3 by Enzyme 5- iodinase. (the conversion is the first action of hormones in the target tissue)

MOA : 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).

The Affects : يجب ان تعرف ان الهدف الرئيسي من هذا الهرمون هو زياده عمليات الايض وانتاج الطاقه في الجسم لذلك هي تعمل على تحديد

1- Basal metabolic rate (BMR): اشرحها يا ابو حميد اذا انت فاهمها ☺

- Is the energy requirement under basal condition (stat of mental and physical rest 12-18 hours after a meal). يعني الطاقة اللتي يحتاجها الجسم عندما يكون في وضع الإسترخاء " على الكنب " بعد ١٢ إلى ١٨ ساعة من آخر وجبة

BMR : thyroid hormones lead to increase the oxygen consumption and body temperature by inducing and increasing the synthesis of NA K Atpase (Note : thyroid hormones increase oxygen consumption in all tissue except brain , gonads and spleen)

- Complete lake of thyroid hormones 40% in BMR. يعني في الهيبو رح تقل عندي الطاقة المنتجة و بالتالي الإنسان رح يشعر بالبرودة "لأن الطاقة عبارة عن إنتاج للحرارة "

- **Extreme increase of thyroid hormones 60-100% in BMR.** رح يزيد إنتاج الطاقة و يحدث العكس " يشعر الإنسان بالحرارة

2- Metabolism: it affect on : وهنا ايضا تتحكم بعمليات الايض للمواد الغذائيه بالشكل الذي يمكن منه انتاج الطاقه والحراره كما يلي :

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.

بما إنه رح يزيد نشاطية الخلايا فـ الخلايا تحتاج طاقة فـ لازم نوفر جلوكوز و فات للعمليات هذي

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. (by up regulate cardiac B1-adenergic receptors which lead to increase heart rate and contractility)
- increase stroke volume.
- decrease peripheral resistance.
: end result is increase delivery of oxygenated blood to the tissues السبب لكي يصل الى والتي تزداد له الحاجه بسبب عمليات الايض وانتاج الطاقه

This effect by thyroid hormone on CVS (mainly increasing Cardiac output) is achieved by "

1- indirect effect : Thyroid hormones potntiate 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 (Hypothyrodism) 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- decrease mental capacity.

Note : both GH and thyroid hormone deficiency will cause uncompleted growth (short stature , decrease muscle mass …) but the different between GH deficiency and thyroid hormone deficiency is MENTAL RETARDATION which is present with thyroid hormone deficiency . " تذكروا اللي في السيرك " أقزام لكن يفهمون

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- effect on Bone :

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

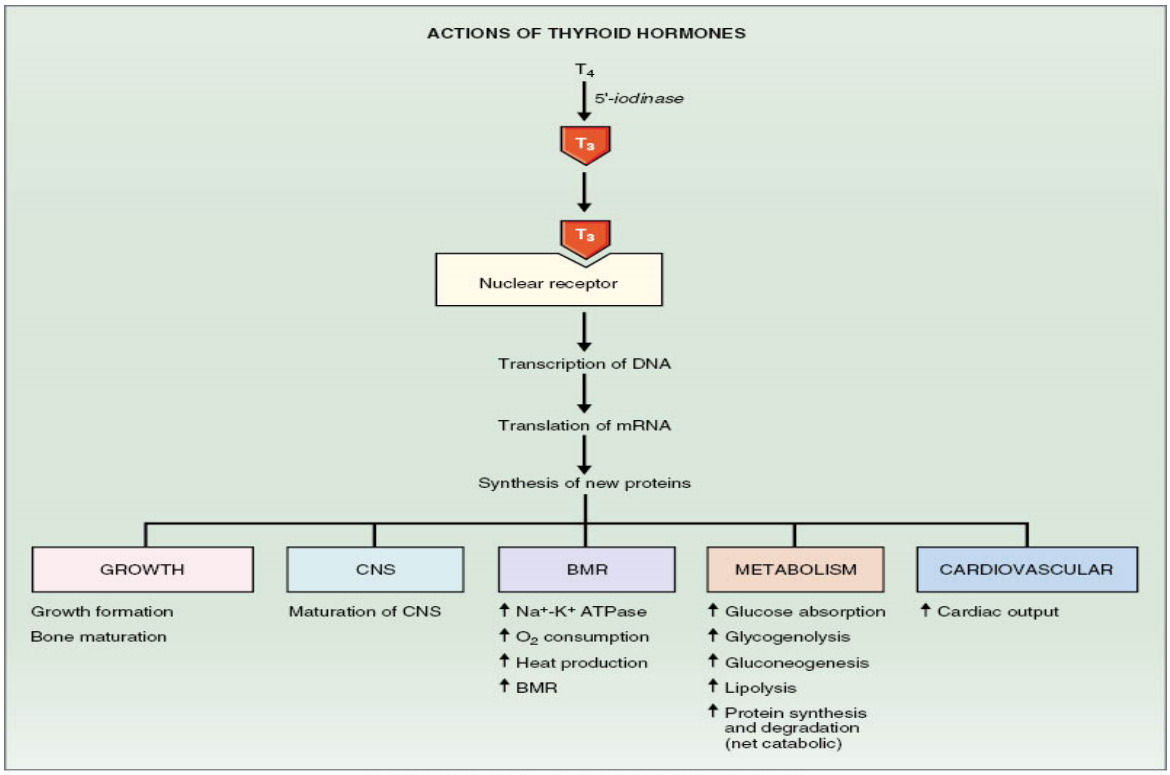
9- Effects on respiration:

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

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.



تعديل وتنسيق :

محمد المومني

مشكورا