





434 Physiology team presents to you:

Endocrine

Thyroid Gland, Hyper and Hypo Thyroidism

Important

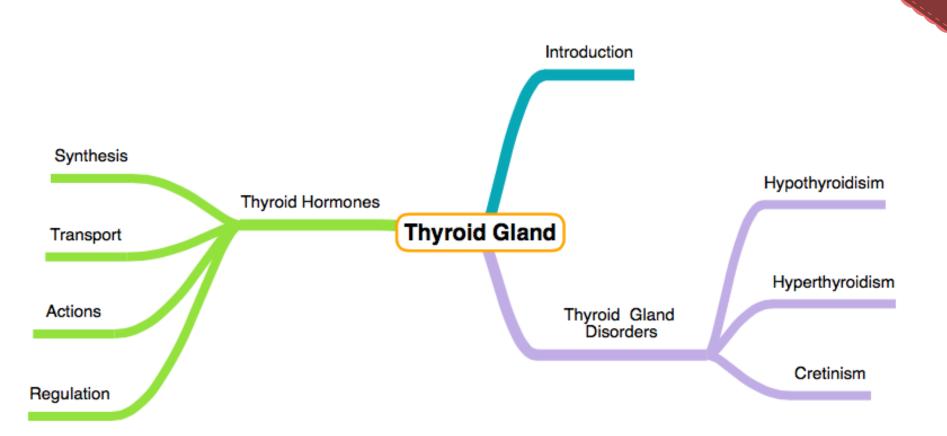
Further explanation

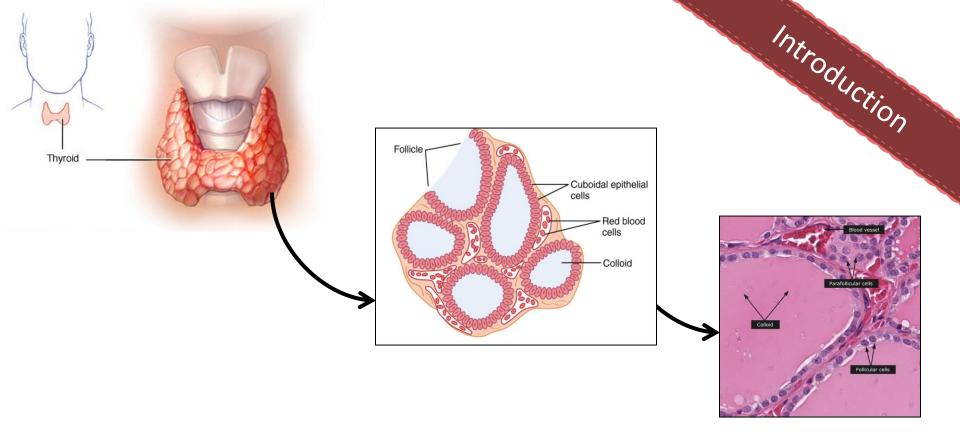
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Please check out this link before viewing the file to know if there are any additions/changes or corrections. The same link will be used for all of our work Physiology Edit

Mindmap





- ♦ Thyroid gland located below larynx on either sides and anterior to the trachea.
- ♦ The first recognized endocrine gland.
- ♦ Normally weighting 20g in adults.
- ♦ It secretes 2 major hormones, thyroxine & triiodothyronine; commonly called T3 & T4.

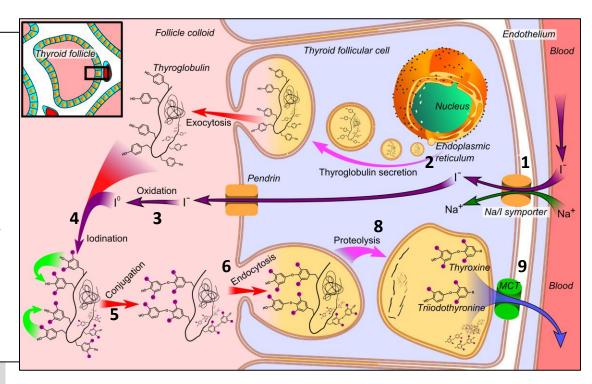
Other hormones secreted by Thyroid gland: Reverse T3 (RT3) ¹ and Calcitonin.

Synthesis and Secretion of the Thyroid Hormones

- **♦** Synthesis of Thyroid hormones has three unique features:
- ✓ Contains large amount of iodine, which is supplied by diet, 1mg/week requirement.
- ✓ Synthesis is partially intracellular and partially extracellular.
- ✓ *Thyroxine* (T4) is the major product 90% while *triiodothyronine* (T3) is 10%.
- 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.

♦ Steps of Synthesis

- 1. lodide pump.
- 2. Thyroglobulin synthesis.
- 3. Oxidation of iodide to iodine.
- 4. Iodination of tyrosine.
- 5. Coupling.
- 6. Endocytosis of thyroglobulin.
- 7. Fusion of lysosomes. -not shown in image-
- 8. Hydrolysis of peptide bonds.
- Release of T3 and T4
- 10. Deiodination of DIT and MIT by Thyroid deiodinase (Recycling).



We advice you to memorize those steps by heart, who knows.. SAQs.. Maybe?

Steps of Thyroid Hormones Synthesis in more details

- + TSH
- Wolff-chaikoff effect1



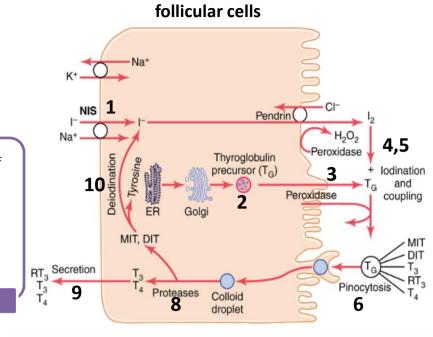
- Pumping iodide actively (because it's against its concentration gradient) to the interior of the cell.
- •The process of concentrating the iodide in the cell is called *iodide trapping*.
- •- Ratio of concentration from 30-250 times.

Iodide Trap

Thyroglobulin Formation & Transport

- Rough endoplasmic reticulum and Golgi apparatus secrete a glycoprotein called Thyroglobulin.
- Each molecule contains about 70 *Tyrosine* amino acids
- •The oxidation of iodide to iodine is by the help of **Thyroid** peroxidase.
- It is located in or attached to the apical membrane.

Oxidation



- Organification of thyroglobulin which is the binding of iodine with thyroglobulin.
- •Catalyzed by thyroid peroxidase as well. To form MIT² / DIT³
- •It will remain attached to thyroglobulin until the gland stimulated to secret.

Coupling

- •DIT + DIT = T4 -faster-.
- •DIT + MIT = T3
- Catalyzed by thyroid peroxidase.
- •It will be stored as colloid which is sufficient for 2-3 months.

Endocytosis of thyroglobulin forming a vesicle.

Fusion of lysosomes immediately with the vesicles.

Now the vesicle contains digestive enzymes from lysosomes mixed with colloid.

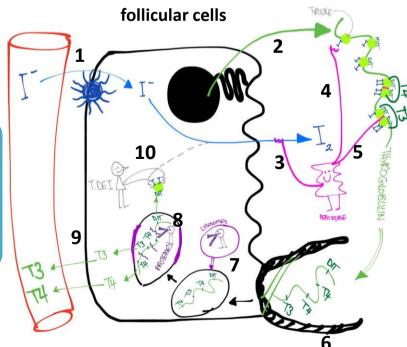
lodination

- •Hydrolysis of the peptide bond to release *DIT+MIT+T4+T*3 from the thyroglobulin in free form.
- •Which is the cleavage of the T4, T3 from the thyroglobulin by the proteases so those free hormone can readily released to circulation.

8 Hydrolysis

Release & Deiodination

- •Delivery of T4 and T3 to the systemic circulation by diffusion.
- Deiodination of DIT and MIT by thyroid deiodinase (It will take the iodide and recycle it)



1: A autoregulatory phenomenon that inhibits organification, the formation and the release of thyroid hormones into the bloodstream. Which is secondary to **elevated levels of circulating iodide**

2: Monoiodotyrosine 3: Diiodotyrosine

Now thyroid hormones are in blood, how are they going to be transported to the targeted tissues?

♦ Thyroid Hormones in The Circulation:

Thyroxine (T4) and Triiodothyronine (T3) Are Bound to Plasma Proteins (99%)

- On entering the blood, more **than 99% of T4 and T3 combines** immediately with several of the plasma proteins, all of these are synthesized by the liver they combine mainly with **thyroxine-binding globulin (TBG)** and much less with thyroxine-binding prealbumin and albumin.
 - Much less amount will be unbound (Free) 0.03% of T4 and 0.3% of T3.

In case of:

Hepatic Failure	

↓TBG

Pregnancy

- ↑ Estrogen ↑ TBG ↓ FreeT3/T4
 - Stimulation of thyroid secretion.





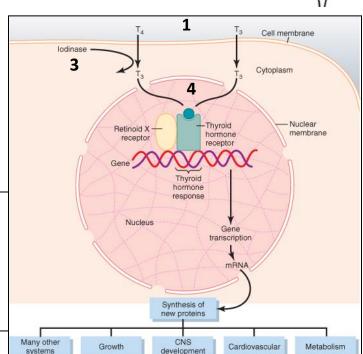
♦ Thyroid Hormones Release to Tissues:

Inhibition of thyroid secretion.

• **↑** Free T3/T4

Because of *high affinity* of the plasma-binding proteins for the TH, these substances -in particular T4- are released to the tissue cells **slowly.**.

- ½ of T4 in the blood is released every 6 days.
- ½ of T3 in the blood is released every one day
- 1. T4 & T3 readily diffuse through the cell membrane.
- 2. Stored in the targeted tissues (days to weeks). -not shown in image-
- 3. 90% of T4 is deionized to T3 by **iodinase** enzyme.
- 4. In the nucleus, T3 mainly binds to thyroid hormone receptor and influence transcription of genes.





Physiological Functions of the Thyroid Hormones

As mentioned previously:

T3 + nuclear receptor → Activation of thyroid regulating element on DNA → ↑ DNA transcription → Formation of mRNA → Translation of mRNA → ↑ Specific protein synthesis.

This is the main concept behind the thyroid hormones actions on the specific targeted tissues.

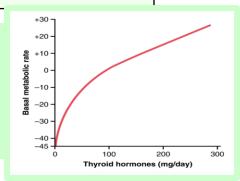
♦ Actions of Thyroid Hormone:

- 1. Metabolism TH increases the metabolic activities of almost all tissues of the body.
- Carbohydrates: TH *stimulates* all aspects of carbohydrate metabolism:
- ✓ Increase glucose uptake by the cells.
- ✓ Increase glycogenolysis.
- ✓ Increase gluconeogenesis.
- ✓ Increase rate of absorption from the GIT.
- Fats: Essentially all aspects of fat metabolism are also *enhanced* under the TH:
- ✓ Increase lipolysis.
- As lipolysis increases there will be free fatty acids moving around this will Increase oxidation of free fatty acids.
- ✓ Decrease plasma cholesterol by increase loss in feces. That's why one diagnostic indication of hypothyroidism is increased blood cholesterol concentration..
- O **Proteins:** Overall effect is catabolic leading to decrease in muscle mass. In contrast to GH which has anabolic effect.

2.Basal Metabolic Rate (BMR): Is the energy requirement under basal condition (mental and physical rest 12-18 hours after a meal). Because TH increases metabolism is almost all cells of the body:

- Complete *lack* of thyroid hormones → There will be a 40-50% *decrease* in BMR.
- Extreme *increase* of thyroid hormones → There will be a 60-100% *increase* in BMR.

The metabolic effects are due to the induction of metabolic enzymes.



Effects of Thyroid Hormone on Various Systems of the Body:

System	Effect		
CVS	 Indirectly potentiating the effect of catecholamine in the circulation: ✓ Activation of β-adrenergic receptors. Directly induction of: The TH itself – ✓ myocardial β-adrenergic receptors, sarcoplasmic reticulum, Ca+2 ATPase and Myosin. Will cause the following: Increase heart rate and stroke volume = Increases cardiac output up to 60% Decrease peripheral resistance. End result is increase delivery of oxygenated blood to the tissues. 		
CNS	 In peri-natal period: TH are essential for maturation of the CNS. ✓ Decrease of hormones secretion → irreversible mental retardation ✓ Screening is necessary to introduce hormone replacement. In adults: ✓ Increase in thyroid hormone secretion: Hyperexcitability. Inpaired memory. Decrease Mental capacity. 		
Skeletal (Bones)	Promote: bone formation, ossification, fusion of bone plate and bone maturation.		
GIT	 Increase: appetite thus food intake, increase digestive juices secretion and G.I tract motility. ✓ Excess TH secretion → Diarrhea. ✓ Lack of TH secretion → Constipation 		
Respiratory	 Increase ventilation rate Increase dissociation of oxygen from Hb by increasing RBC 2,3-DPG (2,3 diphosphoglycerate). 		
Autonomic Nervous System	Produced the same action as <u>catecholamines</u> via β-adrenergic receptors including: ✓ Increase BMR. ✓ Increase heat production. ✓ Increase heart rate. ✓ Increase stroke volume. i.e. β-blocker (propranolol) is used in treatment of hyperthyroidism.		

Regulation of Thyroid Hormone Secretion

It is regulated by the hypothalamic-pituitary axis.

Thyrotropin-Releasing Hormone (TRH)

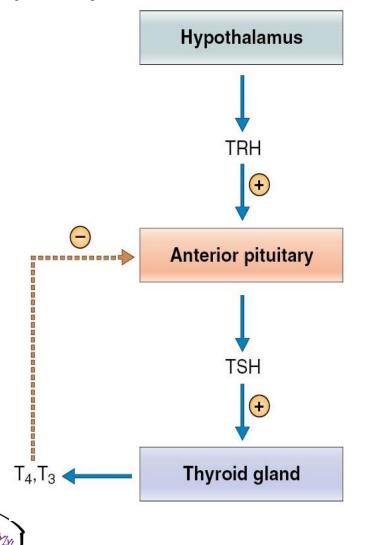
A tripeptide, released from *paraventricular* nuclei of the hypothalamus, act on the **thyrotrophs of the anterior pituitary** by phospholipid second messenger system. Leads to transcription and secretion of TSH

Thyroid-Stimulating Hormone (TSH)

Glycoprotein, From Anterior pituitary. TSH secretion started at 11-12 of gestational weeks.

- ✓ Increase proteolysis of the thyroglobulin.
- ✓ Increase pump activity.
- ✓ Increase iodination of tyrosine.
- ✓ Increase coupling reaction.
- ✓ **Trophic effect**. Trophic hormone is a hormone that has a growth effect, hyperplasia or hypertrophy, on the tissue it is stimulating.

TSH + receptor → activation of adenylyl cyclase via Gs protein → cAMP → activation of protein kinase → multiple phosphorylation, increases secretion and thyroid growth.

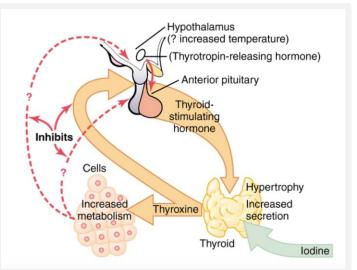


Effects

Regulation of Thyroid Hormone Secretion cont.

TSH is regulated by:

- 1. TRH we discussed previously.
- Thyroid Hormones: inhibit the secretion of TSH by down-regulation the TRH receptors. -negative feedback-



THIS PART WAS NOT MENTIONED IN OUR SLIDES HOWEVER WE ARE INCLUDING IT FOR THE SAKE OF COMPLETION IT'S EASY ANYWAY...

Factors Affecting Thyroid Hormone Secretion

Stimulatory Factors	Inhibitory Factors	
TSH	I ⁻ deficiency ;(T3 and T4 will decrease in the circulation)	
Thyroid stimulating immunoglobulin	Deiodinase deficiency ;(T3 and T4 will decrease in the circulation)	
Increases TGB levels (eg., pregnancy)	Excessive I ⁻ intake (Wolff-chaikoff effect)	
	Decreased TGB levels (e.g., liver failure)	
	Anti-hyperthyroidism drugs (e.g.,Perchlorate and Propylthiouracil)	

Most of the points presented in this table were discussed in previous slides.

Diseases of Thyroid Gland

<i>Hyper</i> thyroidism	<i>Hypo</i> thyroidism
Over activity of the thyroid gland. ○ Women : men ratio (8:1). ○ Activity of gland : ✓ 5- 10 times increase in secretion. ✓ 2-3 times increase in size.	Under activity of the thyroid gland
Cau	ıses
Graves' disease: an autoimmune disorder. Increased circulating level of thyroid- stimulating immunoglobulins (TSI). 95% most common cause of hyperthyroidism 4-8 times more common in women than men • Thyroid Gland Tumor: 95% is benign and 5% is malignant.	 Inherited abnormalities of thyroid hormone synthesis: ✓ Peroxidase defect. ✓ Iodide trapping defect. ✓ Thyroglobulin defect. ○ Endemic Colloid Goiter: -before table salt-: Viodide > Vermone formation > ↑TSH > ↑Thyroglobulin size (> 10 times)
History of head and neck irradiation and family history. • Exogenous T3 and T4 –rarely –	 Idiopathic nontoxic colloid goiter: I intake is normal: Inflammation > ↑ cell damage > ♥ hormone secretion > ↑TSH > ↑activity of normal cells > ↑size Inflammation > ↑ Inflammation > ↑
○ Excess TSH secretion:	 Gland destruction (surgery).
✓ Diseases of the hypothalamus (TRH).	 Pituitary diseases or tumor.
✓ Diseases of the pituitary (TSH).	 Hypothalamus diseases or tumor

Diseases of Thyroid Gland cont.

*Hyper*thyroidism

Hypothyroidism

Diagnosis/Symptoms

- o Goiter¹ in 95%.
- o Skin: Smooth, warm and moist
 - -Heat intolerance, night sweating.
 - Musculoskeletal: Muscle atrophy.

Neurological: tremor, enhanced reflexes and irritability.

- Cardiovascular: increase heart rate, increase stroke volume, arrhythmias and hypertension.
- Gastrointestinal tract: weight loss and diarrhea.
- Renal function: ↑glomerular filtration rate.
- Exophthalmos: anxious staring expression and protrusion of eye balls.
- Menstrual cycle disturbance.

- o **Skin:** dry skin. and cold intolerance.
- Musculoskeletal: ↑muscle bulk.
 in skeletal growth, muscle sluggishness
 and slow relaxation after contraction
- Neurological: slow movement, impaired memory and decrease mental capacity
- Cardiovascular: Decrease blood volume, heart rate and stroke volume.
- Gastrointestinal tract: Increase weight and constipation.
- Myxoedema: An edematous appearance through out body
- o Loss of libido¹.
- Menstrual cycle disturbance.



Diseases of Thyroid Gland cont.

*Hyper*thyroidism

Hypothyroidism

Investigations

- Serum T3, T4 are high.
- o Serum TSH:
- In primary hyperthyroidism:
- ✓ **Ψ** TSH.
- In secondary hyperthyroidism:
- ✓ ↑ TSH.

- Serum T3,T4 are low.
- Serum TSH:
- In primary hypothyroidism:
- ✓ ↑ TSH.
- In secondary hypothyroidism:
- 🗸 🎍 TSH.

Treatment

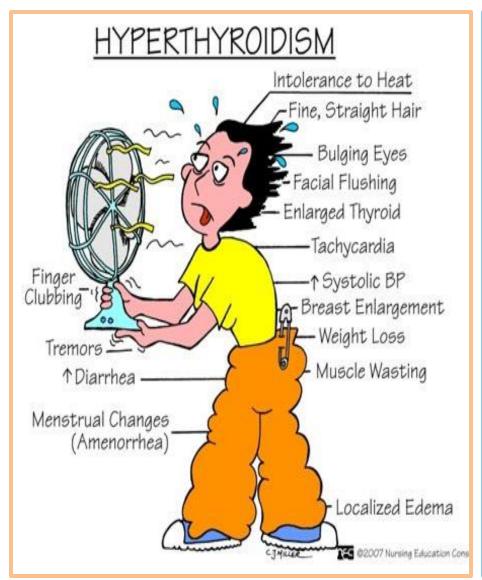
- Medical therapy: e.g.propylthiouracil
- ✓ Usually for 12-18 months course.
- ✓ With 3-4 monthly monitoring.
- Surgery: Subtotal thyroidectomy.
- Indication for surgery:
- ✓ Relapse after medical treatment.
- ✓ Drug intolerance.
- ✓ Cosmetic¹.
- ✓ Suspected malignancy

- Medical therapy:
- L- thyroxine
- ✓ Starting dose is 25-50 μ g.
- ✓ Increase to 200 μ g.
- ✓ At 2-4 weeks period.

The first response seen is the weight loss



Disease of Thyroid Gland SUMMARY





Diseases of Thyroid Gland cont.

Cretinism

A condition of severely stunted physical and mental growth due to untreated congenital deficiency of thyroid hormones (congenital hypothyroidism).

Causes

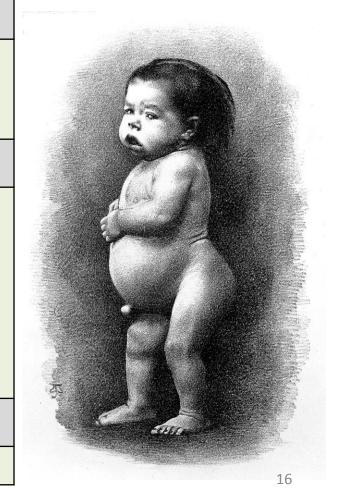
- Congenital lack of thyroid gland (congenital cretinism).
- Genetic deficiency leading to failure to produce hormone.
- o lodine lack in the diet (endemic cretinism).

Symptoms

- Infant is normal at birth but abnormality appears within weeks.
- Protruding tongue.
- Dwarf with short limbs.
- Mental retardation.
- Often umbilical hernia.
- Delayed appearance of teeth.

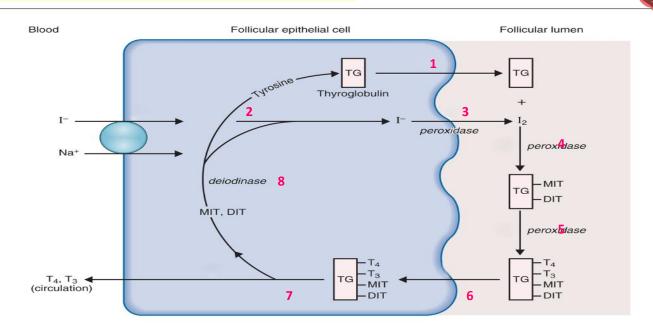
Treatment

Changes are irreversible unless treatment is given early.



♦ Biosynthesis of Thyroid Hormones

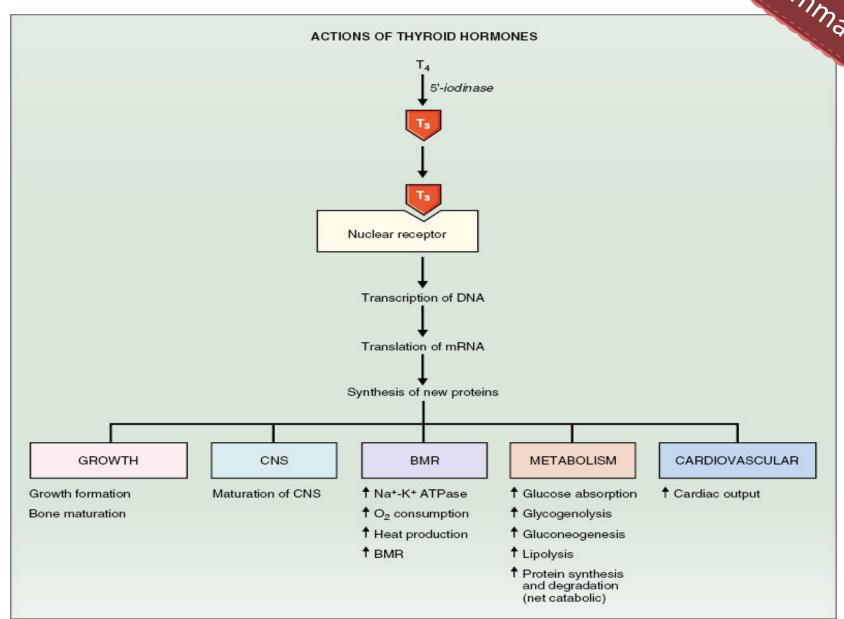




Event	Site	Enzyme	Inhibitor
Synthesis of TG; extrusion into follicular lumen	Rough ER, Golgi apparatus		
2 Na+ - I ⁻ cotransport	Basal membrane		Perchlorate, thiocyanate
	Apical (luminal) membrane	Peroxidase	PTU
4 Organification of I ₂ into MIT and DIT	Apical membrane	Peroxidase	PTU
Coupling reaction 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	
Deiodination of residual MIT and DIT Recycling of I ⁻ and tyrosine	Intracellular	Deiodinase	

♦ Physiological Actions of Thyroid Hormones

Summ



♦ Hyperthyroidism VS Hypothyroidism

Summary

	Hyperthyroidism	Hypothyroidism
Symptoms	Increased basal metabolic rate Weight loss	Decreased basal metabolic rate Weight gain
	Negative nitrogen balance	Positive nitrogen balance
	Increased heat production	Decreased heat production
	Sweating	Cold sensitivity
	Increased cardiac output	Decreased cardiac output
	Dyspnea (shortness of breath)	Hypoventilation
	Tremor, muscle weakness	Lethargy, mental slowness
	Exophthalmos	Drooping eyelids
	Goiter	Myxedema
	orter.	Growth retardation
		Mental retardation (perinatal)
		Goiter
Causes	Graves' disease (increased thyroid-stimulating	Thyroiditis (autoimmune or Hashimoto's thyroiditis)
	immunoglobulins)	Surgery for hyperthyroidism
	Thyroid neoplasm	I ⁻ deficiency
	Excess TSH secretion	Congenital (cretinism)
	Exogenous T ₃ or T ₄ (factitious)	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)
	Increased (if defect is in anterior pituitary)	Decreased (if defect is in hypothalamus or anterior pituitary)
Treatment	Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis)	Thyroid hormone replacement therapy
	Thyroidectomy	
	¹³¹ I ⁻ (destroys thyroid)	
	β-Adrenergic blocking agents (adjunct therapy)	
	p-nateliergic blocking agents (aujunct therapy)	

MCQs

1- Which of the following statements concerning thyroid *function* are correct?

- **A.** T3 and T4 stimulate the secretion of TSH by the anterior pituitary.
- **B.** Most of the iodide in the body is present in the thyroid gland
- **C.** Thyroid hormones are essential for the early development and maturation of the central nervous system

2- Which of the following are *NOT* symptoms of myxoedema?

- A. Constipation
- B. Dry Skin
- C. Heat-intolerance

3-A patient presents with signs of hypothyroidism. To investigate the matter, you measure the levels of T4 and TSH. You can expect the following results:

- A. T4 elevated, TSH elevated
- **B.** T4 reduced, TSH elevated
- C. T4 reduced, TSH normal

4-Thyroid hormones can increase cardiac output. From the following table, pick the row that correctly lists the mechanisms by which T3 increases cardiac output.

	Rate of atrial pacemaker depolarization	Expression of cardiac Na ²⁺ /exchanger	Expression of cardiac β- adrenergic receptors	Expression of Cardiac Na ⁺ ,K ⁺ - ATPase
Α	Increase	Decrease	Decrease	Increase
В	Decrease	Increase	Increase	Decrease
С	Increase	Increase	Decrease	Decrease
D	Increase	Increase	Increase	Increase

A or B or C or D

- 5- What is the unique feature of the antibody produced in Graves' disease that stimulates growth of the thyroid gland?
- A. Enhanced secretion of TSH
- B. Has similar effect to TSH
- C. Has similar effect to TRH

6-A patient presents with signs of hyperthyroidism (thyrotoxicosis). To investigate the matter, you measure the levels of T4 and TSH. If the patient has a benign thyroid adenoma ("toxic nodule"), you can expect the following results:

- A. T4 reduced, TSH reduced
- B. T4 elevated, TSH reduced
- C. T4 elevated, TSH elevated



7- Which of the following statement regarding thyroid hormone synthesis is correct?

A. Binding of iodine with thyroglobulin catalyzed by thyroid peroxidase enzyme

B. lodide in transported to the follicular cells by passive diffusion

C. Oxidation of iodide to iodine is catalyzed by iodase enzyme

8- What is the correct relationship between changes in plasma levels of T3 & T4 and release of TRH and TSH?

	T ₃ & T ₄	TRH	TSH
Α	Increase	Increase	Decrease
В	Decrease	Increase	Increase
C	Decrease	Decrease	Decrease

A or B or C or D

9- Which of the following sequences is correct regarding thyroid hormone synthesis:

- A. Oxidation > Iodination > Coupling.
- B. Oxidation > Coupling > Iodination .
- C. Iodination > Oxidation > Coupling.

10- What is the correct feature regarding thyroid hormone circulation in a pregnant lady

- A. Decreased TGB
- B. Increased TBG
- C. Increases free T4/T3

11- Which of the following statement regarding Cretinism is correct?

- A. Stunted physical and mental growth
- **B.** Acromegaly
- C. Heat-intolerance

12- Which of the following is NOT a feature of hypothyroidism?

- A. Constipation
- **B.** Heat-intolerance
- C. Cold-intolerance

13- Which of the following is considered as an Inhibitory factor of thyroid hormone?

- A. TSH
- **B**. Thyroid stimulating immunoglobulin
- C. Wolff-chaikoff effect

Q1: The increase in delivery of blood to tissue by TH is mediated by?

Ans: 1- Indirect induction: Potentiate the effect of catecholamines.

2- Direct induction of beta adrenergic receptors

Q2: Mention the effect of TH on CNS.

Ans: 1- Perinatal period: Maturation of CNS.

2- Adults: Hyperexcitability and irritability.

Q3: How does TH secretion is regulated?

Ans: Regulated by the hypothalamic-pituitary axis> TRH > TSH.

Q4: What are the actions of TSH?

Ans: Increase proteolysis of the thyroglobulin.

- 2- Increase pump activity.
- 3- Increase iodination of tyrosine.
- 4- Increase coupling reaction.

Q5:List the steps of T4 and T3 release to the tissues.

Ans: 1- T4 and T3 readily diffuse through the cell membrane.

- 2- Stored in targeted tissue.
- 3- T4 deionized to T3 by idoinase.
- 4- In nucleus, T3 mainly binds to thyroid hormone receptor.
- 5- Influence transcription of genes



THANKS FOR CHECKING OUR WORK

Good Luck

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