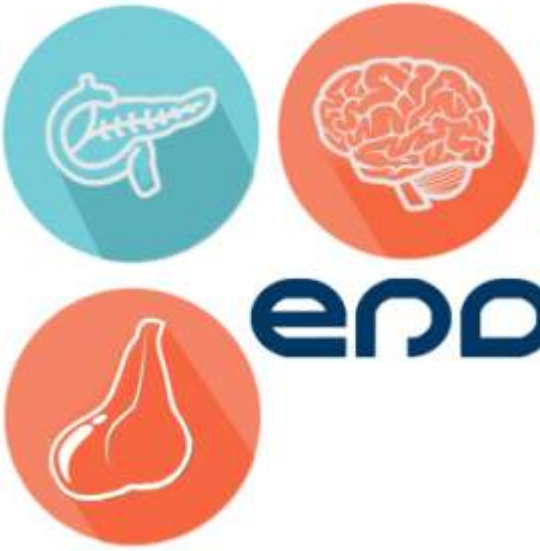


endocrine system

physiology

Sheet Slide

number 4

Done by Enas Ajarma

Correction Ahmad Al-Tarefe

Doctor Saleem

"اللهم إني استودعتك ما حفظت وما قرأت ، فردّه إلي عند حاجتي إليه ولا تنسني إياه

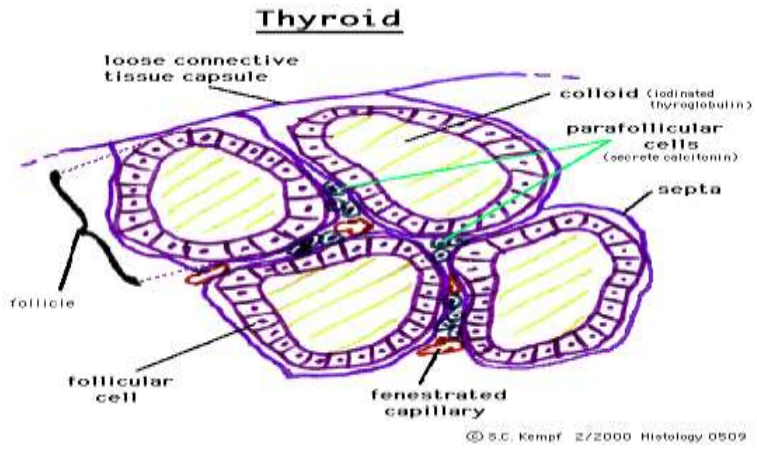
Anatomy of Thyroid gland

- It's composed of two lobes right and left joined together by a stalk called **isthmus**, it lies in front of trachea and it is richly supplied with blood capillaries.

-At 12th week of gestation, the thyroid and pituitary glands begin to function for normal development of CNS and skeleton because maternal thyroid hormones, anterior pituitary and the hypothalamic hormones can't cross the placenta. SO the fetus must synthesize its own hormones.

- When taking cross section from thyroid gland you can see follicles lined by cuboidal epithelium. In between the follicles there is **parafollicular cells** that produce the unrelated hormone **calcitonin** which functions on decreasing the Ca+ plasma level.

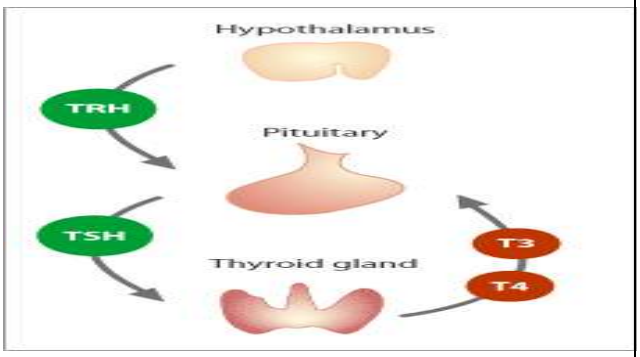
- The epithelial (follicular) cells secrete hormones into the **<u>colloid</u>** which is filled with fluid that contains hormones , amino acids , enzymes .. etc.



Physiology of Thyroid gland

- **The secretion of the thyroid hormones is controlled by the anterior pituitary and the hypothalamus**.

➢ Thyroid gland is stimulated by TSH (thyroid-stimulating Hormone from the anterior pituitary gland). TSH is stimulated by TRH (Thyrotropin-releasing hormone, a hypothalamic hormone).



The Hypothalamic–pituitary control is achieved through:

A. **TRH:** secreted by the hypothalamus and stimulates the secretion of **TSH** by the anterior pituitary.

A. **TSH:** stimulates the growth of the cells of thyroid gland and increases both the synthesis and secretion of thyroid hormones by the follicular cells.

C. **TSH:** acts on the cells by producing c-AMP for the synthesis and secretion of the thyroid hormones, and the two second messengers DAG & IP3 for the growth and the metabolism of the cells.

Consequently, **TSH** stimulates the growth of the cells as well as the synthesis and secretion of hormones.

Note: **TSH** is **inhibited** by the Dopamine, Somatostatin, cortisol and growth hormone.

TSH is a glycoprotein, and its receptor is on the cell membrane. It is composed of two peptides subunits:

1- **Alpha (α) subunit** is nonspecific because it is also part of the three unrelated hormones (LH, FSH, CGH).

2- **Beta (β) subunit** is the specific biological active site of the hormone , it differs between TSH & (LH ,FSH, CGH), and it doesn't function unless it is bound with alpha .

- **Thyroid gland is unique because of two aspects :**

  1- Incorporation of inorganic substances (iodine) with organic substances (tyrosine).
  2- It is the only gland that stores a lot of hormones inside the **colloid**. Stored hormones are sufficient for about 2- 3 months and at least for one month. It varies from person to another depending on many factors such as diet.

Now depending on the second aspect, think of this: If we isolate thyroid gland by cutting the blood supply, what will happen to the patient?

Answer: The patient won't need thyroid hormones supplement for 2-3 months because he/she has stored thyroid hormones.

- The thyroid gland produces **iodothyronines** and **iodotyrosines** (iodotyrosines are the **<u>iodinated</u>** amino acids) :

  1- Tyrosine with one iodine forms **monoiodotyrosine(MIT) ,** with another iodine you will have **Diiodotyrosine(DIT) .** This is called **<u>Iodination.</u>**

  2- One monoiodotyrosine binds with diiodotyrosine to form **triiodothyronine (T3) hormone**, but when two diiodotyrosine binds; **tetraiodothyronine (T4)or thyroxine hormone** is formed. This is called **<u>Coupling</u>**.

-There is an enzyme that inactivates T3 or T4 to produce inactive hormone called **Reverse T3** , the difference between T3 & reverse T3 is the location of the iodine on the tyrosine which is <u>3,5,3</u> and <u>3,3,5</u> for **T3** and **Reverse T3** respectively .

- Tyrosine maximally carries 2 iodines.
- Thyroid gland produces mainly T4, little of T3, and little of reverse T3.
- T4 is the pro-hormone that produces the other hormones. The functioning hormone is T3, while T4 is either inactive or has a little activity and reverse T3 is totally inactive .

(0 – 11 min)

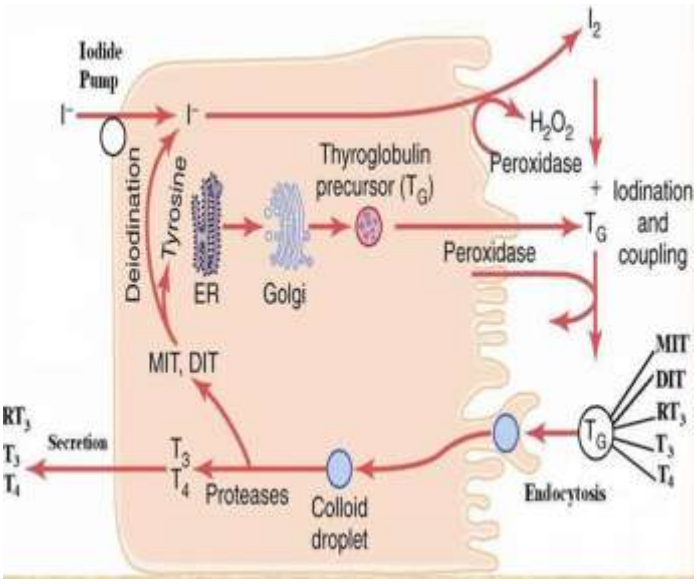
❖ **Synthesis and the secretion of the thyroid hormones:**

Synthesis needs iodine, iodine is taken from the plasma or from inside the cells, then iodine is taken inside the follicular cells through iodide pump or Na+/ I- cotransport (active transport). In the follicular cell membrane there are peroxidases that oxidase I- into I2 and after the oxidation, the iodination and coupling occurs.

- The epithelial cells also produce protein called **thyroglobulin(Tg)** that is secreted into the colloid which is composed of amino acids Tyrosine ranged in 100- 120 (varies from one person to another) .

-In the thyroglobulin not the 100 tyrosine bind to iodine just 70 bind to iodine .

- Some of these tyrosine residues can carry iodine and the others carry thyroid hormones.



- Only 4 to 8 of 70 tyrosine residues are normally incorporated into thyroid hormones.

-The iodination and coupling don't occur on free tyrosine, but occur on the tyrosine in the structure of thyroglobulin .

- As a result, thyroid hormones are stored in the colloid on the thyroglobulin, each thyroglobulin carries mainly T4, T3, reverse T3 and monoiodotyrosine diesters.

- Tg carrying (T3, T4, MIT & DIT) is transported from the colloid into the cells by **pinocytosis**. Inside the cell, under the effect of enzymes (proteases) these hormones become free, then the hormones (T4, T3, rT3) are released into the blood to perform their function.

*To understand it better watch this video:

https://www.youtube.com/watch?v=uCjpGlnCjeA

***Metabolism of thyroxine (T4)**

As we said it's a pro-hormone from which other hormones are synthesized. T4 either produces inactive substances; reverse T3 (95%) or Tetrac (tetraiodoacetic acid), or it produces active substances; T3 (75%) or (DIT) di-iodotyrosine.

(11-20 min)

- Thyroid hormones are very dangerous; therefore almost their entire portion is bound to proteins; 99.5% of T3 and 99.98% of T4.

	Actual binding T4 %	Actual binding T3 %
TBG	75	75
Albumin	10	25
TBPA	15	0 T3 doesn't bind to TBPA.

- Three proteins can bind to thyroid hormones: thyronine-binding globulin (TBG) , Albumin and thyroxine-binding pre-albumin (TBPA) .

- **Binding of thyroid hormones to proteins have two advantages :**
  1- Prevention of filtration. 2- Elongation of their half-life.

Table 53-1 Thyroid hormone turnover

	T_4	T_3	rT_3
Daily production (μg)	90	35	35
From thyroid (%)	100	25	5
From T_4 (%)	—	75	95
Extracellular pool (μg)	850	40	40
Plasma concentration			
Total (μg/dl)	8.0	0.12	0.04
Free (ng/dl)	2.0	0.28	0.20
Half-life (days)	7	1	0.8
Metabolic clearance (L/day)	1	26	77
Fractional turnover per day (%)	10	75	90

The Physiological Actions of Thyroid Hormones (they affect almost all the systems of the body):

●Thyroid hormone intracellular action is a good example of lipid soluble hormones signaling pathways:

1- Thyroid hormones can penetrate the cell membrane.

2- They bind the receptor inside the cell membrane or nuclear membrane

3- Activating DNA.

4- Producing mRNA.

5- Producing physiological response.

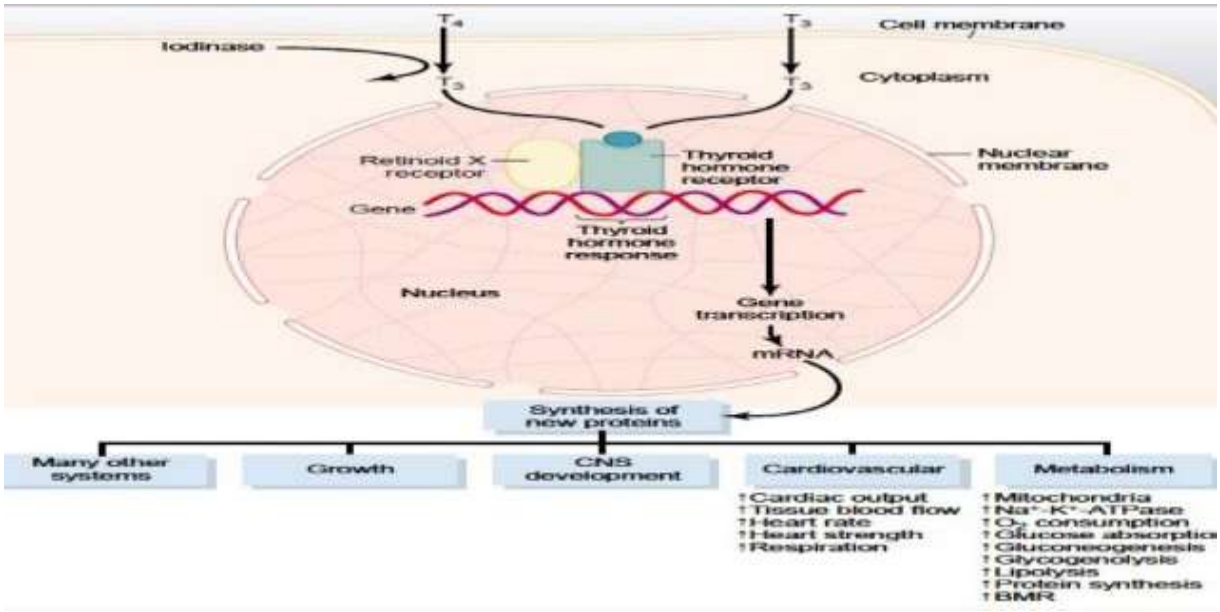
●Physiological responses are due to gene expression of many enzymes, thus activating all metabolic activities, major responses are:

➢ Enhance cellular metabolic activities by increasing Na+, K+ ATPase, Increasing respiratory enzymes as well as Increasing other enzymes and proteins for growth and maturation.

➢ This leads to Increase in consumption of oxygen by Increasing cardiac output as well as Increasing ventilation.

➢ this requires taking substrates, then subsequently increasing food intake and increasing mobilization of carbohydrates, proteins and fat.

➢ The end result is; Increasing CO2 production and thermogenesis.



●The figure above summarizes thyroid hormone functions and mechanism of action.

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

- Thyroid-stimulating immunoglobulins are proteins that are increased in a cancerous condition.

* Multiple hormones, including growth hormone (GH), insulin-like growth factors (IGF-I and -II), insulin, thyroid hormones, glucocorticoids, androgens & estrogens contribute to the growth process in humans. Among these, GH & IGF-I have been implicated as the major determinants of growth in normal post-uterine life.

* Thyroid hormones are essential in normal amounts for growth; excess does not produce overgrowth as with GH, but causes increase catabolism of proteins & other nutrients.

* Thyroxine at normal concentrations has synergistic effect on the action of GH on protein synthesis. In the absence of thyroxine, amino acids uptake & protein synthesis are not much stimulated, similar to adrenaline.

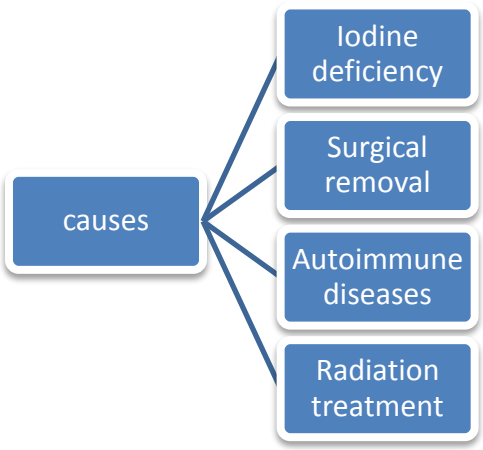
Clinical applications:

1-Pituitary dwarfism vs. cretinism:

- Reduced thyroid activity in childhood produces dwarfs who are mentally retarded, whereas reduced GH in childhood produces dwarfs with normal intelligence.
- Dwarfs due to thyroid deficiency during childhood called **cretins** (cretinism disease), they have failure of skeletal, mental growth, sexual "sms" and development.

2 **Hypothyroidism:** means under activity of thyroid.

The Deficiency of thyroid hormones during adulthood causes **myxoedema** , results in slowing down of all bodily processes (Tissue oxidation, Gut movements, Basal Metabolic Rate (BMR), Heart and Respiratory Rates, Body temperature falls, Thought processes, Blood Cholesterol increases, Slow husky voice, Appetite is reduced, Hair-Brittle, dry.



3-Hyperthyrodisim:

●Causes: increased production of thyroid stimulating immunoglobulins (TSI) (Graves' disease), secondary to excess hypothalamic and pituitary secretion, hypersecreting thyroid tumor (Adenoma**).**

* In Graves ' disease there is:

1-Exophthalmus: the protrusion of the eye balls. Most but not all patients with hyperthyroidism develop some degree of protruding of eye balls, It usually occurs due to increased production of antibody called Thyroid Stimulating Immunoglobulin (TSI) which acts against a protein of the extraocular muscles and the connective tissue behind the eye which causes these tissues to swell, It is not due to an excess of the thyroid hormones .The patient cannot close his eyes and he is exposed to blindness.

2- Goiter: enlargement of the thyroid gland, it does occur in both hypothyroidism and hyperthyroidism because of the continuous stimulation of thyroid cells.

●When T3, T4 levels are low, this is simple nontoxic goiter (benign goiter) .

● When T3, T4 levels are high, this is toxic malignant goiter (hyperthyroidism) .

●Sometimes although there is high or low levels of T3, T4 but there is no goiter.

●Even when it's enlarged, your thyroid may produce normal amounts of hormones.

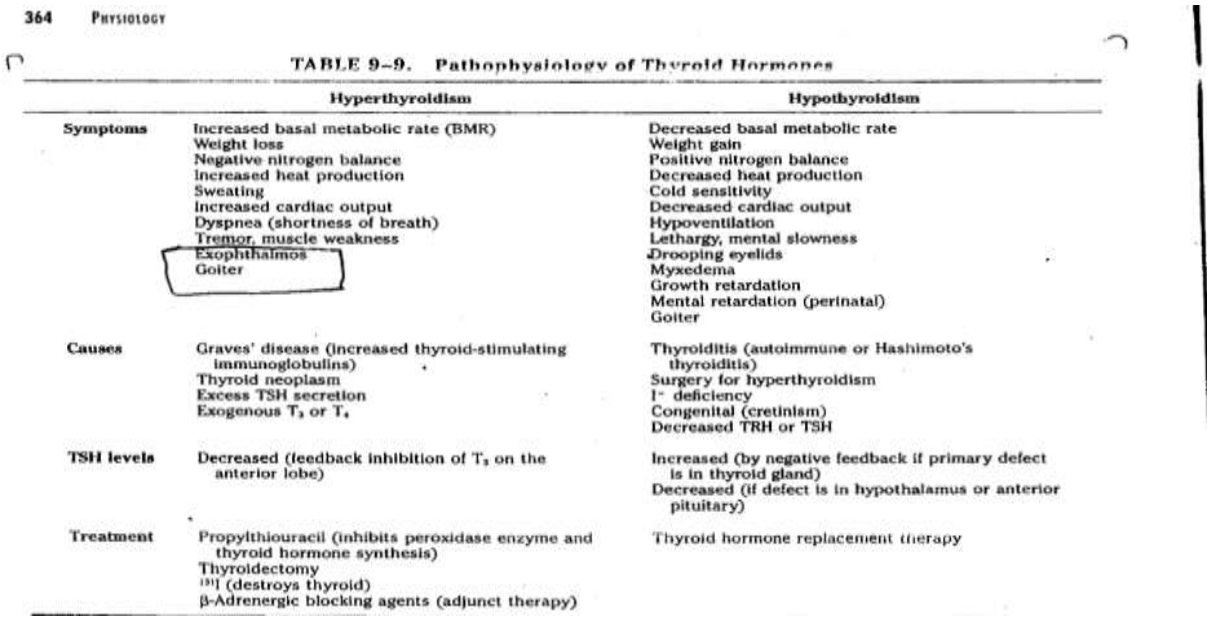


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TABLE 9–9. Pathophysiology of Thyroid Hormones

	Hyperthyroidism	Hypothyroidism
Symptoms	Increased basal metabolic rate (BMR) Weight loss Negative nitrogen balance Increased heat production Sweating Increased cardiac output Dyspnea (shortness of breath) Tremor, muscle weakness Exophthalmos Goiter	Decreased basal metabolic rate Weight gain Positive nitrogen balance Decreased heat production Cold sensitivity Decreased cardiac output Hypoventilation Lethargy, mental slowness Drooping eyelids Myxedema Growth retardation Mental retardation (perinatal) Goiter
Causes	Graves' disease (increased thyroid-stimulating immunoglobulins) Thyroid neoplasm Excess TSH secretion Exogenous T_3 or T_4	Thyroiditis (autoimmune or Hashimoto's thyroiditis) Surgery for hyperthyroidism I^- deficiency Congenital (cretinism) Decreased TRH or TSH
TSH levels	Decreased (feedback inhibition of T_3 on the anterior lobe)	Increased (by negative feedback if primary defect is in thyroid gland) Decreased (if defect is in hypothalamus or anterior pituitary)
Treatment	Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis) Thyroidectomy ^{131}I (destroys thyroid) β-Adrenergic blocking agents (adjunct therapy)	Thyroid hormone replacement therapy

(20 – 34 min)

Past papers:

1-Which is false about the thyroid : Iodine deficiency doesn't cause goiter.

2-) Which is false about T4 : It acts more rapidly than T3

3-Which is true about thyroglobulin: Contains MIT & DIT

4-True about Thyroxin synthesis: Iodide (I-) is oxidized to Iodine (I2)

5-Which of the following when found in excess amounts causes protein catabolism : T3.

6-What happens to most of T4 ? converted to T3

7-which of the following does not occur in thyroid hormone synthesis: >>> 4 molecules of iodine bind to one molecule of tyrosine to form tetraiodothyronine (must 2 T2 to combine not 4 I at the same time).

8-Most abundant thyroid hormone produced is : T4 and most potent? T3.

BE LIKE STEM CELLS, DIFFERENTIATE YOURSELF FROM OTHERS !