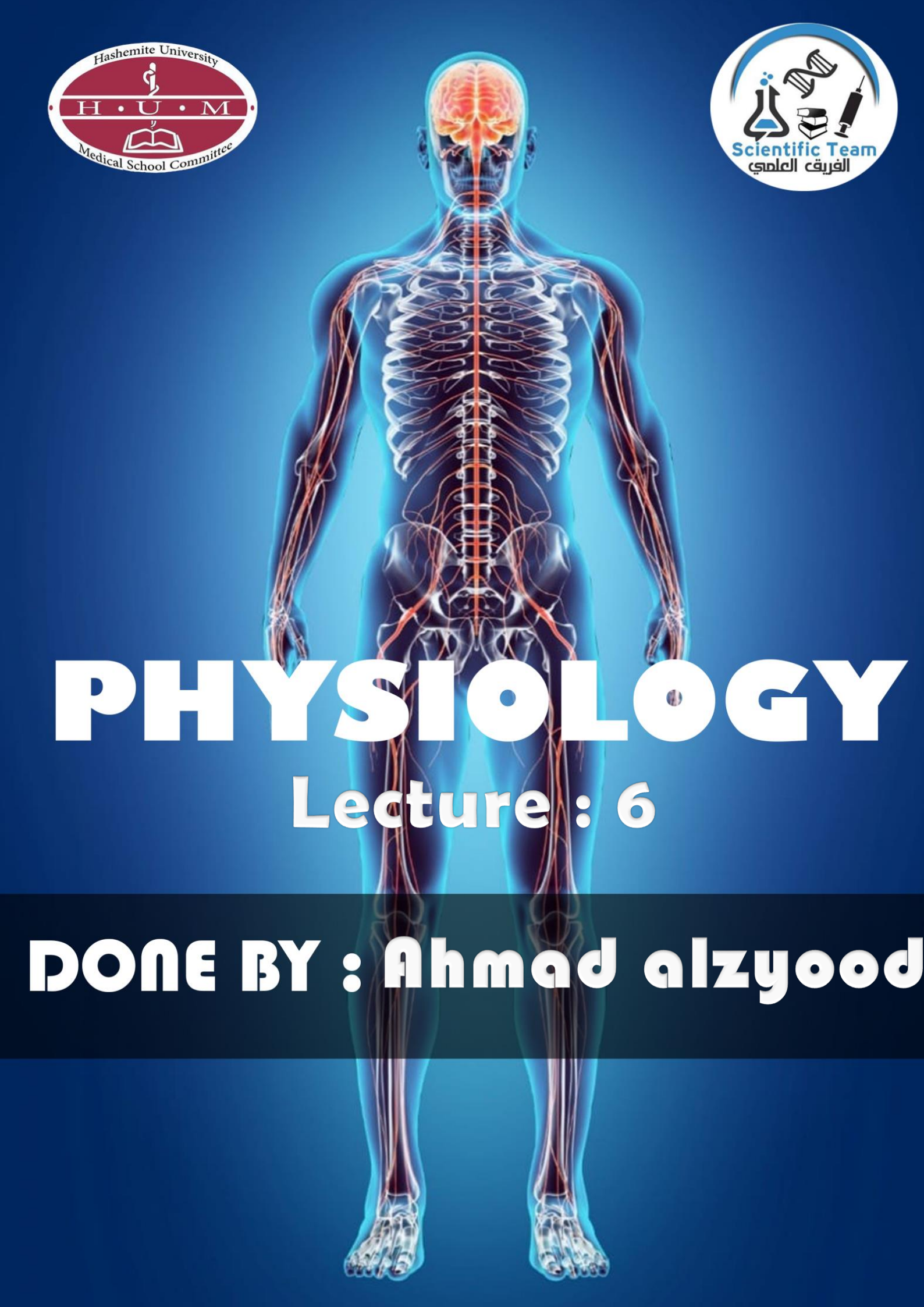


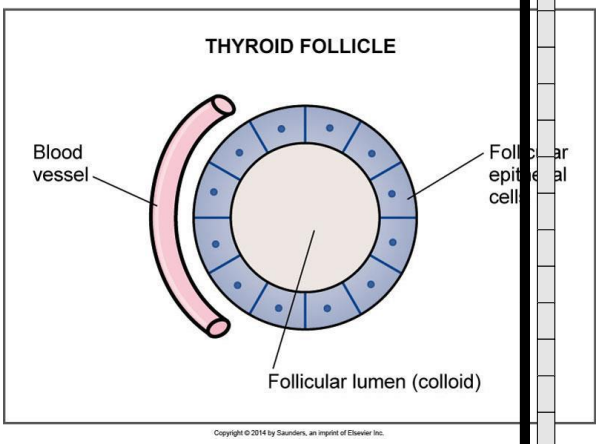
PHYSIOLOGY

Lecture : 6

DONE BY : Ahmad alzyood

الشرح بالازرق والسلايدات بالاسود

Thyroid Gland



• Involved in production, storage, and release of thyroid hormone

• Largest Endocrine organ in the body

• Complete lack of thyroid secretion decreases the BMR by 40%- 50%. the thyroid induces Basal Metabolic rate by mechanism that we will know later in this lecture.

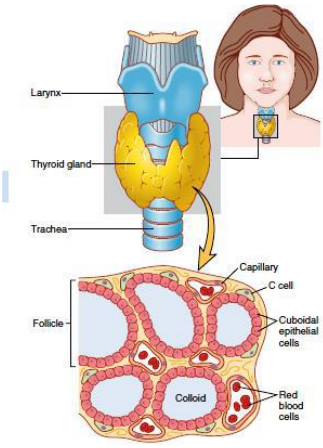
• Extreme excess of its secretion increases the BMR by 60% -100%.

the thyroid gland is anterior to the trachea

so any enlargement will affect the airway or esophagus or vessles in the region.

• Function influenced by

- ❖ Hypothalamic Pituitary axis
- ❖ TRH
- ❖ TSH
- ❖ Environmental factors (iodide intake)
- ❖ Secrets two hormones T4, T3 by thyrocytes and calcitonin by c cells.



-The thyroid gland consist of follicles.

the follicle consist of

1- epithelial cells that synthesize the Thyroid hormones

2- lumen that has colloid.

* the epithelial cells has two membranes

1- apical that faces the lumen

2- basal that faces the blood

each one has its own proteins

- the hypothalamus secrets TRH that stimulate Anterior pituitary gland to secret TSH then TSH act on thyroid gland to stimulate release and synthesize of thyroid hormones.

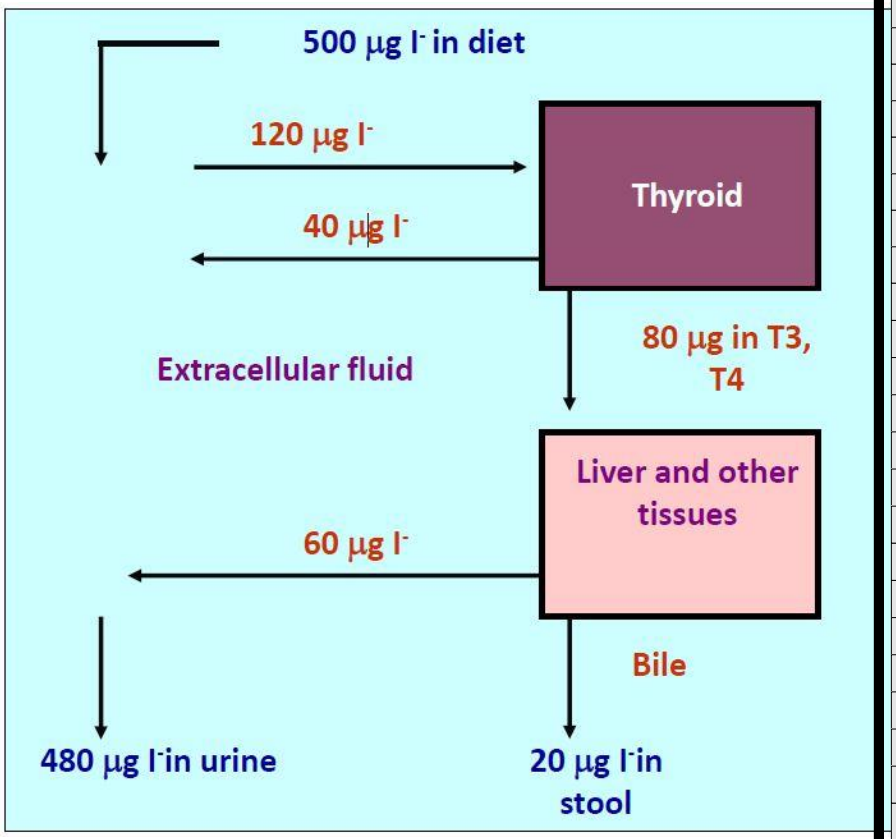
- the gland utilizes Iodide to form these hormones

➢ Iodine homeostasis:

Seafood, meat, dairy products,
bread, iodinated salts

here, in our diet there is 500 nanogram (numbers are not important)
first, the gland uptakes 120 nanogram that is used in synthesis of T4 and T3.

* 40 nanogram of free I are released into blood
* 80 nanogram of I in T4 and T3
* by metabolism of T hormones in the tissues, free I are secreted into blood (60 nanogram) then into urine
* the liver excrets free I into bile.



• The minimum daily iodine 150 µg in adults

• about 50 milligrams of ingested iodine in the form of iodides are required each year, or about 1 mg/week

• About 1/5 of ingested iodide is taken by the thyroid in the form form of I —, for synthesis make thyroid hormones,

• Most iodine after metabolic degradation of thyroid hormones is excreted by and the kidneys in the urine.

• About 120 µg /day enter the thyroid at normal rates of thyroid hormone synthesis and secretion.

• The thyroid secretes 80 µg /day in the form of T3 and T4 .

• 40 µg /day diffuses back into the extracellular fluid (ECF).

• Circulating T3 and T4 are metabolized in the liver and other tissues, with the release of a further 60 µg of I- per day into the ECF.

• Some thyroid hormone derivatives are excreted in the bile, and some of the iodine in them is reabsorbed(enterohepatic circulation)

• Net loss of I- in the stool of approximately 20 µg / day.

Outline of thyroid hormone synthesis

1. Synthesis of thyroglobulin and its

extrusion to the follicle lumen

2. Iodide Uptake (Iodine trapping)

3. Oxidation of I– to I2 Ion.

4. Organification of thyroglobulin. *organification means adding Iodine to TG

5. Formation of MIT and DIT

6. Coupling of DIT and MID to form of T3 and T4

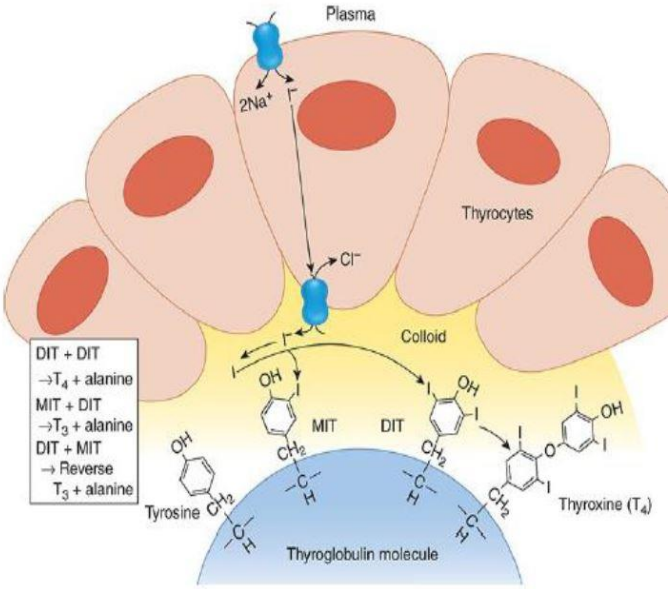
7. Endocytosis of thyroglobulin to thyrocyte

8. Hydrolysis and release of T3 and T4

9. deiodination of residual MIT and DIT

10. Recycling of tyrosine and I

11. Peripheral Conversion of T4 To T3



Iodine transport (trapping and organification)

1- in the apical membrene,

there is protein transport that transfer the sodium ions down its conc. gradient

with iodide up its conc. gradient (secondry active transport)

this is **iodide trapping**

2- in the basal membrane,

there is pendrin (I-/Cl- exchanger protein) that transfer I- to the lumen.

*I- (iodide) is converted to I2 = I0 (iodine) by TPO (thyroid peroxidase)

• Na +/I- symport : protein transport for iodide uptake from plasma to thyroid cells. (Iodine trapping)

• Iodide pump concentrates iodide to about 30% times more in cells

than in plasma can be increased to **250 times by TSH**.

• Iodide trapping is mainly influenced by TSH level

• Iodide (I-1) is converted into Iodine (I0).

• This occurs at the apical surface of thyrocyte by the enzyme thyroid

peroxidase (TPO).

• Hashimoto disease autoimmune antibodies against TPO are formed impairing thyroid hormone synthesis Anti TPO antibodies).

Iodine transport and metabolism

• Perchlorate is a contaminant that can be found in drinking and groundwater, and occasionally in cow's

milk.

• Thiocyanate ions, perchlorate ions, and nitrate ions inhibit cause competitive inhibition of iodide

transport into the cell that is, inhibition of the iodide trapping

• Ingestion of high levels of iodine , as with consumption of well water, can lead to inhibition of iodine transport into the follicular cells. (Wolff Chaikoff effect)

• Thiouracil and propylthiouracil inhibit iodine organification .

• Severe iodine deficiency of the mother may lead to insufficient thyroid hormone synthesis in both

mother and fetus resulting in developmental brain injury.

• Excess iodine supplementation may inhibit fetal thyroid function, leading to hypothyroidism (iodine

toxicity).

• Iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of phases of

thyroid activity, they slightly decrease the size of the gland

• For this reason, iodides are frequently administered to patients for 2 to 3 weeks before surgical removal of the thyroid gland to decrease the necessary amount of surgery, and especially to decrease the amount of bleeding.

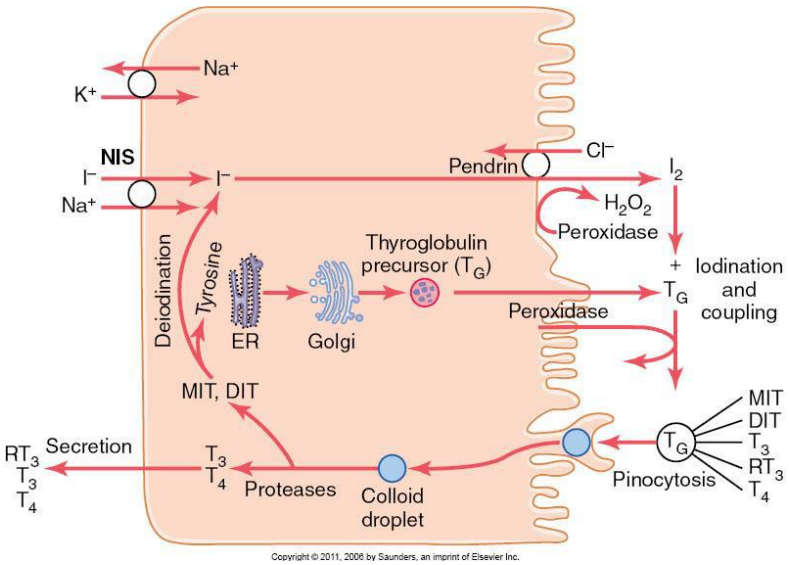
Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine

formation, and thyroxine and triiodothyronine release into the blood.

Cl–/I- exchanger known as pendrin.

This protein was first identified as the product of the gene responsible for the

Pendred syndrome, which causes thyroid dysfunction and deafness.



شرح الصورة

1- Na/K pump decrease the Na inside the cell.

2- Na/I secondary active transport traps the iodide inside the cell.

3- by pendrine, iodide is transferred inside the lumen

4- TPO converts I- to I2

5- thyroglobulin TG is tyrosine derivatives

6- TPO binds I2 to TG (organification)

more accurate (to tyrosine residues of TG)

7- if one I is added to the residue, MIT is formed

if two --> DIT

8- combination of DIT and MIT occurs

DIT + DIT --> T4

DIT + MIT --> T3

9- the release of these hormones occur when TSH stimulate the gland

firstly, TG is transferred inside the cell by pinocytosis.

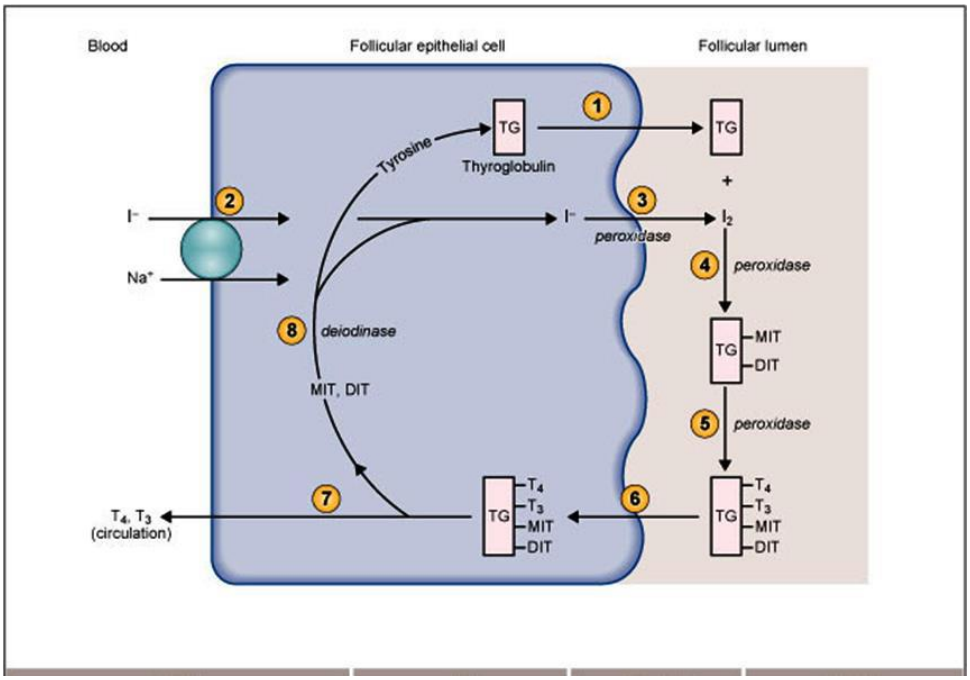
then protease act on the colloid droplet and spilt T3 and T4 from TG

10- by deaminases T4 is converted into either T3 or rT3

*rT3 is physiological inactive

Summary from Costanzo

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	



قرأهم الدكتور وواضحين لهيك ما رح احطهم عشان التلخيص ما يكبر كثير From slide 13 to --17

As we know, thyroid hormones are lipophilic so most of them are carried by plasma proteins.

Specific as TBG and not specific as albumin and prealbumin

Binding of T3 and T4

- In the circulation, most of the T3 and T4 is bound to thyroxine-binding globulin (TBG)

Transport Protein	Principle Hormone Transported
Specific	
Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Nonspecific	
Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine, some steroids

• In hepatic failure, TBG levels decrease, leading to a decrease in total thyroid hormone levels, but normal levels of free hormone.

because of the feedback mechanism, free hormone act on Ant. pituitary that control TSH secretion.

•In pregnancy, TBG levels increase, leading to an increase in total thyroid hormone levels, but normal levels of free hormone (i.e., clinically, euthyroid).

- Conversion of T4 to T3 and reverse T3 (rT3)

• In the peripheral tissues, T4 is converted mainly to T3 or rT3 by iodinase

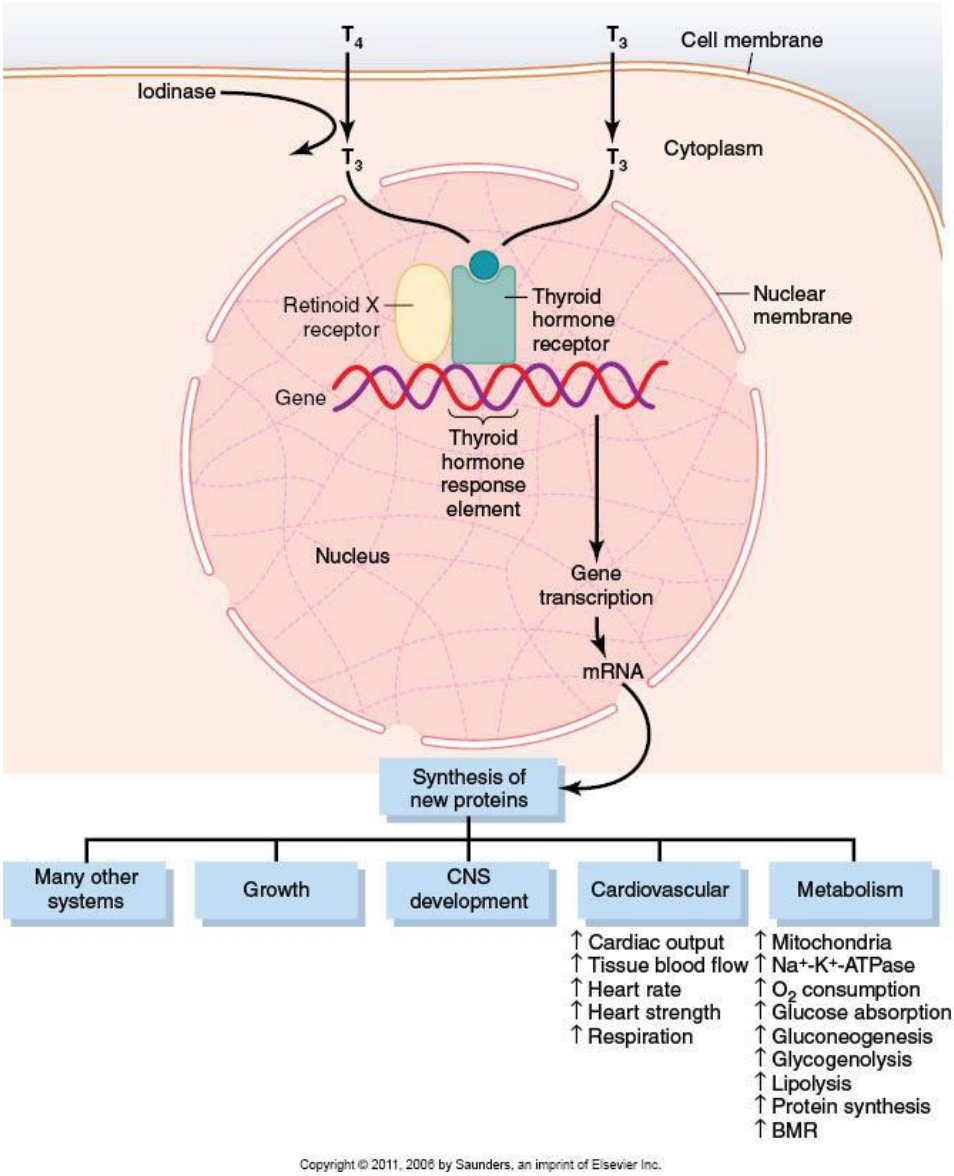
• T3 is more biologically active than T4.

• rT3 is inactive

Most of thyroxin is converted into T3.

90% of thyroid H molecules that bind with the receptors (Intracellular)→T3

10% of thyroid H molecules that bind with the receptors → T4



Effects of thyroid hormones on growth

Growth

• Attainment of adult stature requires thyroid hormone.

• Thyroid hormones act synergistically with growth hormone and somatomedins to promote growth

• in children. thyroid hormone appears to be permissive or act synergistically with growth hormone or growth factors acting directly on bone

Thyroid hormone is required for growth to adult stature. Thyroid hormones act synergistically with growth hormone and somatomedins to promote bone formation. Thyroid hormones promote ossification and fusion of bone plates and bone maturation.

In hypothyroidism, bone age is less than chronologic age→ this means that if we take two bones of two children at same age, the boy with hypothyroidism has a bone less mature as the other

bone formation

 Thyroid hormones stimulate bone maturation as a result of ossification

and fusion of the growth plates.

 In thyroid hormone deficiency, bone age is less than chronologic age

CNS development

 Thyroid hormones are critical for development during the fetal and immediate

Post-natal period.

 They regulate

- neuronal proliferation
- differentiation, myelinogenesis
- synapse formation

❖ Thyroid hormone deficiency causes irreversible mental retardation
 a brief perinatal period when thyroid hormone replacement therapy is helpful

 Cerebral cortex basal ganglia, and cochlea are most affected Consequently,

thyroid hormone deficiency during prenatal or postnatal development causes

mental retardation, motor rigidity, and deafness.

Thyroid hormones have multiple effects on the CNS, and the impact of

these effects are age dependent. In the perinatal period, thyroid hormone is essential for normal maturation of the CNS. Hypothyroidism in the perinatal period causes irreversible mental retardation.

For this reason, screening of newborns for hypothyroidism is mandated; if it is detected in the newborn, thyroid hormone replacement can reverse the CNS effects. In adults, hypothyroidism causes listlessness, slowed movement, somnolence, impaired memory, and decreased mental capacity. Hyperthyroidism causes hyperexcitability, hyperreflexia, and irritability.

the child is obese and short due to low maturity and growth of bones

+ low BMR lead to weight gain

***read slides 23-28**

Effects of thyroid hormones on Basal Metabolic Rate (BMR)

(CALORIGENIC ACTION)

•Increase O2 consumption and BMR: in all tissues except adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary

•increases the synthesis of Na+, K+ ATPase and consequently increases O2 consumption related to Na+ K+ pump activity.

•Increases metabolism of the fatty acids they mobilization of fatty acids

One of the most significant and pronounced effects of thyroid hormone is increased oxygen consumption and a resulting increase in BMR and body temperature. Thyroid hormones increase oxygen consumption in all tissues except brain, gonads, and spleen by inducing the synthesis and increasing the activity of the Na+-K+ ATPase. The Na+-K+ ATPase is responsible for primary active transport of Na+ and K+ in all cells; this activity is highly correlated with and accounts for a large percentage of the total oxygen consumption and heat production in the body. Thus when thyroid hormones increase Na+-K+ ATPase activity, they also increase oxygen consumption, BMR, and heat production.

Metabolic effects of thyroid hormones

• Glucose absorption from the gastrointestinal tract is increased.

• Glycogenolysis, gluconeogenesis, and glucose oxidation (driven by demand for ATP) are increased.

• Lipolysis is increased.

• Protein synthesis and degradation are increased.

• The overall effect of thyroid hormone is catabolic

Ultimately, increased oxygen consumption depends on increased availability of substrates for oxidative metabolism. Thyroid hormones increase glucose absorption from the gastrointestinal tract and potentiate the effects of other hormones (e.g., catecholamines, glucagon, growth hormone) on gluconeogenesis, lipolysis, and proteolysis. Thyroid hormones increase both protein synthesis and degradation, but overall their effect is catabolic (i.e., net degradation), which results in decreased muscle mass. These metabolic effects occur because thyroid hormones induce the synthesis of key metabolic enzymes including cytochrome oxidase, NADPH cytochrome C reductase, α-glycerophosphate dehydrogenase, malic enzyme, and several proteolytic enzymes.

Read slides 31-36

Cardiovascular vascular effects of thyroid hormone

Thyroid hormone increase O2 consumption leads into metabolic excessive metabolic end products. slight rise in body temperature. This lead to

• an increase in heart rate, stroke volume and cardiac output.

• The increased myocardium strength likely to be due

• The increased enzymatic activity caused by increased thyroid hormone production

• increase responsiveness catecholamines

• Total peripheral resistance decreases because of cutaneous vasodilation.

Because thyroid hormones increase O2 consumption, they create a higher demand for O2 in the tissues. Increased O2 delivery to the tissues is possible because thyroid hormones produce an increase in cardiac output and ventilation. The increase in cardiac

output is the result of a combination of increased heart rate and increased stroke volume (increased contractility). These cardiac effects are explained by the fact that thyroid hormones induce the synthesis of (i.e., upregulate) cardiac β1-adrenergic receptors. Recall that these β1 receptors mediate the effects of the sympathetic nervous system to increase heart rate and contractility. Thus when thyroid hormone levels are high, the myocardium has an increased number of β1 receptors and is more sensitive to stimulation by the sympathetic nervous system. (In complementary actions, thyroid hormones also induce the synthesisof cardiac myosin and sarcoplasmic reticulum Ca2+

ATPase.)

Cardiovascular vascular effects of thyroid hormone

• Prolonged excess thyroid hormone (can cause heart

failure and cardiac decompensation)

• Cardiac decompensation and Myocardial Failure is secondary to

• load imposed on the heart by the increase in cardiac output.

• Excess secretion of thyroid hormones Increase protein catabolism

depress myocardium contractility

• Excessive thyroid hormone causes tachycardia and palpitation

Changes in blood pressure in changes in thyroid disorders

➢ Hyperthyroidism

• mean arterial pressure is **normal**.

• The systolic BP is increased (10 15 mmHg) because of increased cardiac

output

• diastolic pressure is reduced due to decrees TPR

• Pulse pressures often increased, with the systolic pressure elevated 10 to 15 mm Hg

• diastolic pressure reduced a corresponding amount .(wide pulse

➢ Hypothyroidism

• β -adrenergic synthesis is impaired

• α -adrenergic activity may predominate

• **Increased TPR causing ↑ BP**.

Thyroid hormone and sympathetic nervous system activity

 T3 induces synthesis of α adrenergic receptors it up regulates b adrenergic receptors in the heart.

 Therefore, a useful adjunct therapy for hyperthyroidism is treatment with a ß adrenergic blocking agent, such as propranolol ever hyperthyroidism .

 Signs of hyperthyroidism which reflects increased adrenergic activity:

- Tachycardia (increased heart rate)
- ↑ Cardiac output
- Wide pulse pressure (High systolic and low diastolic).
- anxiety
- During thyroid storm, an individual's heart rate, blood pressure , and body temperature can soar to dangerously high levels. Without prompt, aggressive treatment, thyroid storm is often fatal.

Thyroid hormones interact with the sympathetic nervous system in ways that are not fully understood. Many of the effects of thyroid hormones on BMR, heat production, heart rate, and stroke volume are similar to those produced by catecholamines via β-adrenergic receptors. The effects of thyroid hormones and catecholamines on heat production, cardiac output, lipolysis, and gluconeogenesis appear to be synergistic.

The significance of this synergism is illustrated by the effectiveness of β-adrenergic blocking agents (e.g., propranolol) in treating many of the symptoms of hyperthyroidism.

Effect of Thyroid Hormone on Sexual Function

- In men, a great excess of the hormone sometimes causes impotence.
- In women, lack of thyroid hormone often causes menorrhagia and polymenorrhea that is, excessive and frequent menstrual bleeding, respectively.
- In other women a lack of thyroid hormone may cause irregular periods and occasionally even amenorrhea

Thyroid and sexual functions

• Hypothyroidism in women, as in men, is likely to decreased libido.

• Women with hyperthyroidism, oligomenorrhea (greatly reduced bleeding) is common, and occasionally amenorrhea occurs.

• The action of thyroid hormone on the gonads probably results from a combination of direct metabolic effects on the gonads

• as well as excitatory and inhibitory feedback effects operating through the anterior pituitary hormones controlling gonads

Other effects thyroid hormones

• Respiration Increased O2 metabolism, Increased CO2 lead into increased rate and depth of respiration.

• Digestive system Thyroid hormones increase increased glucose rate of absorption from the gastrointestinal tract, GI motility and secretion

• Increased Requirement for Vitamins requirements and utilization .

Because thyroid hormone increases the quantities of many bodily enzymes and because vitamins are essential parts of some of the enzymes or coenzymes

• In hyperthyroidism, the need for vitamins increases and vitamin deficiency syndrome may be precipitated

• **Carotene is converted in the liver by thyroxine to vitamin A. In hypothyroidism, elevated serum carotene carotenemia) causes <u>yellow tint (skin lesion)</u>**

read slides (44-47)

how we know if the disorder primary or secondary ?

if the feedback mechanism is working → it is primary (such as in hyper T4 – low TSH)

if it not working → its due to either anterior pituitary or hypothalamus (such as in hyper T4 – high TSH)

	T_4	TSH	TRH
Primary hypothyroidism	↓	↑	↑
Pituitary hypothyroidism (secondary)	↓	↓	↑
Pituitary hyperthyroidism (secondary)	↑	↑	↓
Graves' disease (autoimmune)	↑	↓	↓

read the slides 49-61 (pathology and biochem)

بعرف انه فيه كثير سلايدات اختصرتها والسبب انه الدكتور بحط باثو وبيوكم بالماده زيادة لهيك التفاصيل اكثر واعمق هناك يعني لو جاب دكتور الفسيو سؤال عنهم وانت بس دارس البيوكم وباثو لمرة وحده كفهم بدون حفظ حتى رح تحل اسئلته لهيك الدكتور راح يركز عجانب مادة الفسيو وهاي انا ركزت عليها وشرحت من عندي واستعانه من مصادر خارجيه بتمنى تكونو استفدتو وبالتوفيق وسامحوني اذا فيه اخطاء او تقصير