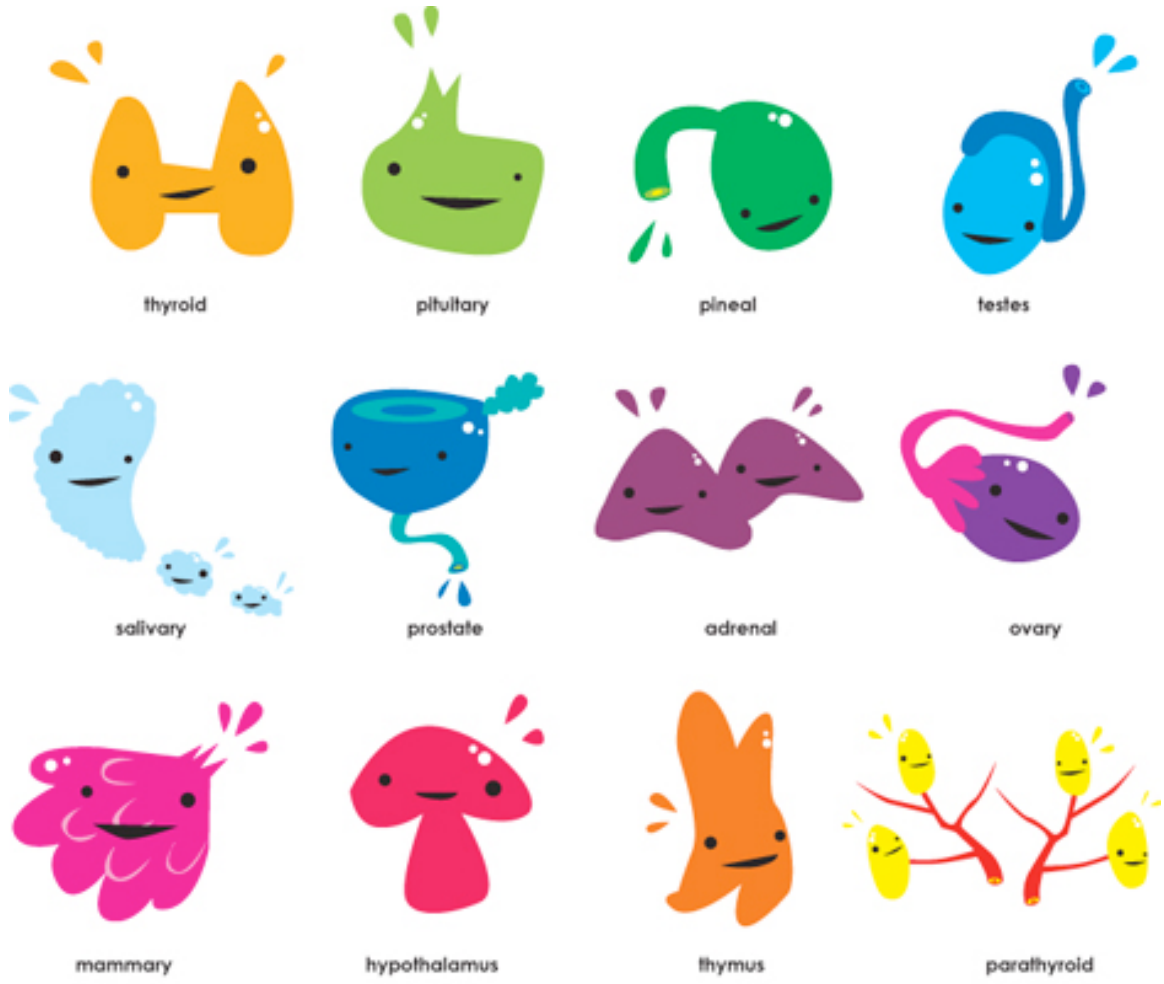
Lecture 6 & 7: Physiology of Thyroid Gland & Its Disorders



Note: 1) This is a rearrangement of the slides + Few notes

2) Focus on every figure and graph. Do not ignore them!

notes are in purple

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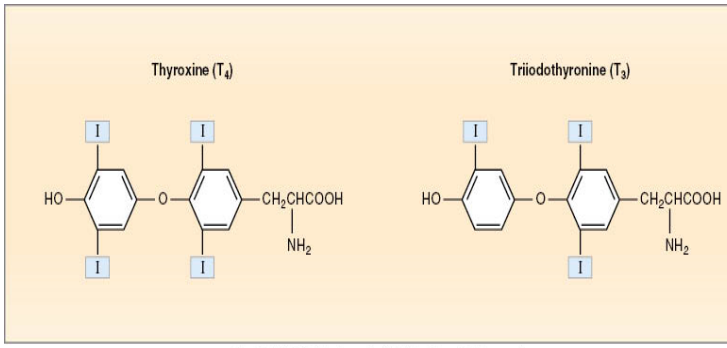
THE THYROID GLAND

- It is located below the larynx on either sides and anterior to the trachea.
- The first recognized endocrine gland.
- 20g in adult.

HORMONES:

- T3 Triiodothyronine.
  - Three iodine atoms
  - 10% of thyroid hormones AMOUNT.
  - More active
- T4 thyroxine (Tetraiodothyronine)
  - Four iodine atoms
  - 90% of thyroid hormones AMOUNT.
  - Less active
- Reverse T3: Has no activity.
- Calcitonin.



SYNTHESIS OF HORMONES:

Three Unique Features:

1- Contains a large amount of iodine.

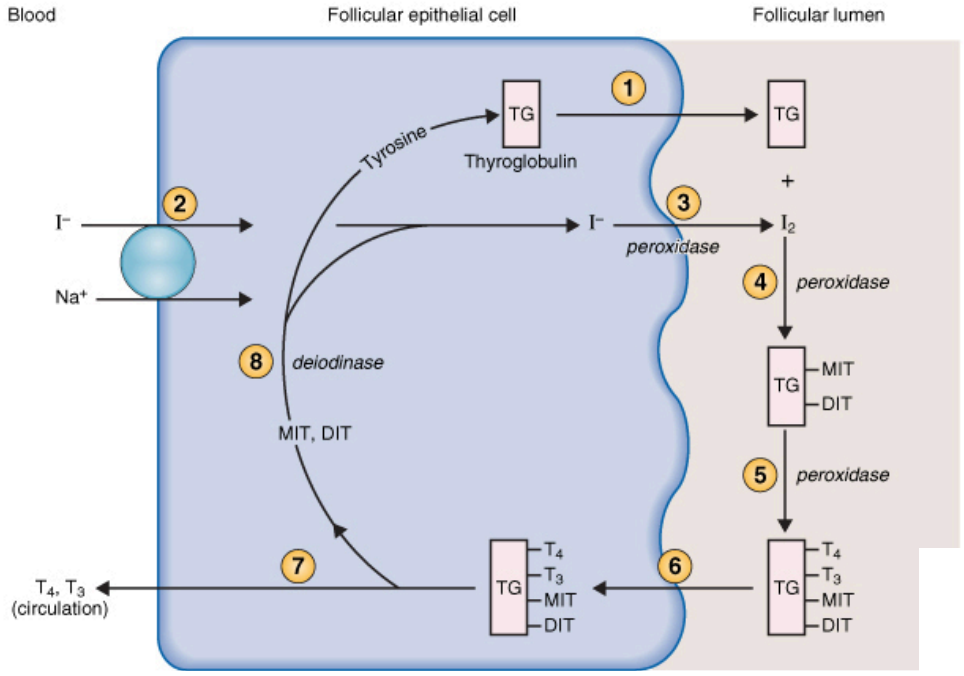
- supplied in diet.
- 1mg/week.

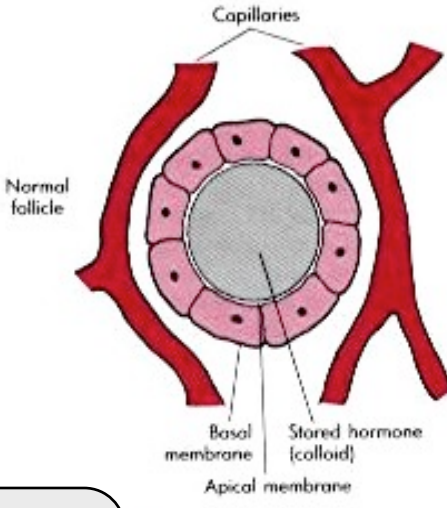
2- Synthesis is partially intracellular and partially extracellular. **hormones are stored extracellularly in the lumen before secretion**

3- T4 is the major product. ***Despite that, it's not the most active form [T3 is].***

This 'problem' of secreting the less active form [T4] is solved by the target tissues, which convert T4 >> T3.

❖ STEPS IN BIOSYNTHESIS:





1- THYROGLOBULIN FORMATION AND TRANSPORT:

- **They're formed in Rough endoplasmic reticulum and Golgi apparatus of follicular cells and then cross the apical membrane into the follicular lumen.**
- **Formed of 140 tyrosine molecule which later will be iodinated.**

Remember thyroid hormones are amine hormones derived fro the AA **tyrosine**.

2- IODIDE PUMP OR IODIDE TRAP: Na-I cotransport:

- **Actively transport iodide from blood into follicular cell against its chemical and electrical gradient in exchange of sodium.***
- **Wolff-chaikoff effect:** High I levels >> reduce I uptake. While, low I levels >> stimulate the pump.

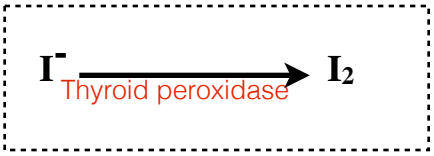
However, If the deficiency is severe the pump cannot compensate no matter how much it's stimulated so the net effect will be ↓ thyroid hormone

- **Ratio of concentration from 30-250 times more in the follicular cell than blood levels**
- **The pump is stimulated by TSH.**

* There's more I in than out, whereas there's more Na out than in .

So, Na moves down it's gradient while I moves against its gradient, both on the same direction out to in [Active Cotransport]

3- OXIDATION OF IODIDE TO IODINE:



- by the enzyme **Thyroid peroxidase**.

4- ORGANIFICATION OF THYROGLOBULIN

- **Binding of iodine with Thyroglobulin,** specifically with the tyrosine molecules of thyroglobulins.
- Happens at the apical membrane just inside the lumen.
- **Catalyzed by thyroid peroxidase to form monoiodotyrosine [MIT] or diiodotyrosine [DIT]**
- **Remain attached to thyroglobulin in the follicular lumen until the gland stimulated to secret.**

Note : High levels of I- inhibit the organification and synthesis of thyroid hormones which known as the Wolff-Chaikoff effect .

5- COUPLING REACTION:

- **MIT + DIT = T3**

  DIT + DIT = T4

A faster reaction >> 10 times more T4 is produced than T3

- **Catalyzed by thyroid peroxidase**
- **This iodinated thyroglobulin is stored as colloid in the follicular lumen until the gland is stimulated to secrete.**
- **T4 and T3 are store in the colloid for 2-3 months. This store is sufficient for 2-3 months.**
- Not all MIT & DIT enter the coupling reaction, so, what's left get recycled [see step 8]

6- ENDOCYTOSIS OF THYROGLOBULIN: When the thyroid gland is stimulated, iodinated thyroglobulin (with its attached T_4, T_3, MIT, and DIT) is endocytosed into the follicular epithelial cells.

7- HYDROLYSIS OF T4 AND T3 FROM THYROGLOBULIN BY LYSOSOMAL ENZYMES:

- **Hydrolysis of the peptide bond to release *DIT+MIT+T4+T3* from the thyroglobulin**

MIT & DIT remain in the follicular cell and are recycled into the synthesis of new thyroglobulin.

T3 & T4 are transported across the basal membrane into nearby capillaries to be delivered to the systemic circulation

8- DEIODINATION [removal of **I**] **of DIT and MIT inside the follicular cell by the enzyme thyroid deiodinase. I will recycled and added to I that was transported by the pump . Tyrosine will be incorporated into synthesis of new thyroglobulin .**

A deficiency of thyroid deiodinase has the same effect of dietary I^- deficiency = ↓ thyroid hormones

	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	Propylthiouracil (PTU)
4	Organification of I_2 into MIT and DIT	Apical membrane	Peroxidase	Propylthiouracil
5	Coupling reaction of MIT and DIT into T_3 and T_4	Apical membrane	Peroxidase	Propylthiouracil
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	

Steps involved in the synthesis of thyroid hormones in thyroid follicular cells. Also see the text for an explanation of the *circled numbers*. DIT, Diiodotyrosine; ER, endoplasmic reticulum; MIT, monoiodotyrosine; PTU, propylthiouracil; TG, thyroglobulin; T_3, triiodothyronine; T_4, thyroxine.

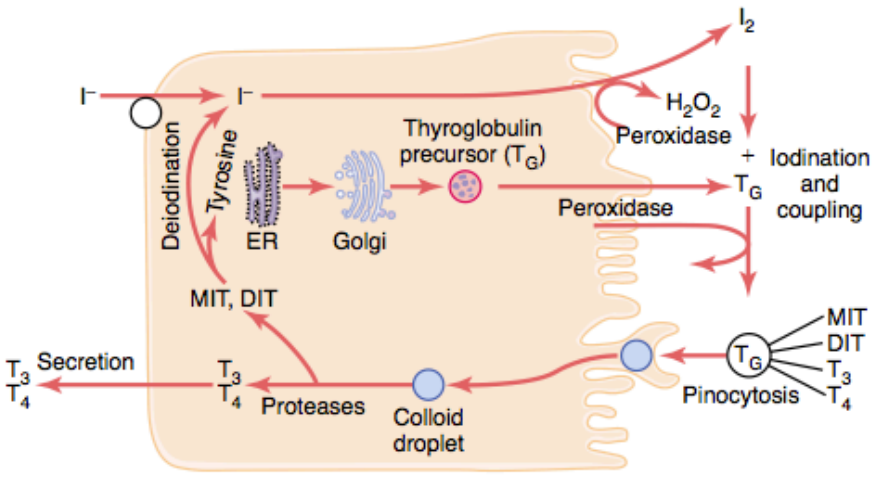


Figure 76–2

Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. MIT, monoiodotyrosine; DIT, diiodotyrosine; T_3, triiodothyronine; T_4, thyroxine; T_G, thyroglobulin.

THYROID HORMONES IN THE CIRCULATION:

1- Unbound:

- **0.03% of T4 and 0.3% of T3.**
- **Only free [unbound] thyroid hormones are physiologically active.**

2- Mostly Bound:

- **70- 80% bound to thyroxine-binding globulin (TBG) synthesized in the liver.**
- **The reminder is bound to albumin.**
- **TBG acts as a reservoir for thyroid hormones which help in slow release of them.**

Some conditions alter the level of TBG >> change the level of free [active] thyroxine. Such as liver failure and pregnancy:

1) In hepatic failure:

decreased protein synthetic function of liver is

>> ↓ **TBG**

>> ↑ **free T3 + T4 levels**

>> **more inhibition of thyroid secretion [by negative feedback]**

>> ↓ **secretion of thyroid hormones**

2) In pregnancy:

high levels of estrogen

>> inhibit breakdown of TBG

>> ↑ **TBG**

>> ↓ **free T3 + T4 free level**

>> **less negative feedback [less inhibition]**

>> ↑ **secretion of thyroid secretion.**

RELEASE OF T4 AND T3 TO THE TISSUES:

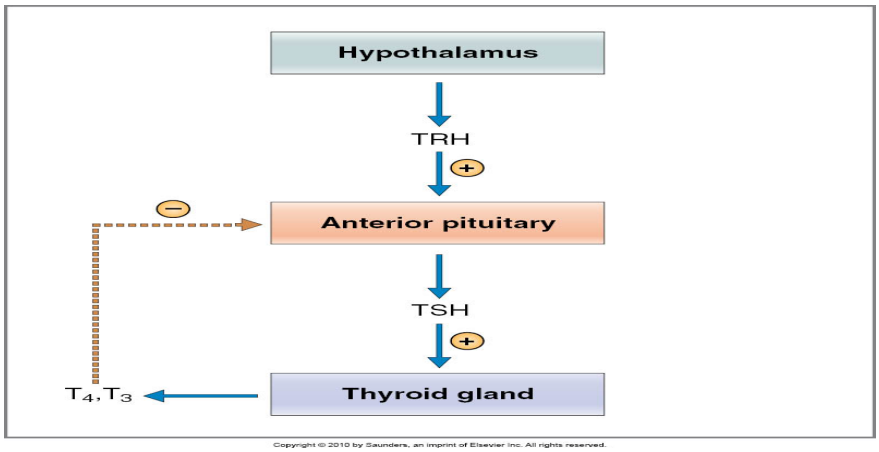
1. **The release is slow because of the high affinity of the plasma binding proteins.**
   - **½ of T4 in the blood is released every 6 days.**
   - **½ of T3 in the blood is released every one day.**

2- Stored in the targeted tissues .

3- Enzyme 5'-iodinase converts T4 [more abundant] to T3 [more active] by removal of one I_2 atom.

Symptoms of hypothyroidism take time to appear because: thyroid hormones ①have slow release from globulins [long t1/2] ②are stored in the gland itself and ③are stored in target tissues

REGULATION OF HORMONES SECRETION:



1- THYROTROPIN-RELEASING HORMONE (TRH):

- **Tripeptide**
- **Secreted by Paraventricular nuclei of the hypothalamus.**
- **Act on the thyrotrophs of the anterior pituitary >> Transcription and secretion of TSH.**
- TRH also stimulates prolactin secretion.

2- THYROID-STIMULATING HORMONE (TSH):

- **Glycoprotein.**
- **Secreted by thyrotrophs in Anterior pituitary.**
- **Regulate metabolism , secretion and growth of thyroid gland (trophic effect,).**
- **TSH secretion starts at 11-13 of gestational weeks.** [the same week that fetus thyroid start secreting]

- Action of TSH: ↑ **synthesis of thyroid hormones by stimulating each step in the biosynthetic pathway.**

1) **Increase I^- uptake and oxidization [↑ pump activity].**

2) **Increase iodination of tyrosine [↑ organification].**

3) **Increase coupling reaction.**

4) **Increase endocytosis and proteolysis of thyroglobulin.**

5) **Trophic effect.** if sustained >> hypertrophy & hyperplasia of follicular cells and increased blood flow.

- Cellular Mechanism of Action of TSH:

- **TSH + receptor >> activation of adenyl cyclase via Gs protein >> generation of cAMP >> activation of protein kinase >> multiple phosphorylation >> secretion and thyroid growth.**

- **N.B 2nd messenger here is cAMP**

The most important early effect of TSH is to initiate proteolysis *of the thyroglobulin, which causes release of T3 & T4 into the blood within 30 minutes. The other effects require hours or even days and weeks to develop fully.*

Table 9-8 Factors Affecting Thyroid Hormone Secretion

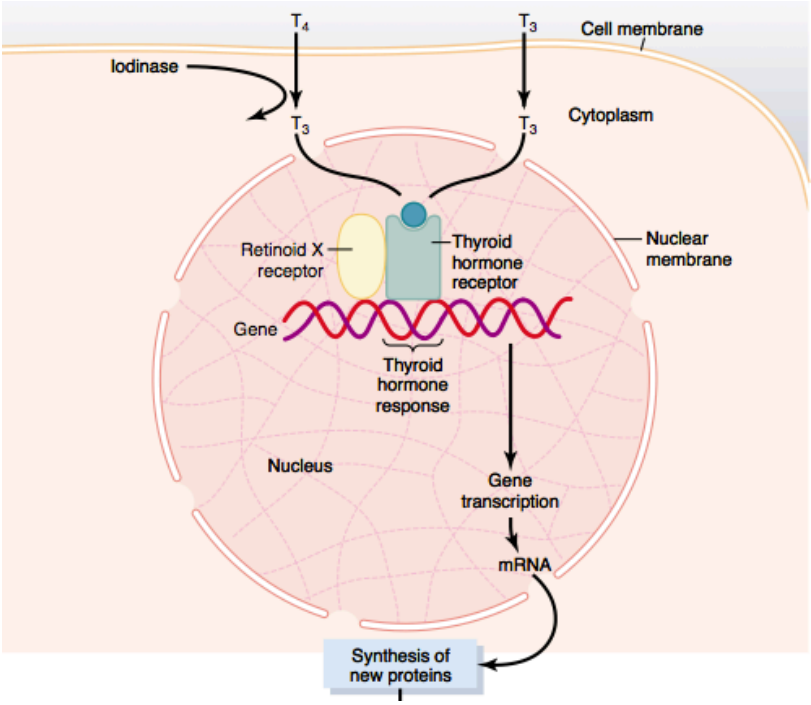
Stimulatory Factors	Inhibitory Factors
TSH	I^- deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I^- intake (Wolff-Chaikoff effect)
	Perchlorate; thiocyanate (inhibit Na^+-I^- cotransport)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

Thyroid-stimulating immunoglobulins : antibodies to TSH receptor. When they bind to TSH receptors they produce the same action of TSH on thyroid cells >> stimulation of synthesis and secretion of thyroid hormones and hypertrophy and hyperplasia of the gland (Graves' disease)

Remember: both iodine deficiency and excess will lead to inhibition of hormone formation; deficiency because there won't be enough I to synthesize the hormone and excess as you know from W-C effect it will inhibit organification >> inhibition synthesis

ACTIONS OF THYROID HORMONES:

- Cellular Mechanism of Action of Thyroid Hormones:



Before binding to the nuclear receptors 90% of T4 is converted to T3 by 5'-iodinase.

T3 enters nucleus and binds to nuclear receptor
>> formation of T3-receptor complex
>> activation of thyroid regulating element on DNA
>> stimulation of DNA transcription
>> formation of mRNA >> translation of mRNA
>> specific protein synthesis (target tissue specific).

Those specific proteins Include:

Na-K ATPase ⟶ ↑ O_2 **consumption, BMR & heat production**

B adrenergic receptors ⟶ ↑ heart rate

Ca ATPase ⟶ ↑ myocardium contractility

lysosomal and proteolytic enzymes

The effects of T3 on various organ systems are as follows:

1- Basal metabolic rate (BMR):

- BMR is the energy requirement under basal condition (stat of mental and physical rest 12-18 hours after a meal).

- Complete lake of thyroid hormones >> ↓ 40% in BMR.

- Extreme increase of thyroid hormones >> ↑ 60-100% in BMR.

Mechanism of BMR increase by T3:

As mentioned, T3 ↑ synthesis of Na-K ATPase which need ATP for its function. ATP generation requires O_2 **consumption and generate heat.**

2- Metabolism:

A)- Effect on carbohydrate metabolism:

1- increase glucose uptake by the cells.
2- increase glycogenolysis.
3- increase gluconeogenesis.
4- increase absorption from the gastrointestinal tract.

B)- Effects on fat metabolism:

1- increase lipolysis.
2- decrease plasma cholesterol by increase loss in feces.
3- increase oxidation of free fatty acids.

C)- Effect on protein metabolism:

overall effect is catabolic leading to decrease in muscle mass.

- **The metabolic effects are due to the induction of metabolic enzymes:**

1- cytochrome oxidase.
2- NAPDH cytochrome C reductase.
3- alpha- glycerophosphate dehydrogenase.
4- malic enzymes.

3- Growth:

- **Thyroid hormone is required for growth to adult stature**
  #deficiency >> short stature

- **T3 acts synergistically with GH and somatomedins to promote bone formation and ossification & fusion of epiphyseal plates.**

4- Effects on the cardiovascular system:

1. **increase heart rate.**
2. **increase stroke volume.**
3. **decrease peripheral resistance.**

So, increase cardiac output

> end result is increase delivery of oxygenated blood to the tissues.

✦ Thyroid hormones potentiate [synergistic action] the effect of catecholamine in the circulation activation of β-adrenergic receptors.

✦ Direct induction of:

a)- myocardial β-adrenergic receptors.
b)- sarcoplasmic reticulum.
c)- Ca+2 ATPase.
d)- myosine.

5- Effects on respiration:

1- increase ventilation rate.

2- increase dissociation of oxygen from Hb by increasing red cells 2,3-DPG (2,3 diphosphoglycerate).

NET EFFECT OF 4 & 5: ↑respiratory rate [ventilation] and ↑heart rate and contractility >> cardiac output.

6- Effects on the CNS:

A)- perinatal period:

Thyroid hormones are essential for maturation of the CNS.

> Note : both GH and thyroid hormone deficiency will cause uncompleted growth (short stature , decrease muscle mass …) but the different between GH deficiency and thyroid hormone deficiency is MENTAL RETARDATION which is present with thyroid hormone deficiency

★ perinatal decrease of thyroid hormones secretion >> irreversible mental retardation

★ Screening for hypothyroidism is necessary to introduce hormone replacement .

B)- In adult:

✤ **Increase in thyroid hormone secretion:**

1-hyperexcitability.

2-hyperreflexia

3- irritability.

✤ **Decrease in thyroid hormones secretion:**

1- slow movement.

2- impaired memory.

3- decreased mental capacity.

7- Effects on Autonomic nervous system:

Produce the same action as catecholamines via

β-adrenergic receptors upregulation including:

a)- increase BMR.

b)- increase heat production.

c)- increase heart rate.

d)- increase stroke volume.

i.e. β-blocker (propranolol) is used in treatment of hyperthyroidism.

8- Effects on the G.I tract:

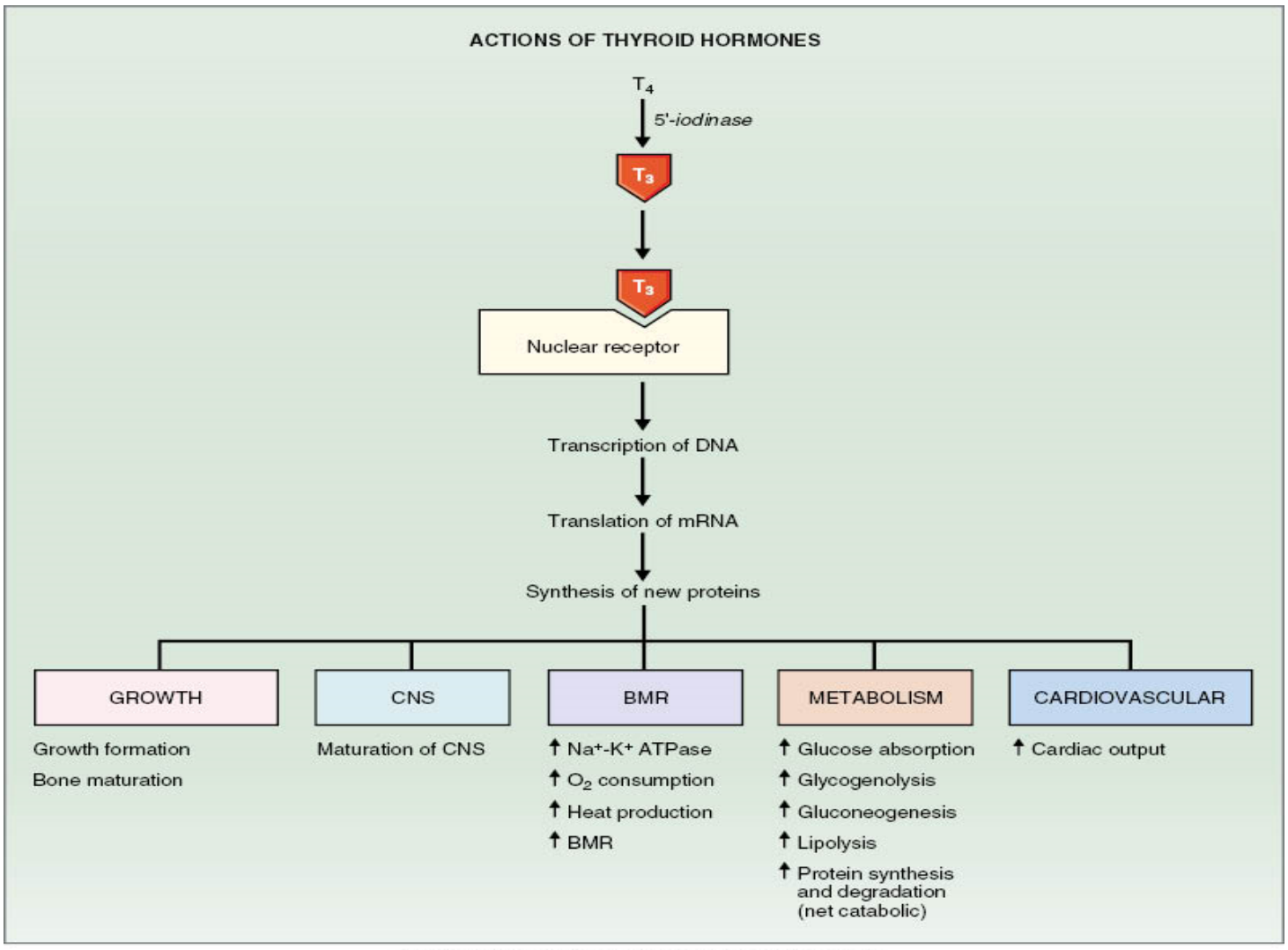
1- increase appetite and food intake.

2- increase of digestive juices secretion.

3- increase of G.I tract motility.

Hyperthyroidism >> diarrhea.

Hypothyroidism >> constipation.



DISEASES OF THE THYROID GLAND

Hyperthyroidism:

- Over activity of the thyroid gland.

- Women : men ratio (8:1).

- activity of gland :

  a)- 5- 10 times increase in secretion.

  b)- 2-3 times increase in size.

CAUSES

1- Graves' disease :

- an autoimmune disorder.

- increased circulating level of thyroid- stimulating immunoglobulin (TSI).

- 4 – 8 times more common in women than men.

2- Thyroid gland tumor:

- 95% is benign.

- history of head and neck irradiation and family history.

3- Exogenous T3 and T4:

(rarely cause)

4- Excess TSH secretion:

- diseases of the hypothalamus (TRH).

- diseases of the pituitary (TSH).

DIAGNOSIS

Signs and symptoms :

1- Goiter in 95%.

2- skin:

- **smooth, warm and moist.**
- **heat intolerance, night sweating.**

3- Muscle atrophy [wasting].

4- Neurological:

- **tremor.**
- **enhanced reflexes [hyperreflexia]**
- **irritability.**

5- Cardiovascular:

- **increase heart rate.**
- **increase stroke volume.**
- **arrhythmias.**
- **hypertension.**

6- G.I tract:

- **Increased appetite.**
- **weight loss.**
- **diarrhea.**

7- Exophthalmos:

- **protrusion of eye balls.**

9- Others:

- **menstrual cycle disturbance.**

Pathophysiology of exophthalmous in Graves' disease:

Cytokine-mediated activation of fibroblasts in orbital tissue behind the eyeball leading to:

1)The inflammation results in a deposition of collagen and glycosaminoglycans in the muscles, which leads to subsequent enlargement and fibrosis.

2) Fibroblasts can differentiate into fat cells (adipocytes). Fat cells and muscles expand and become inflamed. Veins become compressed, and are unable to drain fluid, causing edema

Investigations:

1- Serum T3, T4 measurement.

◉ **In primary hyperthyroidism:**

high T3, T4 and low TSH due to inhibition by -ve feedback of excessive free T3 & T4 .

◉ **In secondary hyperthyroidism:**

high T3, T4 and high TSH.

TREATMENT

1- Medical therapy:

e.g. propylthiourcal [Thyroid peroxidase inhibitor]

- **usually for 12-18 months course**
- **with 3-4 monthly monitoring.**

2- Surgery:

- **Subtotal thyroidectomy**.
  - **Indication for surgery:**
    - a)- Relapse after medical treatment.
    - b)- Drug intolerance.
    - c)- Cosmetic.
    - d)- Suspected malignancy.

Hypothyroidism

- **Under activity of the thyroid gland**

- **more in woman (30- 60 years).**

CAUSES

1- inherited abnormalities of thyroid hormone synthesis :

A)**peroxidase defect.**

B)**Deiodise defect**

C) **Iodide trapping defect.**

D) **thyroglobulin defect.**

2- Endemic Colloid Goiter:

- was common **before iodization of table salt.**

↓ iodide >> hormone formation >> ↑ TSH >> ↑ Thyroglobulin >> ↑ size (> 10 times)

3- Idiopathic Nontoxic Colloid Goiter:

- **I in take is normal.**

- **Unknown cause but most patients have mild thyroiditis**

inflammation >> cell damage >> ↓hormone secretion >> ↑ TSH >> ↑ size

4- Gland destruction (surgery).

5- Pituitary diseases or tumor.

6- Hypothalamus diseases or tumor.

DIAGNOSIS

Signs and symptoms :

1- skin :

- dry skin.

- cold intolerance.

2- Musculoskeletal:

- increased muscle bulk.
- impaired skeletal growth [bones].
- muscle sluggishness
- slow relaxation after contraction

3- Neurological:

- slow movement.
- impaired memory.
- decrease mental capacity

4- Cardiovascular:

- decrease heart rate
- decrease stroke volume.

5- G.I tract:

- decreased appetite
- constipation
- increase weight.

6- Myxoedema:

An edematous appearance through out body.

7- others:

- loss of libido.
- menstrual cycle disturbance.

Investigations:

- Serum T3,T4 are low.

- TSH is elevated in primary.

- TSH is low in secondary hypothyroidism.

TREATMENT

✦ **L- thyroxine [replacement therapy]**

- Starting dose is 25-50 μg.

- Increase to 200 μg.

- At 2-4 weeks period.

The first response seen is the weight loss.

Table 9-9 Pathophysiology of Thyroid Hormones

	Hyperthyroidism	Hypothyroidism
Symptoms	Increased basal metabolic rate 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 (factitious)	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 (if defect is in anterior pituitary)	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

Cretinism

Extreme hypothyroidism during infancy and childhood (failure of growth).

CAUSES

1- Congenital lack of thyroid gland (congenital cretinism).

2- Genetic deficiency leading to failure to produce hormone.

3- Iodine lake in the diet (endemic cretinism).

SYMPTOMS

1- Infant is normal at birth but abnormality appears within weeks.

2- Protruding tongue.

3- Dwarf with short limbs.

4- Mental retardation.

5- Often umbilical hernia.

TREATMENT

Changes are irreversible unless treatment is given early.

Source: Physiology by Linda Costanzo

Guyton and Hall Textbook of Medical Physiology