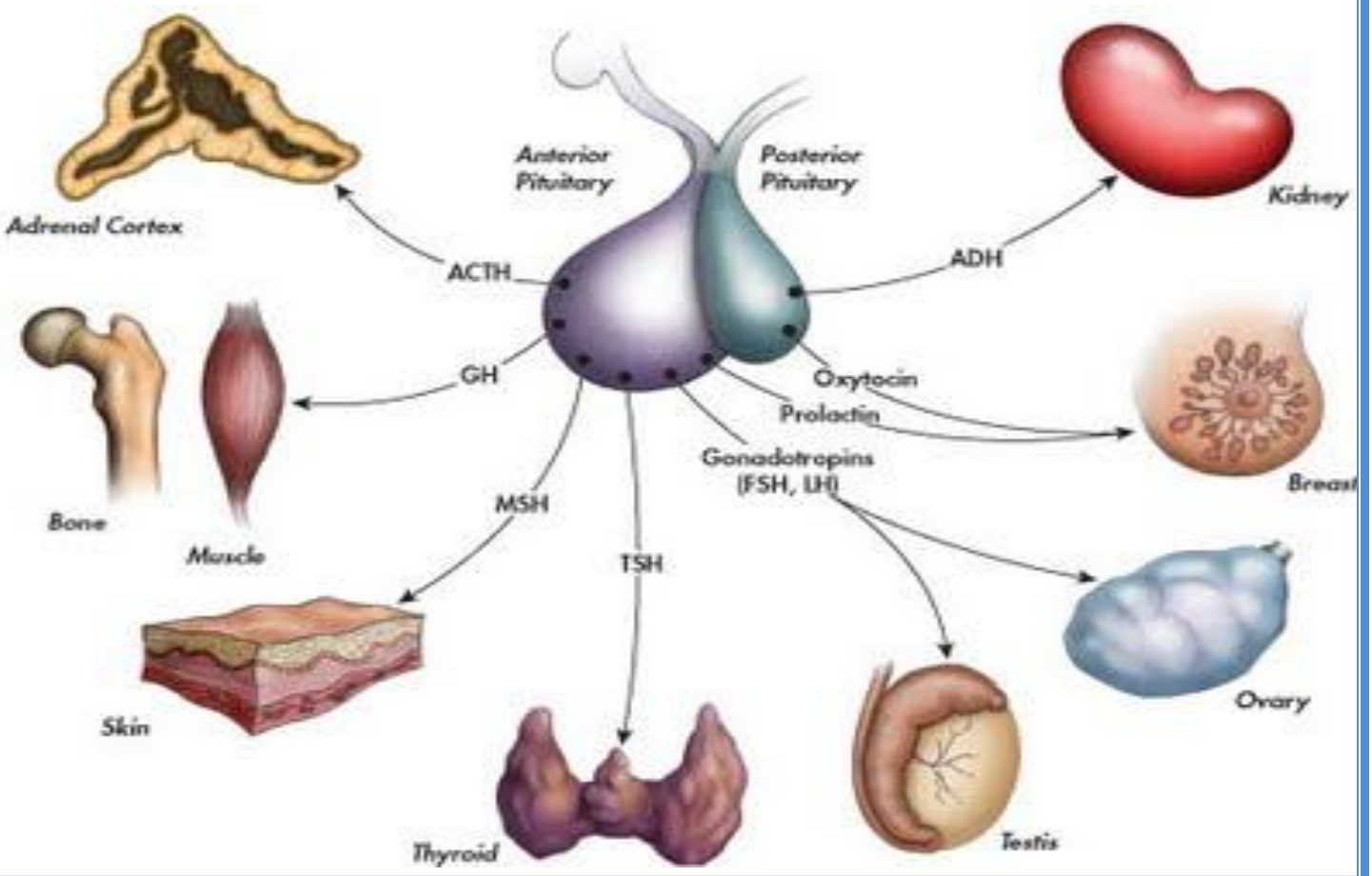
Endocrine Block

6th Lecture

Thyroid Gland



PHYSIOLOGY TEAM – 430

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Thyroid Gland

- **Thyroid Hormones:**

- T3 Triiodothyronine 10% → (more potent)
- T4 thyroxine (tetraiodothyronine) 90% → (more abundant)
- Reverse T3 (inactive)
- Calcitonin

- **Three Unique Features:**

1. Contains a large amount of iodine:

✓ supplied in diet

✓ Amount needed: 1 mg/week

2. Synthesis is partially intracellular and partially extracellular
3. T4 is the major product

- **Steps in Biosynthesis:**

1) Thyroglobulin Formation And Transport:

- 140 tyrosine
- Rough endoplasmic reticulum and Golgi apparatus

2) Iodide Pump Or Iodide Trap:

- Active transport
- Wolff-chaikoff effect (Increase amount of iodine in blood → decrease the activity of iodide pump vice versa)
- Ratio of concentration from 30-250 times
- It is stimulated by TSH.

3) Oxidation Of Iodide To Iodine:

- It is catalyzed by Thyroid peroxidase which is located in or attached to the apical membrane
- Iodine is the reactive form, which will be "organified" by combination with tyrosin on thyroglobulin

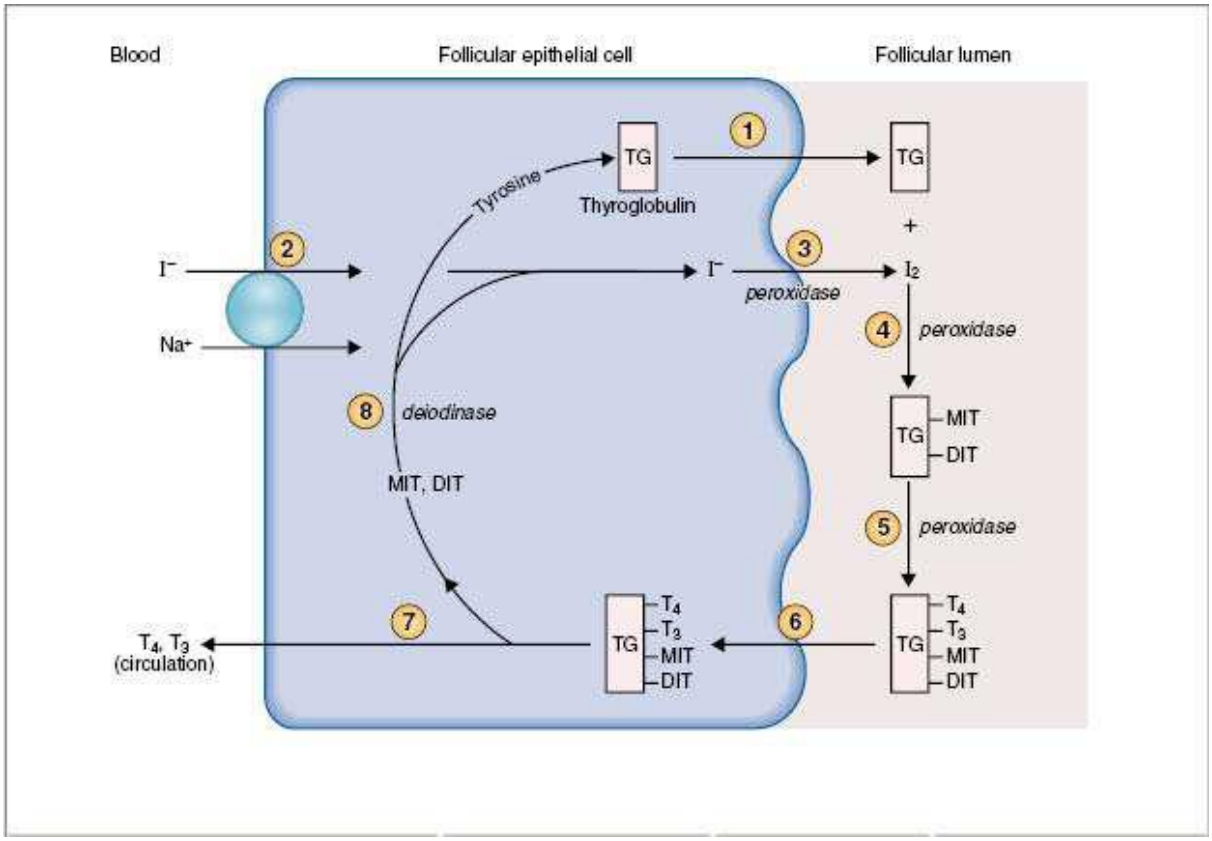
4) Organification Of Thyroglobulin

- Binding of iodine with Thyroglobulin
- Catalyzed by thyroid peroxidase to form: monoiodotyrosine MIT - Diiodotyrosine DIT
- Remain attached to thyroglobulin until the gland stimulated to secret.

5) Coupling Reaction:

- DIT + DIT = T4 (faster)
- DIT + MIT = T3
- Catalyzed by thyroid peroxidase
- It is stored as colloid until thyroid gland is stimulated to secrete thyroid hormone.
- Is sufficient for 2-3 months

6) Endocytosis of thyroglobulin
7) Fusion of lysosomes immediately with the vesicles
8) Hydrolysis of the peptide bond to release DIT+MIT+T4+T3 from the thyroglobulin
9) Delivery of T4 and T3 to the systemic circulation.
10) Deiodination of DIT and MIT by thyroid deiodinase (Recycling)



- **Summary of biosynthesis:**

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	

- **Thyroid Hormones in the Circulation:**

1. **Bound:**

- 70- 80% bound to thyroxine-binding globulin (TBG) synthesized in the liver.
- The reminder is bound to albumin.

2. **Unbound (Free):**

- 0.03% of T4
- 0.3% of T3.

✓ **In hepatic failure:**
↓ TBG → ↑ free T3/T4 → inhibition of thyroid secretion

✓ **In pregnancy:**
↑ Estrogen → ↑ TBG → ↓ free T3/T4 → stimulation of thyroid secretion

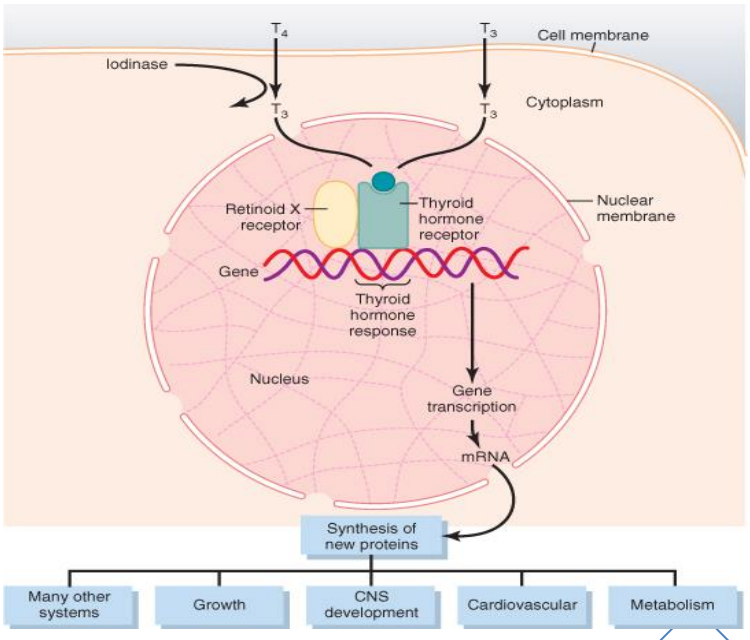
- **Release of T4 and T3 to the Tissues:**

- 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

- T4 & T3 readily diffuse through the cell membrane
- Stored in the targeted tissues (days to weeks)
- Most of T4 is deionized to T3 by iodinase enzyme
- In the nucleus, T3 mainly binds to "thyroid hormone receptor" and influence transcription of genes



- **Action of Thyroid Hormones:**

- Before binding to the nuclear receptors 90% of T4 is converted to T3
- T3 + nuclear receptor → activation of thyroid regulating element on DNA → ↑ DNA transcription formation of mRNA → translation of mRNA specific protein synthesis → (target tissue specific)

1) Basal Metabolic Rate (BMR):

Is the energy requirement under basal condition (mental and physical rest 12-18 hours after a meal)

Complete lake of thyroid hormones → 40-50% ↓ in BMR

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

2) Metabolism:

✓ Effect on carbohydrate metabolism:

- Increase glucose uptake by the cells.
- Increase glycogenolysis.
- Increase gluconeogenesis.
- Increase absorption from the GIT.

✓ Effects on fat metabolism:

- Increase lipolysis.
- Decrease plasma cholesterol by increase loss in feces.
- Increase oxidation of free fatty acids.

✓ 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:

- Cytochrome oxidase.
- NAPDH cytochrome C reductase
- Alpha- glycerophosphate dehydrogenase
- Malic enzymes
- Several proteolytic enzymes

3) Effects on the Cardiovascular system:

- Increase heart rate
- Increase stroke volume
- Decrease peripheral resistance
  (These effects combine to produce increased cardiac output up to 60%)
- End result is increase delivery of oxygenated blood to the tissues

➢ **The cardiovascular effects are due to:**

A. Thyroid hormones potentiate the effect of catecholamine in the circulation → activation of β-adrenergic receptors

B. Direct induction of:

✓ Myocardial β-adrenergic receptors
✓ Sarcoplasmic reticulum
✓ Ca^{+2} ATPase
✓ Myosine

4) Effects on the CNS:

A. Peri-natal period:

- Thyroid hormones are essential for maturation of the CNS → Decrease of hormones secretion → Irreversible mental retardation
- Screening is necessary to introduce hormone replacement

B. In adult:

✓ Increase in thyroid hormone secretion:
- Hyperexcitability
- Irritability

✓ Decrease in thyroid hormones secretion:
- Slow movement
- Impaired memory
- ↓ Mental capacity

5) Effects on bone:

- Promote bone formation
- Promote ossification
- Promote fusion of bone plate
- Promote bone maturation

6) Effects on Respiration:

- Increase ventilation rate.
- Increase dissociation of oxygen from Hb by increasing RBC 2,3-DPG (2,3 diphosphoglycerate)

7) Effects on the GIT:

- Increase appetite and food intake.
- Increase of digestive juices secretion.
- Increase of G.I tract motility.

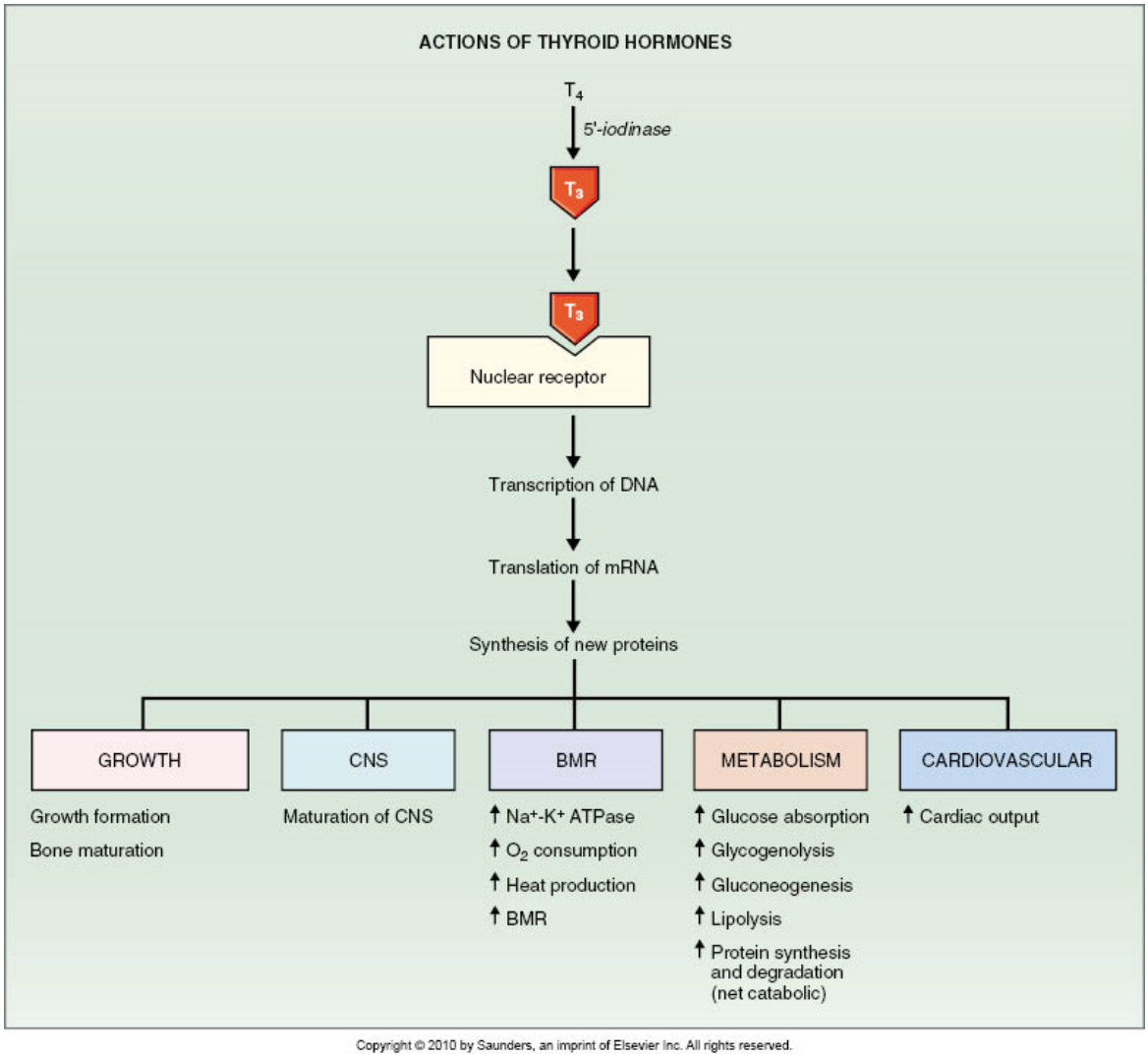
✓ Excess secretion → diarrhea
✓ Lake of secretion → constipation

8) Effects on Autonomic nervous system:

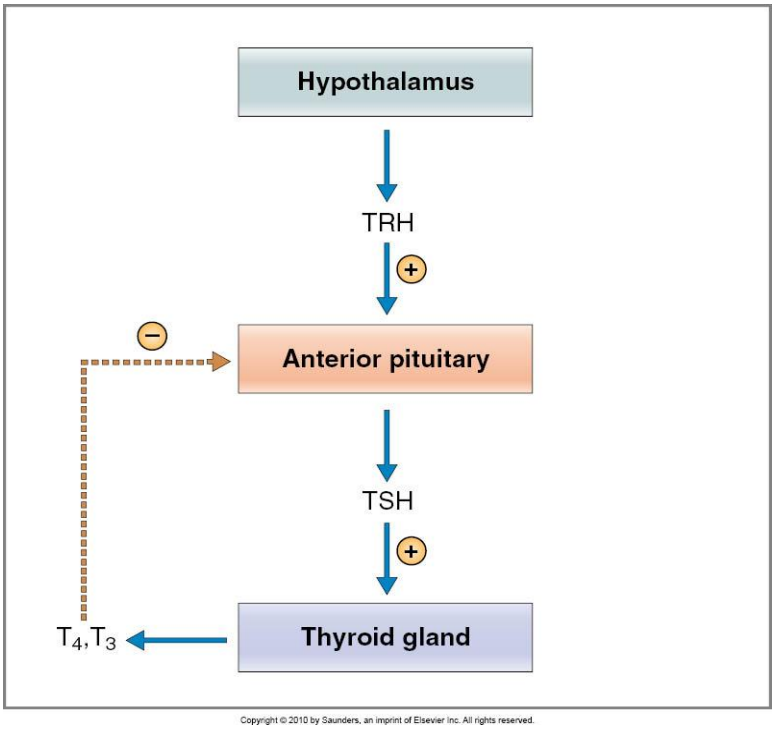
- Produced the same action as catecholamines via β-adrenergic receptors including:

✓ Increase BMR.
✓ Increase heat production.
✓ Increase heart rate.
✓ Increase stroke volume.

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



- **Regulation Of Hormones Secretion:**



Thyrotropin-releasing hormone (TRH):

- Tripeptide
- Paraventricular nuclei of the hypothalamus
- Act on the thyrotrophs of the anterior pituitary
- Transcription and secretion of TSH
- Phospholipid second messenger system

Thyroid-stimulating hormone (TSH):

- Glycoprotein
- Anterior pituitary
- Regulate metabolism, secretion and growth of thyroid gland (trophic effect)

- **Action of TSH:**

- Increase proteolysis of the thyroglobulin
- Increase pump activity
- Increase iodination of tyrosine
- Increase coupling reaction
- Trophic effect

✓ TSH secretion started at 11-12 of gestational weeks

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

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)