PHYSIOLOGY

Sheet 13
1/3/2020

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correction

Dr. Salem

Thyroid-stimulating hormone (TSH)

- As we said, thyroid gland is stimulated by TSH (glycoprotein) which is secreted by pituitary gland TSH hormone stimulates the growth of the gland as well as the production of thyroid gland hormones (synthesis and secretion).
- TSH is stimulated by TRH (hypothalamic hormone) (tripeptide), firstly TRH released into median eminence[1] before it affects the pituitary gland to secrete TSH.

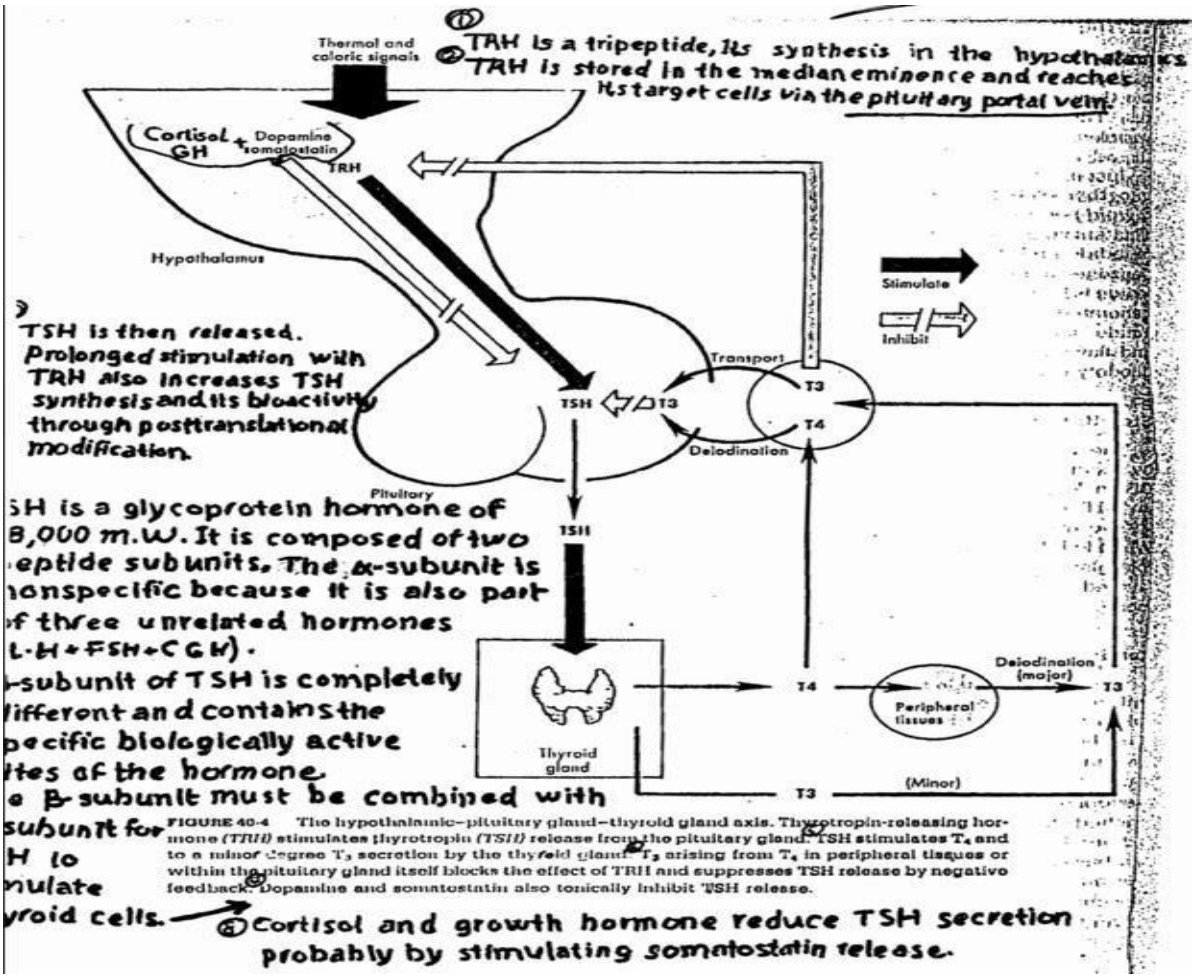


FIGURE 40-4 The hypothalamic–pituitary gland–thyroid gland axis. Thyrotropin-releasing hormone (TRH) stimulates thyrotropin (TSH) release from the pituitary gland. TSH stimulates T_4 and to a minor degree T_3 secretion by the thyroid gland. T_3 arising from T_4 in peripheral tissues or within the pituitary gland itself blocks the effect of TRH and suppresses TSH release by negative feedback. Dopamine and somatostatin also tonically inhibit TSH release.

[1] The **median eminence** is a part of the hypothalamus from which regulatory hormones are released

- TSH is composed of 2 subunits: an α (nonspecific or nonfunctional) subunit and a β (specific or functional) subunit, in order for the β subunit to function it should be bound to the α subunit, as in figure1.
- TSH is inhibited by Dopamine, Somatostatin, Cortisol, and Growth Hormone.
- When TSH binds to its receptor in the membrane of thyroid cells it causes the production of cAMP and other two second messengers to the cytosol (IP_3, DAG), cAMP most probably for the synthesis and releasing of thyroid hormones, and the other two messengers for the metabolism of the gland.

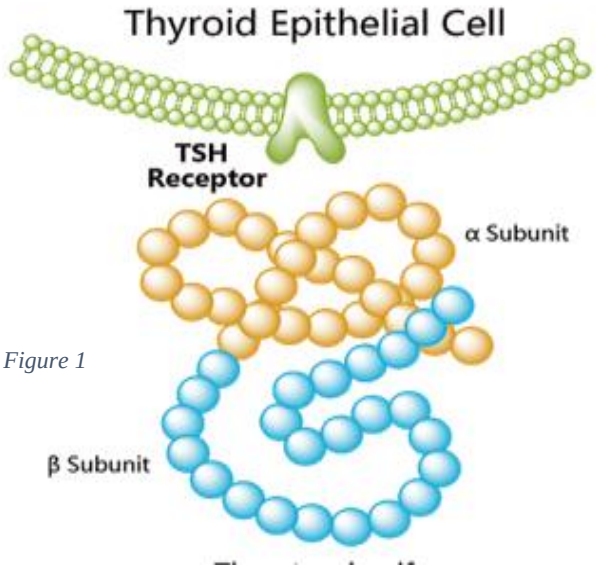


Figure 1

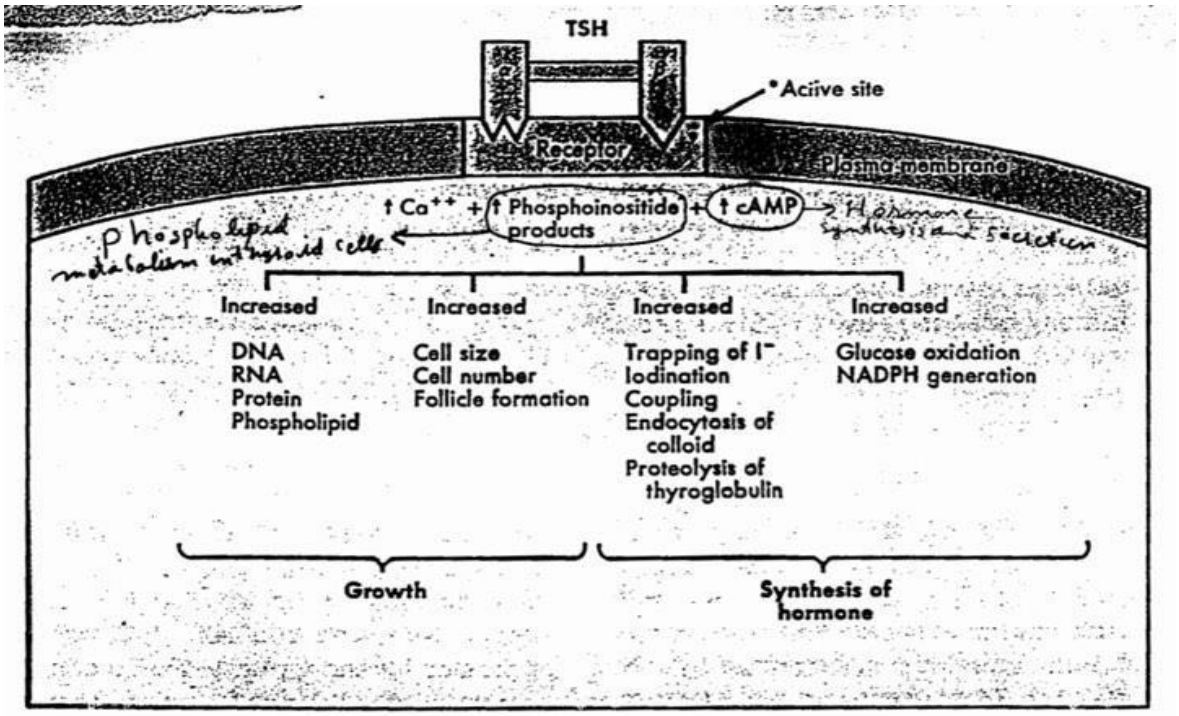
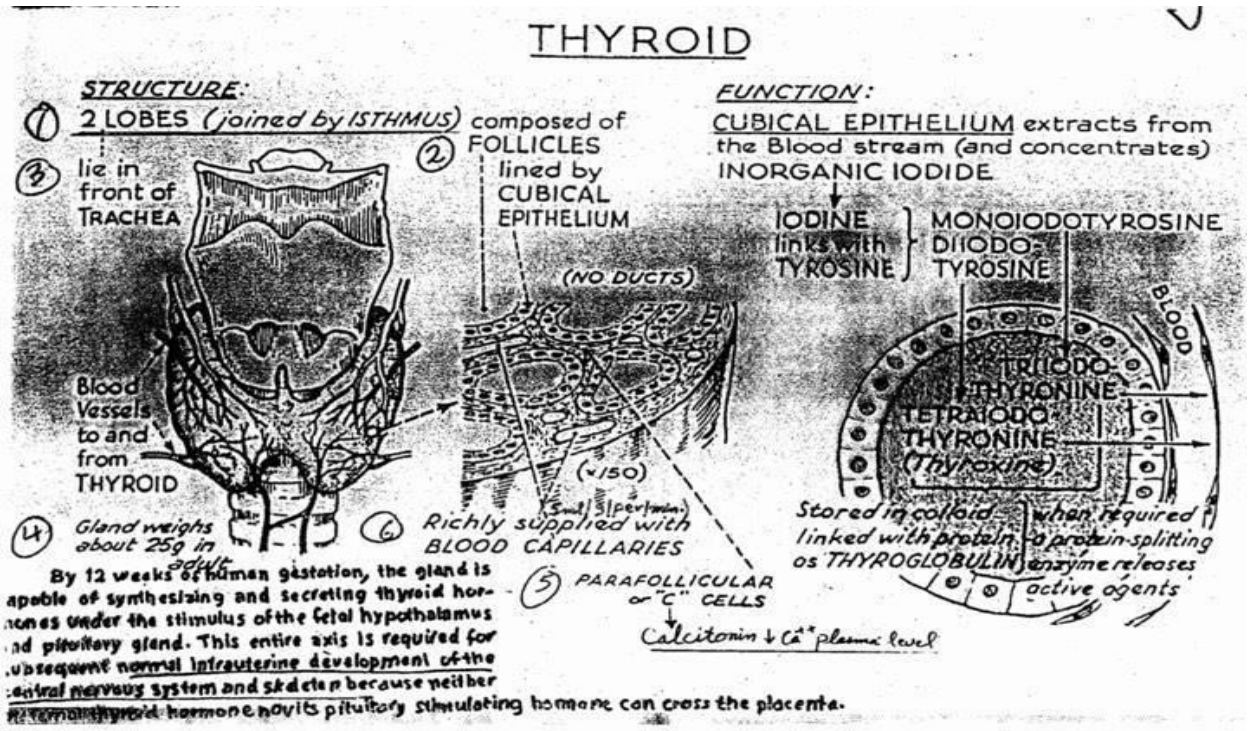


FIGURE 40-5 TSH actions on the thyroid cell. Cyclic adenosine monophosphate *(cAMP)* along with calcium ions *(Ca^{++})* and phosphoinositol products act as second messengers generated by TSH binding to its receptor. All steps in thyroid hormone production, as well as many aspects of thyroid cell metabolism and growth, are stimulated by TSH.

Thyroid gland

- Thyroid gland lies in front of the trachea, weighs 30 g.
- Composed of right and left lobes joined by an isthmus.
- It has a rich blood supply, and that indicates the importance of the gland.
- By 12 weeks of gestation, thyroid gland of the fetus begins to produce hormones under the effect of the pituitary and the hypothalamus of the fetus.
- Production of fetal hormones is essential for the normal development of the skeleton and the nervous system so any deficiency in thyroid hormones in this time will lead to developmental problems in these two systems.



- The fetus does not benefit from maternal thyroid hormones; because they don’t pass through the placenta into the fetal blood .although, they are small.

- Thyroid gland is composed of follicles, which are filled with fluids (fluid full of proteins, enzymes, hormones, …etc.).

- These follicles are encircled by epithelial cells (or thyroid cells or follicular cells), these cells synthesize the hormones and store it in the follicles.

- In between epithelial cells, there are parafollicular cells (or C cells) that produce an unrelated hormone which is calcitonin has a function related to the calcium.

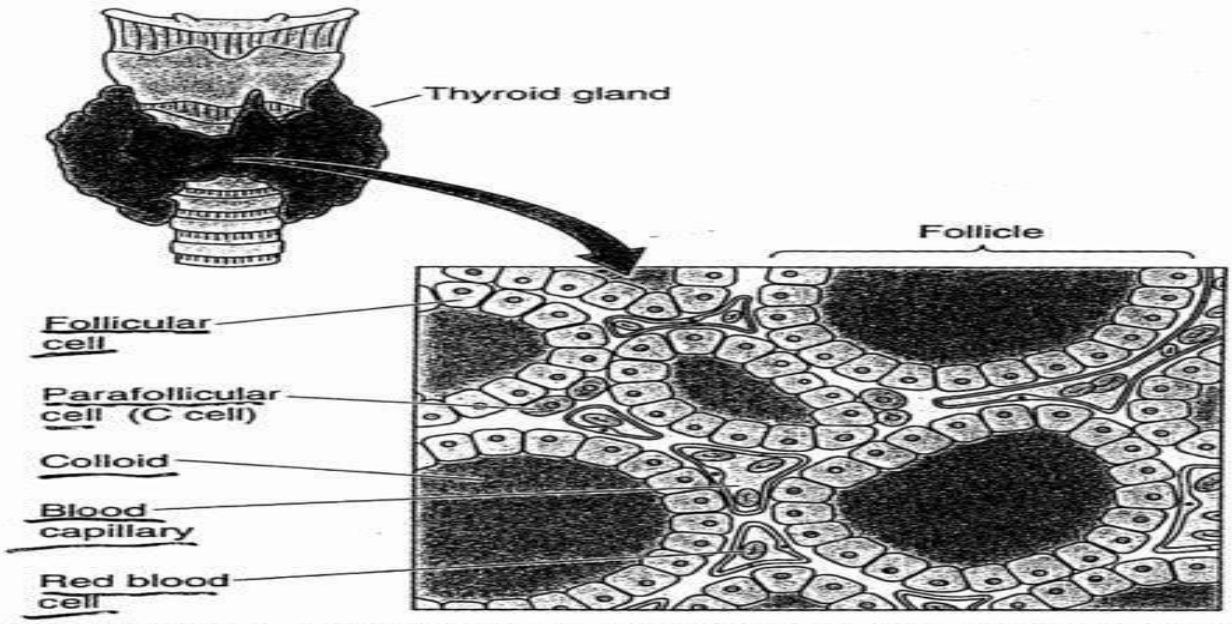


FIGURE 48–1. Structure of the thyroid gland. The thyroid gland is located anterior to the cricoid cartilage in the anterior neck. The gland comprises numerous follicles, which are filled with colloid and lined by follicular cells. These follicular cells are responsible for the trapping of iodine and the synthesis of thyroglobulin, which contains thyroid hormone as part of its primary structure. These cells also secrete thyroglobulin—the major protein of the thyroid colloid—into the lumen of the follicle. The thyroglobulin protein that is stored in the follicular lumen contains numerous iodinated tyrosines and thyronines, which are derivatives of the amino acid tyrosine. On command, the follicular cells take up the thyroglobulin and release the thyroid hormones triiodothyronine (T_3) and thyroxine, or tetraiodothyronine (T_4), into the blood.

Thyroid hormones

- As we know about the chemistry of hormones, they are either proteins or amino acid derivatives or steroids. Thyroid hormones are amino acid derivatives.
- Thyroid hormones (T_3, T_4) exert a negative feedback mechanism on the pituitary gland as well as on the hypothalamus. “understood? Aaah ya 38ab?”
- They are composed of 2 Tyrosine residues, Tyr can bind Iodine. **This is a unique property for the thyroid gland; as it is the only gland in the body that binds an inorganic substance with an organic substance.**
- **Also, the Thyroid gland can store hormones that are sufficient for the human being for about 2 or 3 months. Also, this is a unique property for the gland.**
- The storage of thyroid hormones different than the storage of iodine(6 months).

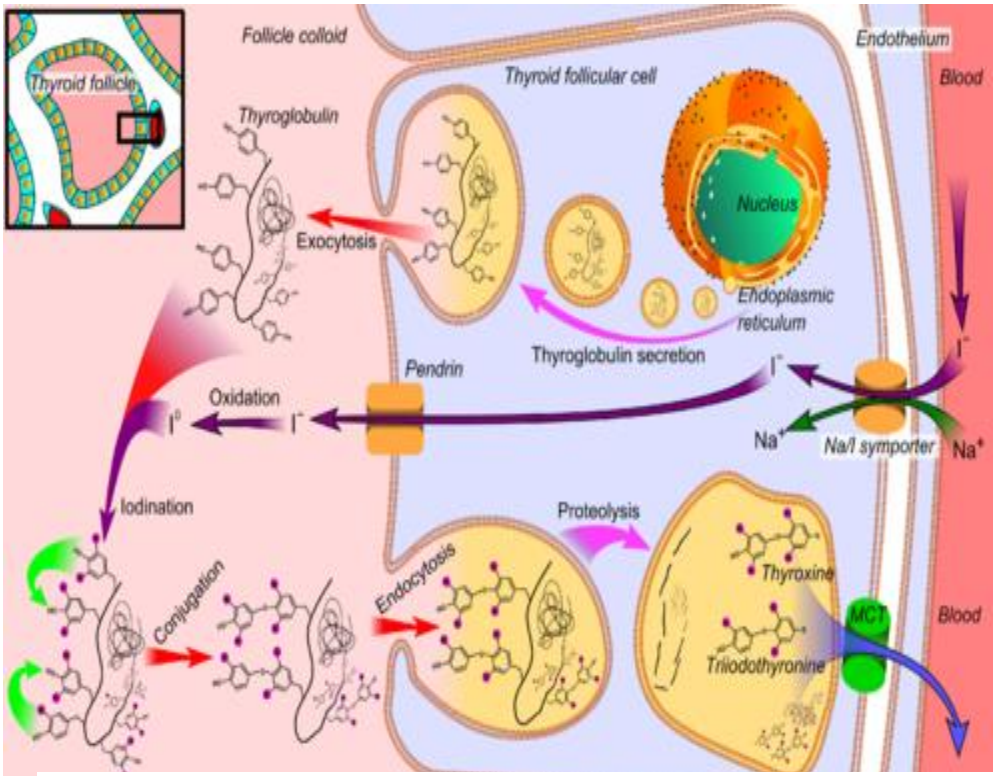
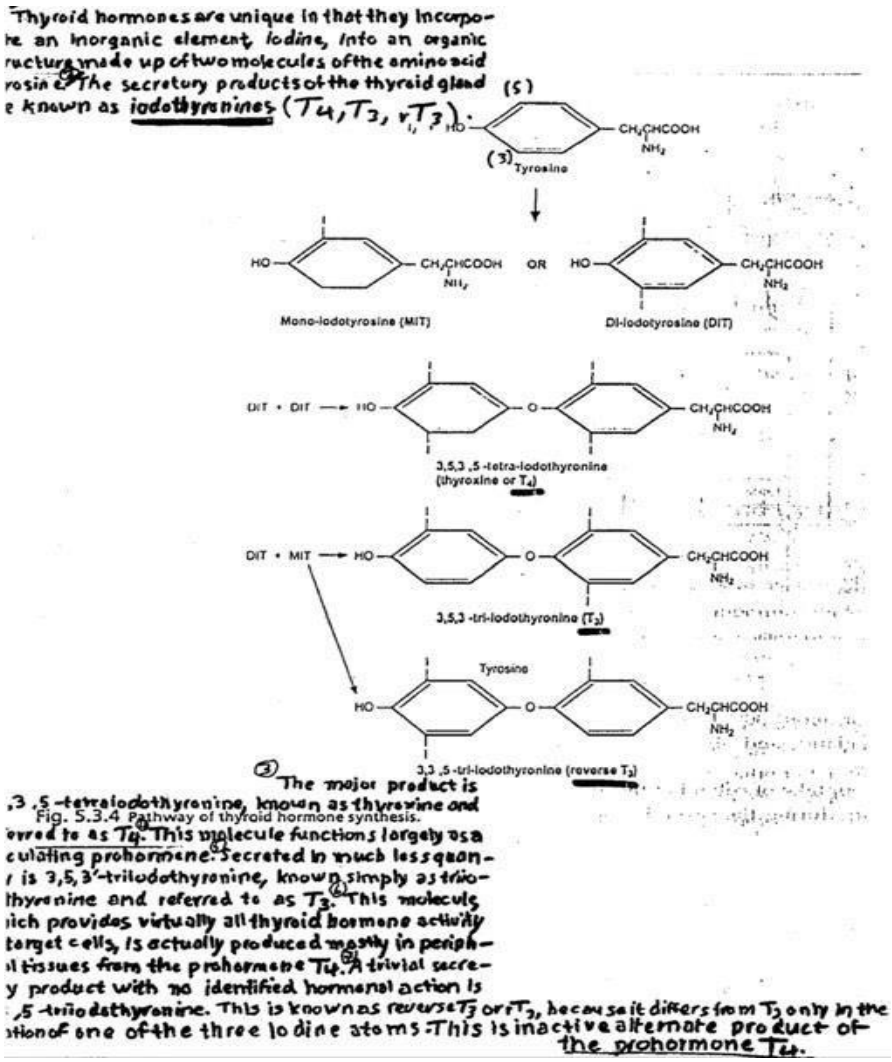


Figure 2

- When Tyr binds one iodine it is called Monoiodotyrosine (MIT), but when it binds two iodine it is called Diiodotyrosine (DIT).

- Binding of Tyr with Iodine is called Iodination.



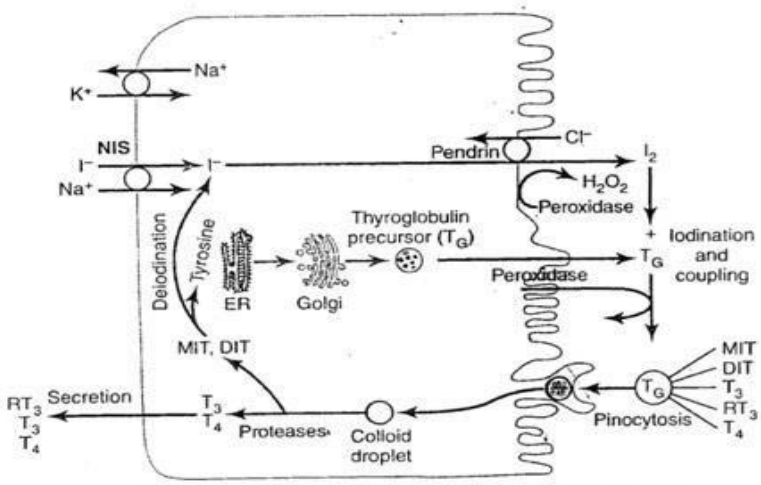
Iodination and Coupling

- When two DIT bind with each other, they produce a hormone called tetraiodothyronine (or Thyroxine or T_4). This is called coupling.
- When one MIT binds with DIT, they produce another hormone called triiodothyronine (or T_3).
- T3 and T4 indicate the number of Iodine.
- There is a third hormone, which differs in the location of iodine on the bonds of Tyr, which is called reversed T_3 (RT_3).
- So, thyroid gland produces 3 hormones:

1- T_4, the main one, has low activity (sometimes becomes inactive under the effect of some enzymes), but it is a prohormone (produces the other hormones T_3 and RT_3, and other products).
2- T_3, the most active one.
3- RT_3, totally inactive hormone.

- So, iodination is an organic mutation (binding of iodine to tyrosine), and **coupling** <u>is binding of two iodinated Tyr.</u> These two iodination and coupling don't occur on free Tyr in the colloid.
- Epithelial cells of thyroid gland produce a protein called Thyroglobulin, which is composed of Tyr residues ranging between 100-130 residues.
- Iodination and coupling occur on Tyr in the structure of Thyroglobulin, but not all Tyr in the protein can bind iodine, about 4-8 of them only can bind.
- So, this protein carries MIT, DIT, T_3, T_4, and RT_3. When in need it is taken inside the cells by pinocytosis, then inside the cell is lysed to release the hormones, then hormones pass into the blood.

Figure 76-2 Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. DIT, diiodotyrosine; MIT, monoiodotyrosine; NIS, sodium-iodide symporter; RT_3, reverse triiodothyronine; T_3, triiodothyronine; T_4, thyroxine; T_G, thyroglobulin.



Storage of Thyroglobulin. The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiologic effects of deficiency are not observed for several months.

Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. But only 4 to 8 of these are normally incorporated into thyroid hormones

- Iodine comes from the plasma or from the cells themselves. There are carriers for iodine and sodium; whenever the sodium enters, iodine enters the cells along with the sodium, then into the colloid by another carrier (pendrin), which is oxidized by peroxidase to function.

Metabolism of thyroxine

- T_3 and RT_3 come mainly from T_4; T_3 75% from T_4, 25% from thyroid.

  RT_3 95% from T_4, 5% from thyroid.

  So, they are mainly from the metabolism of T_4.

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

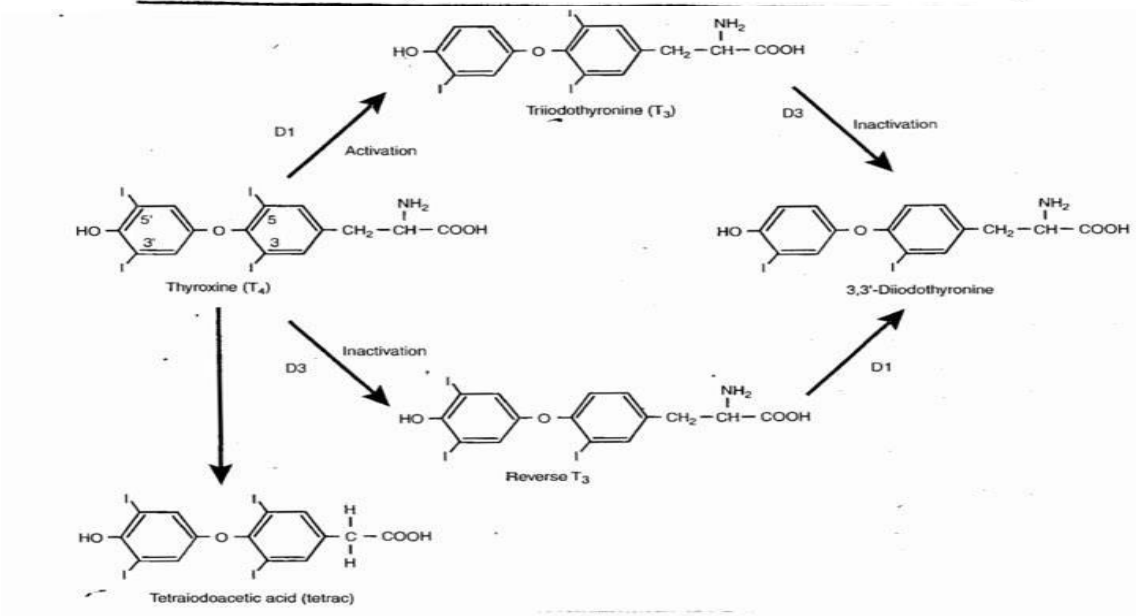


FIGURE 32.4 The metabolism of thyroxine. Deiodinase type 1 (D1) deiodinates thyroxine (T_4) at the 5′ position to form triiodothyronine (T_3), the physiologically active thyroid hormone. Deiodinase type 3 (D3) also enzymatically deiodinates some T_4 at the 5 position to form the inactive metabolite, reverse T_3. T_3 and reverse T_3 undergo additional deiodinations to 3,3′-diiodothyronine before being excreted. A small amount of T_4 is also decarboxylated and deaminated to form the

- T_3 and T_4 are very dangerous hormones if they were free in excess concentrations; they burn everything in the body; catabolize the proteins.
- Therefore, the free percentage should be very low; T_3 just 0.5% is free while T_4 just 0.02% is free.
- Binding of these hormones to proteins has advantages; first to prolong the half-life, second to prevent from filtration, third to maintain the normal level of these hormones in the plasma.

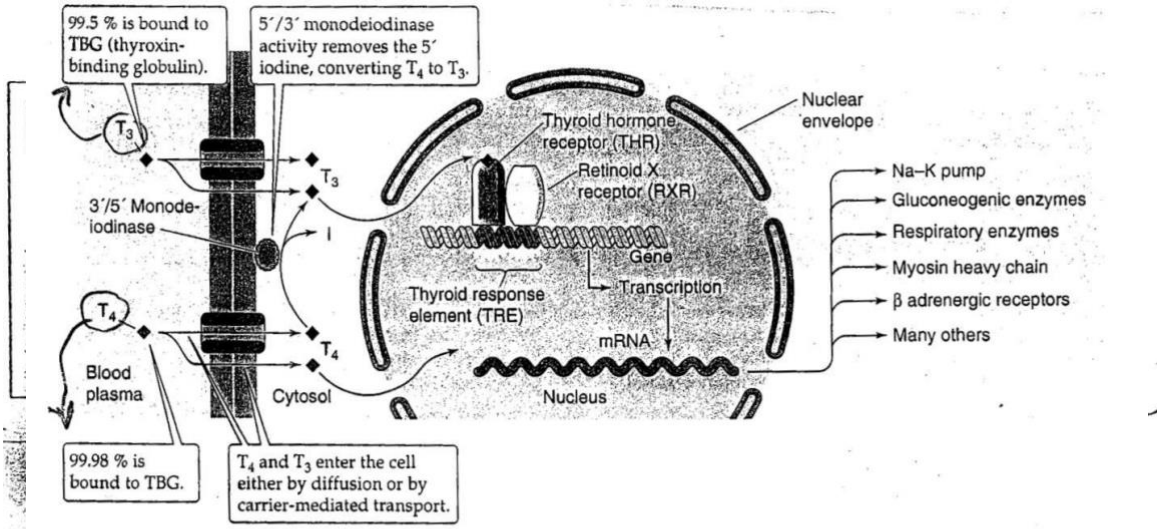


FIGURE 48–5. Action of thyroid hormones on target cells. Free extracellular thyroxine (T_4) and triiodothyronine (T_3) enter the target cell either by diffusion or by carrier-mediated transport. Once the T_4 is inside the cell, a cytoplasmic 5′/3′-monodeiodinase converts much of the T_4 to T_3, so that that cytoplasmic levels of T_4 and T_3 are about equal. Both T_4 and T_3 enter the nucleus. Thyroid hormone receptors bind to DNA at thyroid response elements in the promoter region of genes regulated by thyroid hormones. The binding of T_3 or T_4 to the receptor regulates the transcription of these genes. The receptor preferentially binds T_3. Therefore, of the total thyroid hormone bound to receptor, approximately 90% is T_3. The receptor that binds to the DNA is preferentially a heterodimer of the thyroid hormone receptor and retinoid X receptor. Thyroid hormone promotes the transcription of genes encoding a wide range of proteins. mRNA, messenger RNA.

- **Proteins that bind thyroid hormones** are: Thyroxine Binding Globulin (TBG), albumin, and Thyroxine Binding Pre-Albumin (TBPA)

Table 5.3.3 Thyroid hormone binding proteins

	Concentration (μmol/l)	Binding affinity	Actual binding T_4 (%)	Actual binding T_3 (%)
TBG	0.3	Very high	75	75
Albumin	640	Very low	10	25
TBPA	5.0	Low	15	0

TBG = thyronine-binding globulin; TBPA = thyroxine-binding pre-albumin

Two biologic functions can be ascribed to TBG. First, by creating a circulating reservoir of T_4, it buffers against acute changes in thyroid gland function. Even the sudden addition to the plasma of an entire day's thyroid gland output would cause only a 10% increase in the total T_4 concentration. After removal of the gland, it would take nearly 1 week for the plasma T_4 concentration to fall 50%. Second, by binding

- Thyroid hormones are essential for fetal life for normal development of the nervous system and skeleton, so a deficiency in these hormones causes the nervous system and skeleton not to develop properly.
- These hormones affect the metabolism of all food stuff, cardiovascular system, CNS development, growth, and many other systems.

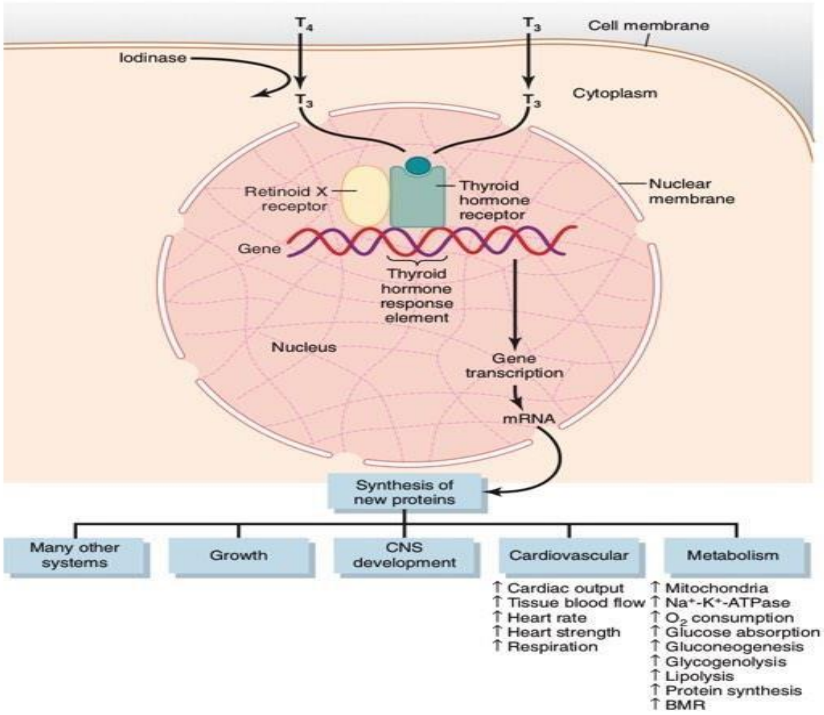


Figure 77-5. Thyroid hormone activation of target cells. Thyroxine (T_4) and triiodothyronine (T_3) enter the cell membrane by a carrier-mediated adenosine triphosphate–dependent transport process. Much of the T_4 is deiodinated to form T_3, which interacts with the thyroid hormone receptor, bound as a heterodimer with a retinoid X receptor, of the thyroid hormone response element of the gene. This action causes either increases or decreases in transcription of genes that lead to the formation of proteins, thus producing the thyroid hormone response of the cell. The actions of thyroid hormone on cells of several different systems are shown. BMR, basal metabolic rate; CNS, central nervous system; mRNA, messenger ribonucleic acid; Na^+-K^+-ATPase, sodium–potassium–adenosine triphosphatase.

Hormones that function on the growth:

Multiple hormones, including growth hormone (GH), insulin-like growth factors (IGF-I and IGF-II), insulin, thyroid hormones, Glucocorticoids, androgens & estrogens contribute to the growth process in humans.

Thyroid hormones deficiency

- We can say Thyroid hormone -as singular-; because the only hormone that functions is T3.

- 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 so it causes loss of weight.

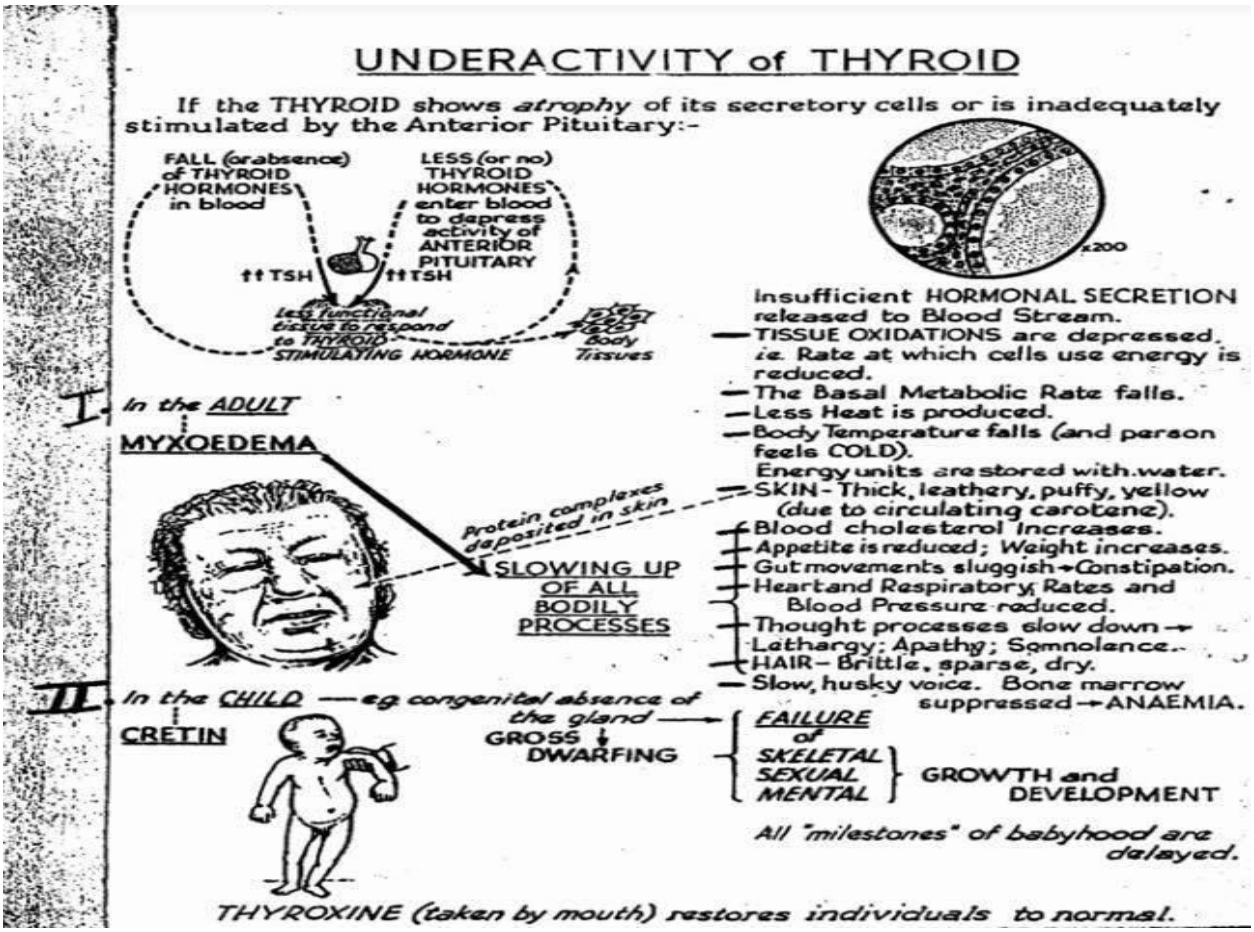
- Thyroxine at normal concentrations has a permissive effect on the action of GH on protein synthesis; in its absence, amino acid uptake, and protein synthesis are not much stimulated.

⇨ <u>Similar to thyroxine and adrenaline on lipid</u>

Note: *Thyroxine* means all thyroid hormones (T3 and T4)

- Reduced thyroid activity in childhood produces dwarfs who are mentally retarded, whereas reduced GH in childhood produces dwarfs with normal intelligence (usually).

Hypothyroidism



Childs deficiency of Thyroid:

- Thyroid hormones are essential even during fetal life; for normal development of the skeleton and nervous system.

- Deficiency in Thyroid hormones produces Dwarfs called *Cretins* (***Cretinism***).
- Cretins have a failure in <u>growth</u> and <u>development</u> of:

- Skeletal -Sexual -Mental

Adults deficiency of Thyroid:

- Deficiency in Thyroid hormones called *Myxoedema.*

- Slowing up of <u>all</u> bodily processes (From Tissue oxidation to voice).

-Thought -Heart -skin -Respiratory -Gut movement -Appetite -Blood cholesterol - Body temperature, etc.…

The ones who has a deficiency in Thyroid hormones (*Thyroxine*) <u>cannot</u> think.

Hyperthyroidism

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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

Exophthalmos (protrusion of the eyeball):

Because of the increase in Thyroid-stimulating immunoglobulin protein TSI, which Results from graves' disease.

Note: Thyroid-stimulating immunoglobulin causes protrusion of the eyeball, **<u>But</u>** not in all hyperthyroidism (not in all conditions).

Goiter (enlargement of thyroid gland):

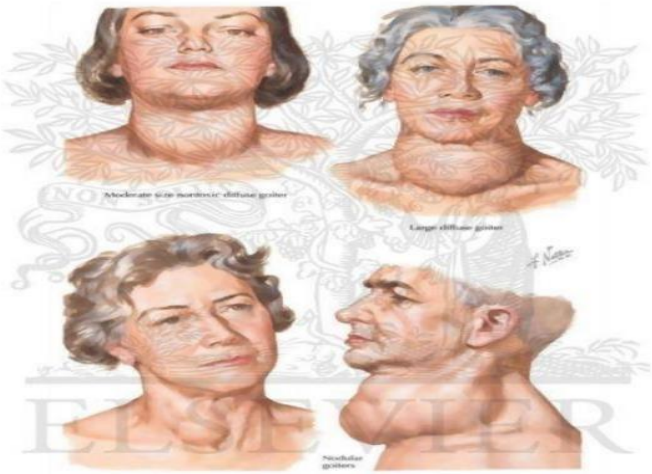
Types of Goiter:

1. T3, T4 are low (Benign non-toxic goiter) (hypothyroidism)
2. T3, T4 increase (malignant toxic goiter) (hyperthyroidism)

TABLE 15-5 Types of Thyroid Dysfunctions

THYROID DYSFUNCTION	CAUSE	PLASMA CONCENTRATIONS OF RELEVANT HORMONES	GOITER PRESENT?
Hypothyroidism	Primary failure of thyroid gland	↓ T_3 and T_4; ↑ TSH	Yes
	Secondary to hypothalamic or anterior pituitary failure	↓ T_3 and T_4; ↓ TRH and/or ↓ TSH	No
	Lack of dietary iodine	↓ T_3 and T_4; ↑ TSH	Yes
Hyperthyroidism	Abnormal presence of thyroid-stimulating immunoglobulin (TSI) (Grave's disease)	↑ T_3 and T_4; ↓ TSH	Yes
	Secondary to excess hypothalamic or anterior pituitary secretion	↑ T_3 and T_4; ↑ TRH and/or ↑ TSH	Yes
	Hypersecreting thyroid tumor	↑ T_3 and T_4; ↓ TSH	No

By making some tests, not by appearance; we can decide whether goiter is toxic or not.



If you have any question don't hesitate to ask me

دروس أخرى مستفادة من المحاضرة:

1. استفيدوا من الكمبيوتر ستيف جوبز بلش شغلو بكراج صيروا مثلو
2. الفليفلة والبرتقال تقي من الكورونا
3. إذا بدك تتثاوب بالمحاضرة حط ايدك عثمك
4. حكى شغلة بخاف أحكيها راكان بسفرني
5. حبيبي راكان بحبك
6. أبو الأحمر ربي يحمل معك

Thank you