**The physiology of thyroid gland** **د.بان جابر**

**Objectives :**

■ Describe the structure of the thyroid gland and how it relates to its function.

■ Define the chemical nature of the thyroid hormones and how they are synthesized.

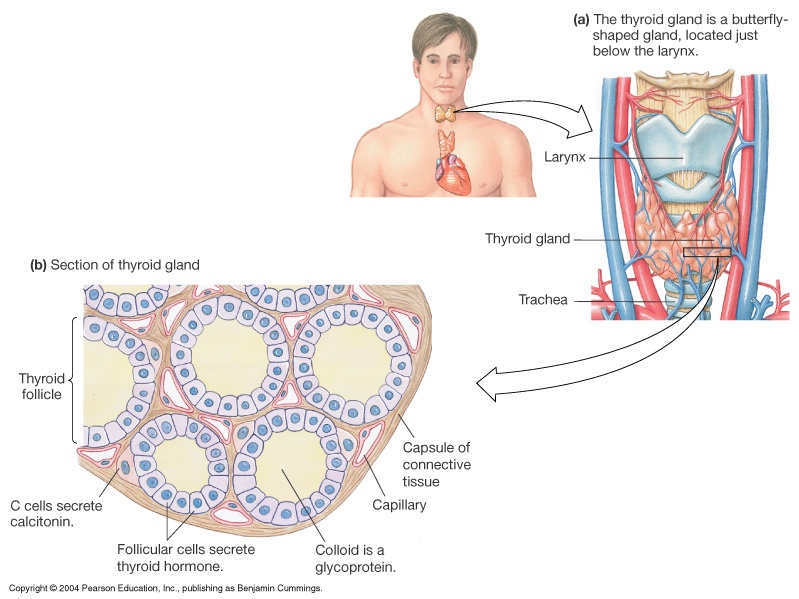
■ Describe the role of protein binding in the transport of thyroid hormones and peripheral metabolism.

■ Identify the role of the hypothalamus and pituitary in regulating thyroid function.

■ Define the effects of the thyroid hormones in homeostasis and development.

■ Understand the basis of conditions where thyroid function is abnormal and how they can be treated.

**The thyroid gland**

The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea. The thyroid gland is composed, of closed *follicles* (figure 1) filled with a secretory substance called *colloid* and lined with *cuboidal epithelial cells* ( called Follicular cells or Principle cells) that secrete into the interior of the follicles. The major constituent of colloid is the large glycoprotein *thyroglobulin,* which contains the thyroid hormones (*thyroxin* (T4) and *Triiodothyronine (T3)*. ) .In addition to Follicular cells, the thyroid contain small number of parafollicular cells (also called C-cell), embedded inside the basal lamina surrounding the follicle which secrete calcitonin. The thyroid gland has a blood flow about five times the weight of the gland each minute. 

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| Figure 1 Histology of thyroid gland  **Synthesis and Secretion of the Thyroid Metabolic Hormones**  About 93 % of the metabolically active hormones secreted by the thyroid gland is T4, and 7 % T3 . However, almost all the T4 is eventually converted to T3 in the tissues, so both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. T3 is about four times as potent as T4, but it is present in the blood in much smaller quantities and persists for a much shorter time than does T4. why?? |

* **Synthesis of thyroid hormones**

The steps involved in synthesis of thyroid hormones(figure 2) are:

1. **Synthesis and secretion of thyroglobulin precursor.**

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| The thyroid cells are typical protein secreting glandular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin. 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. |
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1. **Iodide Trapping**

Iodides ingested orally are absorbed from the gastrointestinal tract into the blood, most of the iodides are rapidly excreted by the kidneys, but only about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland .

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| The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is achieved by the action of a sodium-iodide symporter. The energy for transporting iodide against a concentration gradient comes from …….????? |

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| This process of concentrating the iodide in the cell is called iodide trapping. Iodide is transported out of the thyroid cells across the apical membrane into the follicle by a chloride-iodide ion counter-transporter molecule called pendrin.   |  | | --- | | 1. **Oxidation of the Iodide Ion** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | The first essential step in the formation of the thyroid hormones is conversion of the iodide ions to an *oxidized form of iodine* that is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme *peroxidase*. When the peroxidase system is blocked or hereditarily absent from the cells, the rate of formation of thyroid hormones falls to zero.   |  | | --- | | 4. **Organification" of Thyroglobulin** |  |  | | --- | |  |      |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | The binding of iodine with the thyroglobulin molecule is called *organification* of the thyroglobulin. Oxidized iodine will bind directly but slowly with the amino acid tyrosine. Tyrosine is first iodized to *monoiodotyrosine* (MIT)and then to *diiodotyrosine(DIT).*   1. Coupling reaction   The iodotyrosine residues become *coupled* with one another. The major hormonal product of the coupling reaction is *T4 ,* which is formed when two molecules of DIT are joined together. Or one molecule of MIT couples with one molecule of DIT to form *T3*. Small amounts of *reverse T3 (RT3)* are formed by coupling of DIT with MIT, but RT3 does not appear to be of functional significance in humans.   |  | | --- | | * **Storage of Thyroglobulin** |  |  | | --- | | The thyroid gland is able to store large amounts of hormone as thyroglobulin molecule which contain up to 30 T4 molecules and a few T3 molecules Which is sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months. |  |  | | --- | |  |  |  | | --- | | * **Secretion of thyroid hormone**   The thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form *pinocytic .*Then *lysosomes* in the cell cytoplasm immediately fuse with these vesicles to form digestive vesicles. Multiple *proteases* enzymes digest the thyroglobulin molecules and release T4 and T3 in free form. These then diffuse through the base of the thyroid cell into the surrounding capillaries. |  |  | | --- | | Some of the iodinated tyrosine in the thyroglobulin never become thyroid hormones but remain MIT and DIT which not secreted into the blood. Instead, their iodine is cleaved from them by a *deiodinase enzyme* that makes all this iodine available again for recycling within the gland for forming additional thyroid hormones.  About one half of the T4 is slowly deiodinated by 5'deiodinase enzyme to form additional T3. Therefore, the hormone finally delivered to and used by the tissues is mainly T3, a total of about 35 micrograms of T3 per day. At the end , the remaining hormone are conjugated in the liver and released with bile.  C:\WINDOWS\Desktop\Smaller\Untitled-30.jpg |  |  | | --- | |  |  |  | | --- | |  |  |  | | --- | | (Figure 2):The steps involved in synthesis of thyroid hormones  **Transport of T4 and T3 to Tissues** |      |  | | --- | | On entering the blood, more than 99 % of the T4 and T3 combines immediately with several of the plasma proteins, all of which are synthesized by the liver. They combine mainly with *thyroxin-binding globulin* and much less with *thyroxin-binding prealbumin* and *albumin*. Only free and albumin-bound thyroid hormone is biologically available to tissues. |            |  | | --- | |  |  |  | | --- | |  | |  |  | | --- | |  |   **Mechanism of action**  Receptors for thyroid hormones are nuclear type and its affinity is ten times higher for T3 than T4 . Free thyroid hormone receptor (TR) without bound hormone is bound to hormone response element of DNA (HRE) and corepressor (CoR).After binding T3 to receptor - CoR is liberated and coactivators (CoA) is bound and the transcription to mRNA begins(figure 3).  Thyroid hormones also appear to have nongenomic cellular effects that are independent of their effects on gene transcription. Nongenomic actions of thyroid hormone include the regulation of ion channels and oxidative phosphorylation and appear to involve the activation of intracellular secondary messengers such as cyclic AMP.  C:\WINDOWS\Desktop\Smaller\Untitled-35.jpg                   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **Figure 3:** Mechanism of action of thyroid hormone   |  |  | | --- | --- | | |  | | --- | | **Regulation of thyroid hormone**  The thyroid gland is part of the hypothalamic-pituitary-thyroid axis(figure 4). **Thyroid-releasing hormone (TRH)** from the hypothalamus stimulates [**thyroid-stimulating hormone**](http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/tsh.html) **(TSH)** from the anterior pituitary gland, which stimulates thyroid hormone release. (TRH is also a potent stimulator of other Hormone release from the pituitary?).  Thyroid-stimulating hormone is a peptide hormone with one α-chain and one β-chain.TSH acts through cyclic AMP mechanism.  Binding of TSH to receptors on the membrane of thyroid epithelial cells seems to:   * stimulate all steps of thyroid hormone synthesis & release. * increase the size & vascularity of thyroid gland. Follicular cells becomes columnar & active.   Prolonged stimulation of the gland by TSH------>↑ size (hypertrophy) & number (hyperplasia) of follicular cells -------> enlargement of thyroid gland *(goiter).*  As blood concentrations of thyroid hormones increase, they inhibit both TSH and TRH, leading to inhibit of thyroid epithelial cells. Later, when blood levels of thyroid hormone have decayed, the negative feedback signal fades, and the system wakes up again.  A number of other factors have been shown to influence thyroid hormone secretion , **Excess iodide intake, Stress, Somatostatin ,Glucocorticoids and Dopamine inhibits it** while **exposure to a cold environment increase its secretion** through their effect on TRH secretion from hypothalamus.    http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/thyroid/control.gif | |  |  | | --- | |  |   **Figure 4 :Regulation of thyroid hormone**  **Physiological Actions of the Thyroid Hormones**  The physiological functions of thyroid hormone are summarized in following table:   |  |  |  | | --- | --- | --- | | **Target** | **Effect** | **Mechanism** | | Heart | Increase heart rate | Increase number and affinity of B-adrenergic receptor | | Increase strength of contraction | Increase response to catecholamine  Increase myosin filaments | | Blood vessels | Vasodilatation  Increase blood flow | Accumulation of metabolite | | Muscle | Catabolic | Increase protein catabolism | | Bone | Developmental and metabolic | Promote normal growth and development  Increase bone turnover | | Blood | increase RBC and blood volume | Increase erythropoietic activity | | Brain | Developmental | Promote normal development | | Respiratory | Increase the rate and depth of respiration | Increase oxygen consumption and accumulation of metabolites | | Gut | Metabolic | Increase carbohydrate absorption | | Metabolism | Lipid | Increase lipolysis | | carbohydrate | Increase all aspect of metabolism | | Protein | Increase protein synthesis | | sexual | For normal sexual function (fertility and lipido) | Impressive | | Other | Calorigenic | Increase oxygen consumption by metabolic active tissue | | Basal metabolic rate | Increase 100 % in hyperthyroidism |   Normal Arterial Pressure ..why ????? |   **Thyroid function test (TFT)**  **Thyroid function test (TFT)** include TSH , T3 and T4 but measurement of TSH has become the principal test for the evaluation of thyroid function in most circumstances.  A TSH value within the reference interval excludes the majority of cases of primary overt thyroid disease. If TSH is abnormal, confirm the diagnosis with free thyroxine (fT4).  So **if** TSH above the **reference range** , the condition is hypothyroidism  and if TSH below the **reference range** , the condition is hyperthyroidism.  ["Normal" TSH levels](http://thyroid.about.com/od/gettestedanddiagnosed/a/normaltshlevel.htm) are considered to exclude hypothyroidism or hyperthyroidism.  Measurements of free T4 and free T3 have replaced measurements of total T4 and total T3 levels. Many conventional physicians do not test Total T4 or Free T4. However, in some cases, along with elevated TSH, Total T4 or Free T4 levels that are below the reference range are considered evidence of hypothyroidism. Along with low/suppressed levels of TSH, Total T4 or Free T4 levels that are above the reference range are considered evidence of [hyperthyroidism](http://thyroid.about.com/od/hyperthyroidismgraves/a/risks-symptoms.htm). Measurement of free T3 in patients with suspected hyperthyroidism is rarely indicated. This is reserved for situations where hyperthyroidism is suspected clinically and TSH is suppressed, but the fT4 is not elevated. Measurement of fT3 is not indicated in hypothyroidism   |  |  | | --- | --- | | **Hormone** | **Reference Range** | | TSH | 0.25 - 5 µIU/mL | | Total T4 | 60-120nmol/l | | Free T4 | 10.6 – 19.4 pmol/l | | Total T3 | 0.95 -2.5 nmol/l | | Free T3 | 4-8.3 pmol/L | | |

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**Thyroid Diseases**

Disease is associated with both inadequate production and overproduction of thyroid hormones.

**Hypothyroidism**: is the result from any condition that results in thyroid hormone deficiency. Two well-known examples include:

* *Iodine deficiency*: Iodide is absolutely necessary for production of thyroid hormones; without adequate iodine intake, thyroid hormones cannot be synthesized. This problem was seen particularly in areas with iodine-deficient soils, and iodine deficiency has been eliminated by iodine supplementation of salt.
* *Primary thyroid disease*: Inflammatory diseases of the thyroid that destroy parts of the gland are clearly an important cause of hypothyroidism.

Common symptoms of hypothyroidism arising after early childhood include lethargy, fatigue, cold-intolerance, Constipation Weight gain , weakness, hair loss and reproductive failure. If these signs are severe, the clinical condition is called *myxedema*. In the case of iodide deficiency, the thyroid becomes inordinantly large and is called a *goiter*.

*The most severe form of hypothyroidism is seen in young children with congenital thyroid deficiency.* If that condition is not corrected by supplemental therapy soon after birth, the child will suffer from [cretinism](http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/thyroid/thyroid_preg.html), a form of irreversible growth and mental retardation.

Diagnosis of hypothyroidism by sign and symptom , TFT in addition to imaging techniques.

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| Disease | Types | TFT | | |
| TSH | T3 | T4 |
| Hypothyroidism | Primary | High | low | low |
| Secondary | low | low | low |
| Subclinical | High | Normal | Normal |

Most cases of hypothyroidism are readily treated by oral administration of synthetic thyroid hormone.

**Hyperthyroidism**: results from over secretion of thyroid hormones. It is less common than hypothyroidism. The most common form of hyperthyroidism is *Graves disease*, an immune disease in which autoantibodies bind to and activate the thyroid-stimulating hormone receptor, leading to continual stimulation of thyroid hormone synthesis. Common signs of hyperthyroidism are basically the opposite of those seen in hypothyroidism, and include nervousness, tremor ,Weight loss ,insomnia, high heart rate, eye disease(exophtalmus) and anxiety.

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| Diseases | Types | TFT | | |
| TSH | T3 | T4 |
| Hyperthyroidism | Primary | low | High | High |
| Secondary | High | High | High |
| Subclinical | Low | Normal | Normal |

Diagnosis of hyperthyroidism by sign and symptom , TFT , TSH receptor antibody , in addition to imaging techniques.

Treatment For Hyperthyroidism

A. *By using Antithyroid Substances*

Antithyroid substances are the drugs which suppress the secretion of thyroid hormones. Three well-known antithyroid substances are:

1. Thiocyanate: prevents thyroid hormone synthesis by inhibiting the iodide trapping (it can cause competitive inhibition of iodide transport into the cell).

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| 22. Propylthiouracil Decreases Thyroid Hormone Formation |
| pPropylthiouracil (and other, similar compounds, such as methimazole and ccarbimazole) prevents formation of thyroid hormone by blocking the pperoxidase enzyme and by blocking the coupling reaction. Propylthiouracil, lilike thiocyanate, does not prevent formation of thyroglobulin. The absence of I T3 and T4 in the thyroglobulin can lead to tremendous feedback einhancement of TSH secretion, thus promoting growth of the glandular tissue aand forming a goiter. |

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| 3.High Concentrations Iodides ( Decrease Thyroid Activity and Thyroid Size  High concentration iodide (100 times the normal plasma level), most activities of the thyroid gland are decreased. The endocytosis of colloid is paralyzed , so It has almost immediate shutdown of thyroid hormone secretion into the blood. Because iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of the thyroid gland and especially decrease its blood supply, so it use before thyroidectomy.  B. b. *By Surgical Removal* (thyroidectomy)*:* In advanced cases of hyperthyroidism, antithyroid substances is not effected So, thyroidectomy is dodone. |

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