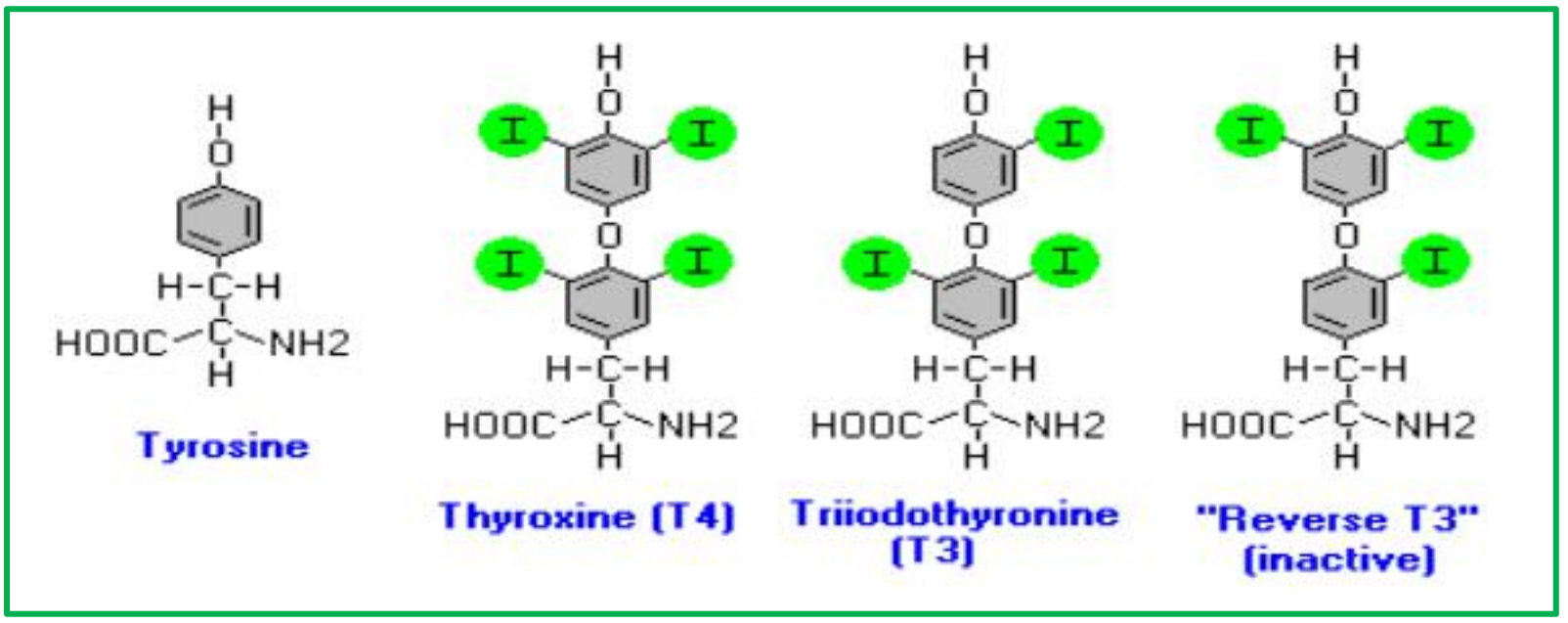
Endocrine System
Biochemistry-Lec(2)

⭐ Brief intro into chemistry of thyroid hormones :



✔Thyroid hormones are derivatives of the the aa tyrosine bound covalently to iodine.

✔The 2 principal thyroid hormones are ⏭ Thyroxine (T4) & Triiodothyronine (T3) .

✔From the diagram above ,the thyroid hormones are basically two tyrosines linked together w/ the critical addition of iodine at 3 or 4 positions on the aromatic rings.

⏭ Keep in mind ,the # and position of the iodines is important. Several other iodinated molecules are generated that have **little or no biological activity**; so called "**reverse T3**"

✔A large majority of the thyroid hormone secreted from the thyroid gland is T4, but **T3 is the considerably more active hormone.** Although some T3 is also secreted, **the bulk of the T3 is derived by deiodination of T4 in peripheral tissues**, especially liver and kidney. **Deiodination of T4 also yields reverse T3**

✔Thyroid hormones are poorly soluble in water, and more than 99% of the T3 and T4 circulating in blood is **bound to carrier proteins** .The principle carrier of thyroid hormones is ⏭ **thyroxine-binding globulin** , Two other carriers of import are **transthyrein** and **albumin**.

⭐ HPT axis :

✔Plays the major role in regulating thyroid hormones homeostasis in the' body .

✔Under the control of neurons located in the median region of the PVN that synthesize and release TRH(Glu-His-Pro) into the pituitary portal circulation .

↓

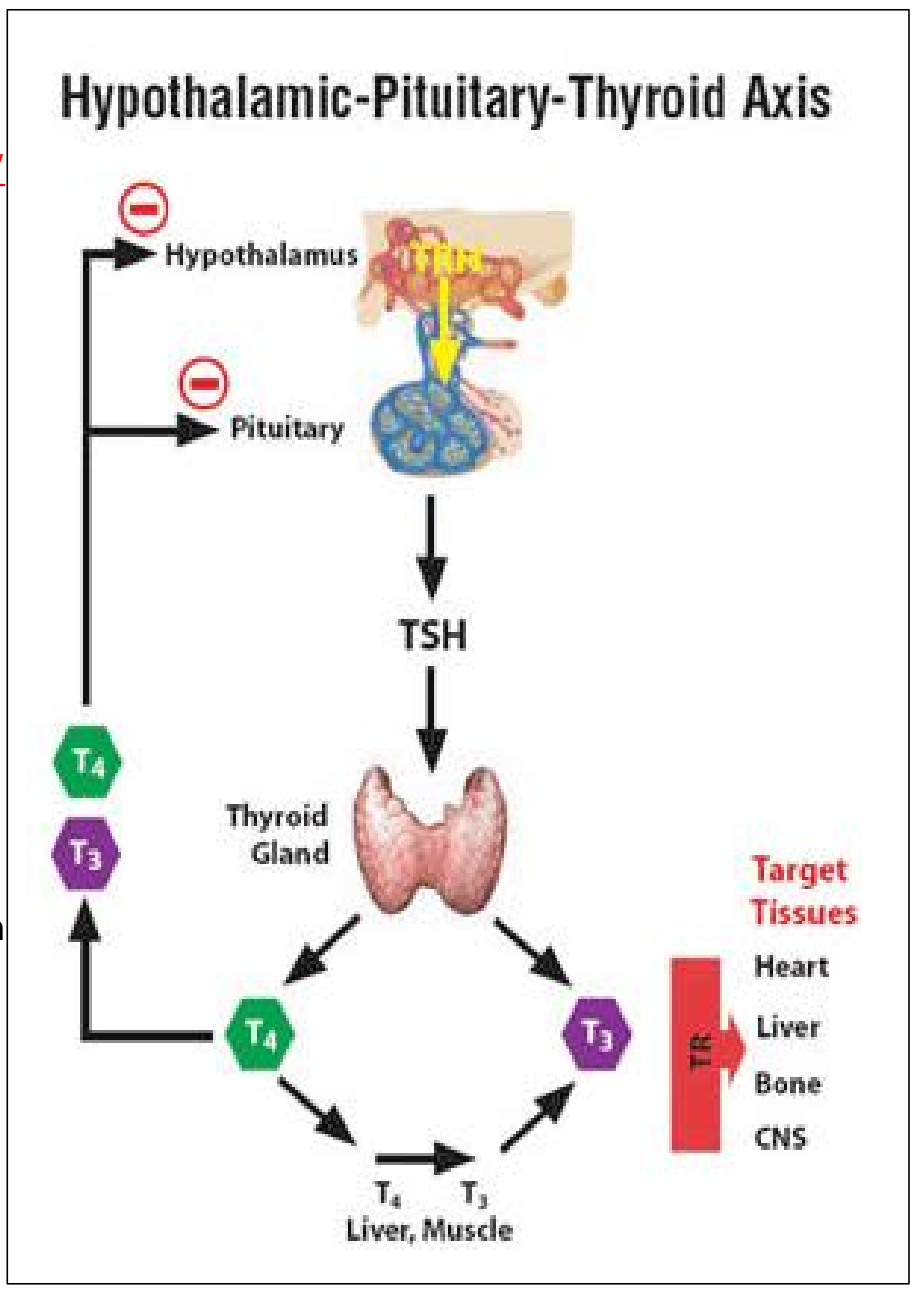
Stimulates secretion of TSH from ant pituitary gland .

↓

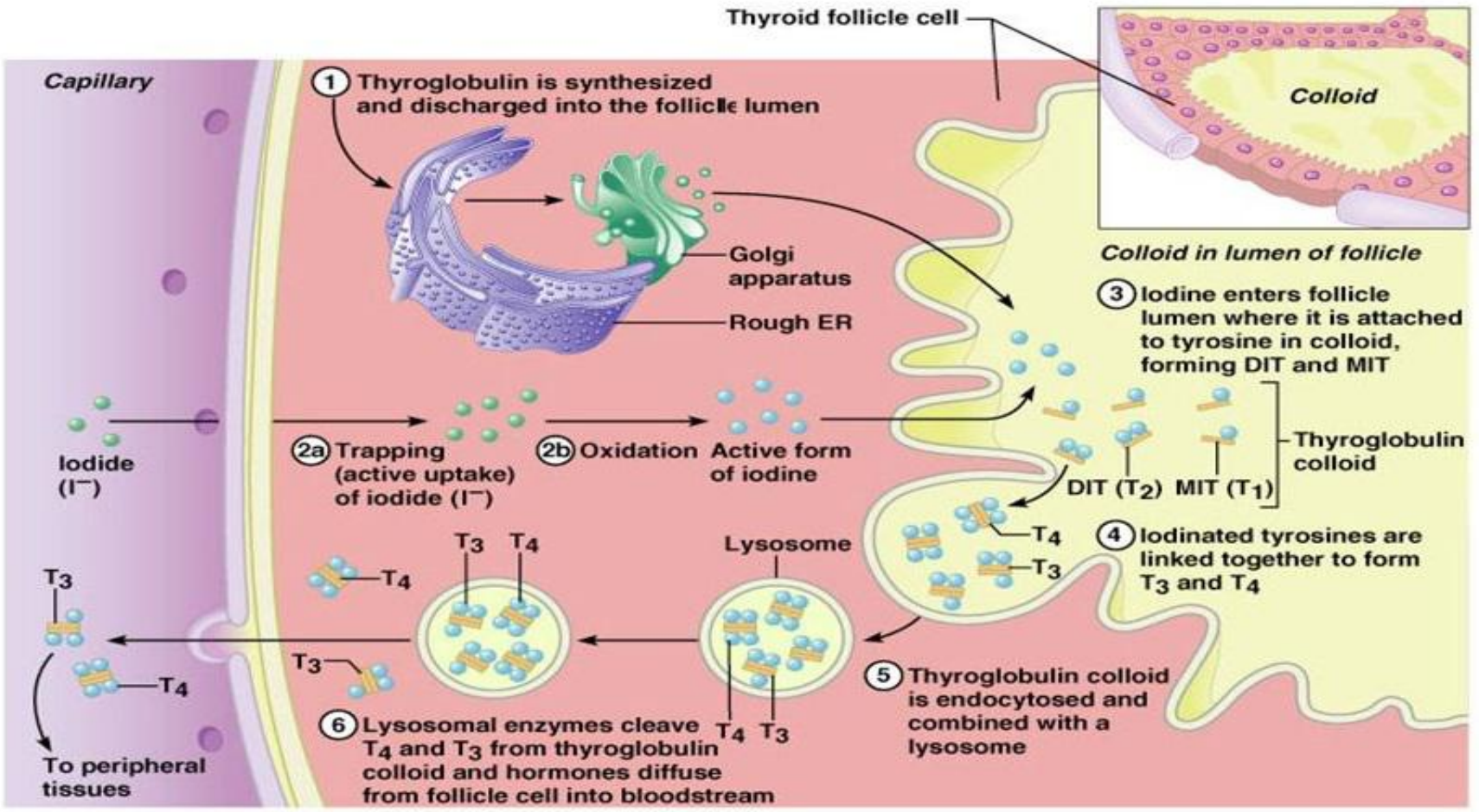
Travels toward the thyroid gland and stimulates synthesis and release of thyroid hormones (T3 & T4)

↓

Control secretion of **TRH and TSH** by ***-ve feedback*** to maintain the physiological levels of the main hormones of HPT axis .



SYNTHESIS OF THYROID HORMONES

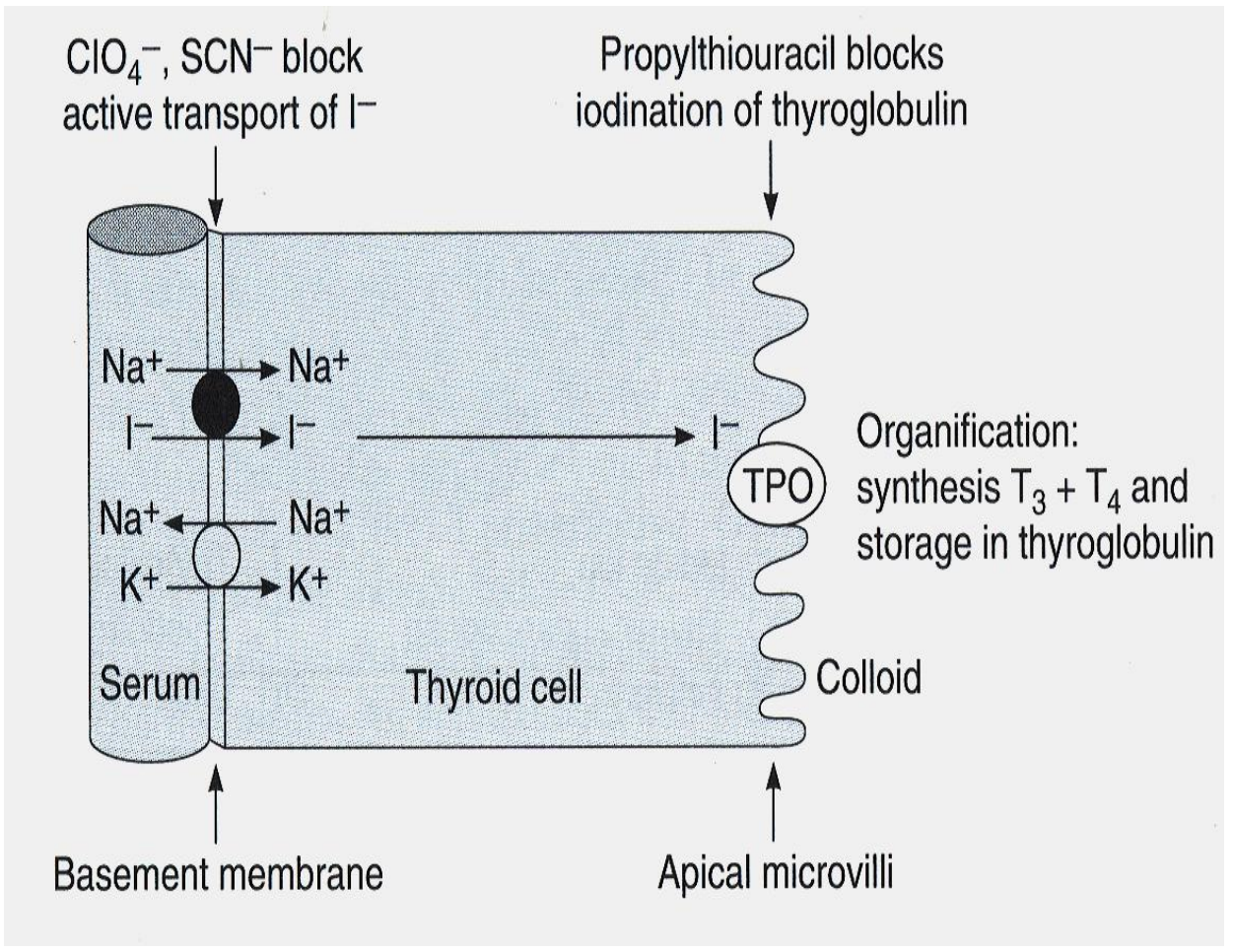


(1) Iodide is actively transported into the thyroid follicle cells (**iodide trapping**) by ⏩ **Na/I symport** .

⭐ I^- is oxidized by **TPO** into Iodine ⏩ uptake of iodine at follicular/colloid interface to be **incorporated onto tyrosine residues of Tg** (which is after being synthesized , released into the follicular lumen)

⭐ The binding of iodine w/ the TG molecule to form MITs and DITs is called ⏩ **Organification** .

⭐ Organification is followed by **Coupling in which T3 and T4 are formed** .



NIS-mediated I- accumulation is a Na^+-dependent active transport process that couples the energy released by the inward translocation of Na^+ down to its electrochemical gradient to the simultaneous inward translocation of I- against its electrochemical gradient. The maintenance of the Na+ gradient acting as the driving force is insured by **Na^+-K^+-ATPase**.

⭐ The normal thyroid maintains a concentration of free iodide **30 to 50x higher than that of plasma**, depending on the amount of available iodine and the activity of the gland.

(2)Tg is synthesized by ER and Golgi apparatus then secreted into the follicle lumen .

(3)Follicles are filled w/ a secretory substance (w/n the lumen) called ⏩ **Colloid** , major constituent of it is ⏩ **Thyroglobulin** .

(4)Thyroglobulin :

✔Gycoprotein of two subunits (each subunit has a MW of : **330KDa**) ,exists as a **homodimer** of MW : **660KDa**

✔Each molecule contains about **130 tyrosine aa** and they are the major substrates that combine w/ iodine to form the thyroid hormones. Thus, the thyroid hormones form w/n the thyroglobulin molecule.

✔Each thyroglobulin molecule contains up to **30 iodinated tyrosine molecules** , but **Only 3 T4 and even fewer T3** .Thus thyroglobulin contains the thyroid hormones, T3 and T4, w/n its molecule.

(5)**Tg** is digested (**proteolysis**) by lysosomal enzymes (w/n the thyroid follicle cell) into **individual aa and T3 & T4** , the aa are recycled in Tg .

(6)T3 and T4 diffuse out of the thyroid follicle and enter the circulatory system .

⏩ In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body w/ its normal requirements of thyroid hormones for ***2 to 3 months***.

Enzyme/Step	Action	Inhibitor
NIS	pump the iodide actively to the interior of the cell	**Perchlorate** (ClO_4^-) **Thiocyanate** (SCN^-)
TPO/H_2O_2	Oxidation of iodide into iodine	Propylthiouracil
Throperoxidase	Incorporation of iodide onto tyrosine residues of TG ⏩ MIts and DITs	Thioureas (or PTU more accurate)
Thyroperoxidase (TPO)	DIT + DIT ➡ T4 MIT + DIT ➡ T3 Coupling of iodotyrosyls	Propylthiouracil (thiourea antithyroid agent)

✔ Release of T4 and T3 into circulation ➡**100 µg T4** & **10 µg T3/day** (~ 10% T4 undergoes mono-deiodination to T3 before secretion)

⭐ ⭐ ***About 93 % of the thyroid hormone released from the thyroid gland is normally T4 and only 7 % is T3. However, after few days, about one half of the thyroxine is slowly deiodinated to form additional T3.***

✔To form normal quantities of thyroxine, about 50 mg. of ingested iodine in the form of iodides are required each year, or about 1 mg/week.

✔Iodides ingested orally are absorbed from the GIT

✔Iodine is removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones.

⭐ **Metabolism of Thyroid hormone** ; it can undergoe one of the following pathways :

(1)Series of deiodinations by deiodinases

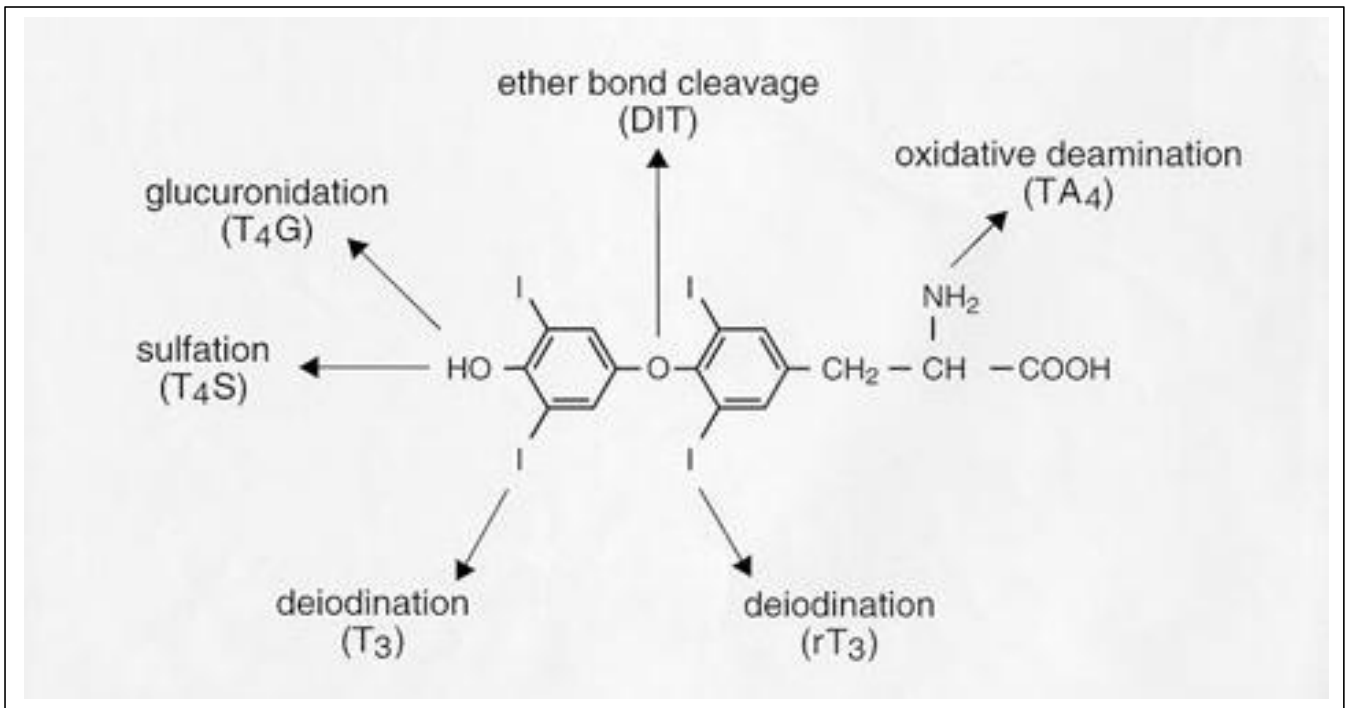
In liver, kidney, thyroid, pituitary gland, CNS brain, brown fat, placenta, pituitary gland

Other metabolic pathways:

(2)Sulphation.

(3)Decarboxylation .

(4)Conjugation w/ glucuronide .



Thyroid hormone transport

TBG

- Highest Affinity

Transthyretin (aka TBPA)

- Intermediate Affinity

Albumin

- Low Affinity & High Capacity

Hereditary	Hereditary
Pregnancy	Androgens
Estrogen therapy	CS
Hypothyrodism	Thyrotoxicosis
Phenothiazines	Nephrotic syndrome
Acute Viral Hepatitis	Malnutrition

⭐ Thyroid hormones are transported in the blood bound to protein carriers

⭐ Only 0.02% of T4, and 0.2% of T3 are free ⏩ The free fraction is responsible for hormone action

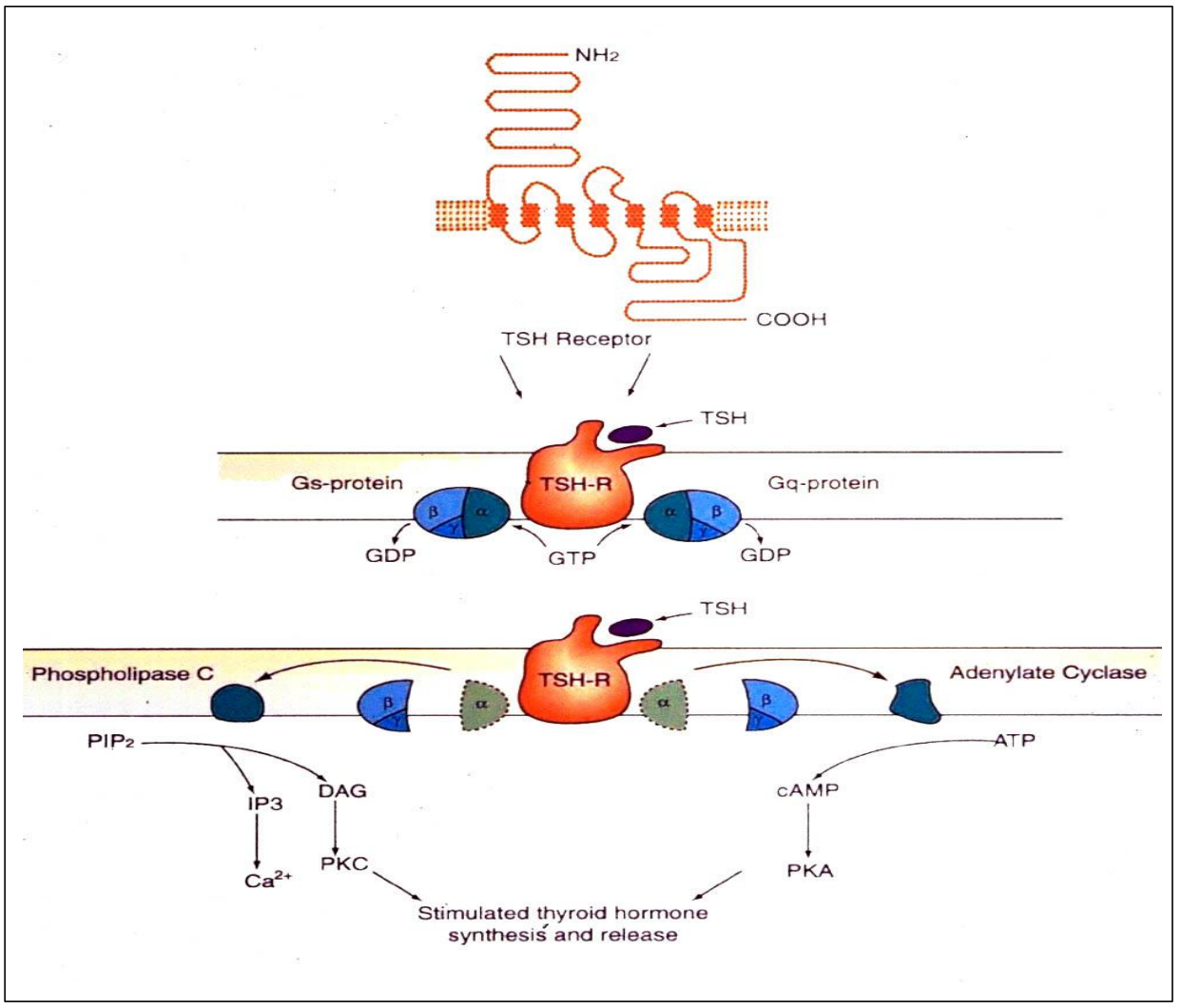
⭐ About 99% of T3 is derived from peripheral conversion of T4 (deiodination)

Thyroid hormone changes during pregnancy

	First trimester	Second trimester	Third trimester
TSH	Normal or decreased	Normal	Normal
Free T4	Normal	Normal	Normal
Free T3	Normal	Normal	Normal
Total T4	High	High	High
Total T3	High	High	High

Antithyroid drugs in pregnancy

- Used in thyrotoxicosis or Grave's Dz :
  - -PTU
  - -MTU
  - -Carbimazole
  - -Radioactive Iodine (I 131)
- All cross placenta .
- All have risk of congenital goiter and hypothyrodism .
- The lowest dose of antithyroid drugs shoud be used .
- PTU ⏩ preferable over others .



TSH binds w/ specific TSH receptors(G-protein linked) on basal membrane surfaces of the thyroid cell.

Most, if not all, of its effects result from activation of the "second messenger" cAMP system of the cell.

Other 2nd messengers (when in high concentrations) ⏩ **IP3**(⬆ Ca+2) & **DAG**(PKC)

TRH resposible for regulation of TSH secretion & TSH glycosylation .

TRHR ⏩ G-protein coupled :

(1)**Ca^{+2}** ➡Stimulates TSH release .

(2)DAG⏩ PKC ➡stimulates TSH α and β subunits transcription

⏩ Actions of TSH :

✔**Active uptake of iodine Stimulates other reactions involved in thyroid hormone synthesis .**

✔**Stimulates the uptake of colloid .**

✔**Induces growth of the thyroid gland .**

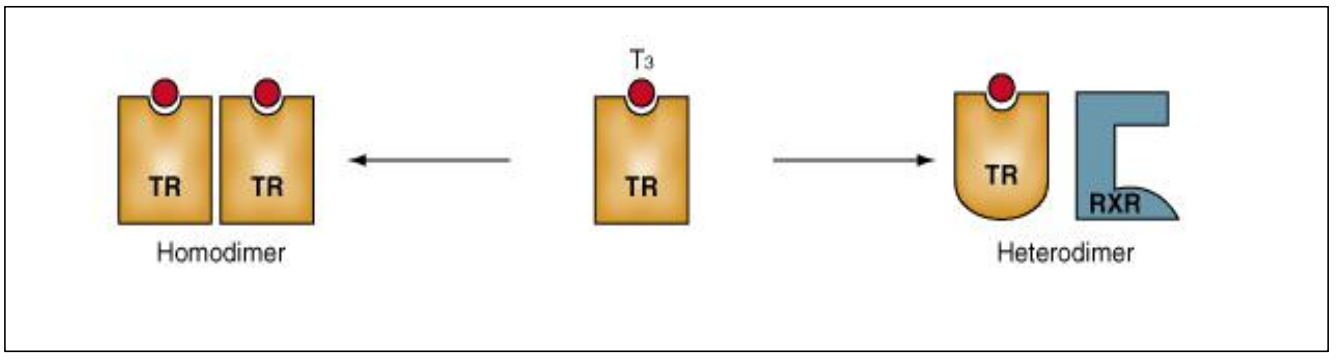
⭐ Basic mechanisms of thyroid hormone regulation

Classic HPT axis	Pituitary and peripheral deiodinases.	Thyroid autoregulation, response to iodine.	TSH receptor antibodies.

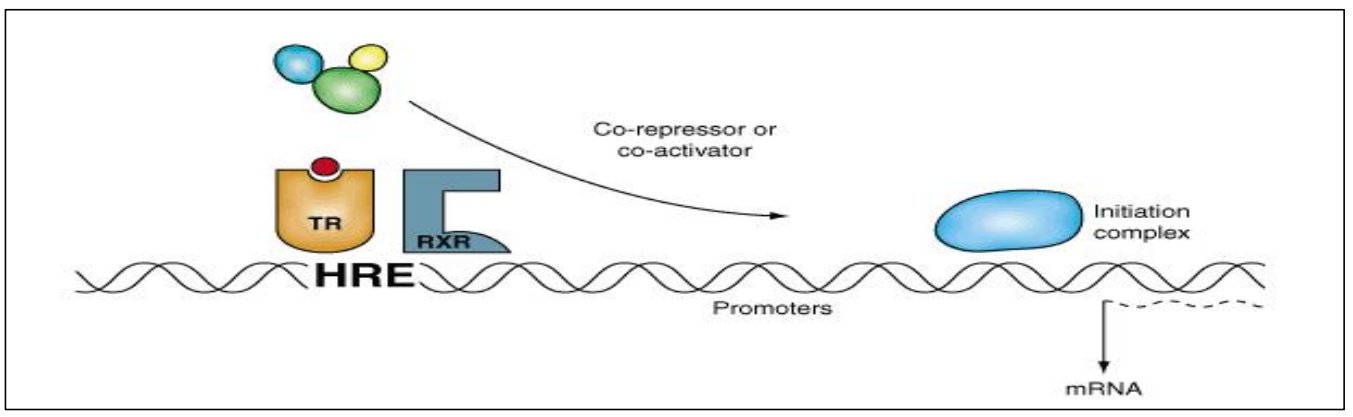
Thyroid hormone receptors

- Receptors for thyroid hormones are nuclear and their affinity is **10x higher for T3 than T4** .
- **Four variants of nuclear receptor were observed and mitochondrial receptor for T3 was also described**.
- T3 receptor dimerize w/ another T3 receptor (**homodimer**) or retinoic acid receptor(RXR) (**heterodimer**)

Dimerized receptor + other transcription factors ➡ **gene transcription**



- Free thyroid hormone receptor (TR) w/o bound hormone is bound to HRE and CoR .



Thyroid hormones inc expression of the following proteins :

1. Glycerol 3-phosphate dehydrogenase
2. Cytochrome c oxidase
3. ATPases
4. Carbamyl phosphate synthase
5. GH

Mechanisms of increasing body temp in hyperthyroidism?

- Reducing efficiency of ATP synthesis ➡ increased synthesis of glycerol 3-phosphate dehydrogenase ⏩ increased transport NADH by this shuttle than malate/aspartate shuttle .
- Increased synthesis of ATP .
- Increased consumption of ATP .
- Uncoupling of phosphorylation and oxidation in mitochondria .

Keep in mind , one of the main sx of HT is ⏩ Heat intolerance .

Increased Respiration in Hyperthyrodism ?

Inc synthesis of cyt c oxidase

⏬

Inc OP (⬆ consumption of Oxygen)

⏬

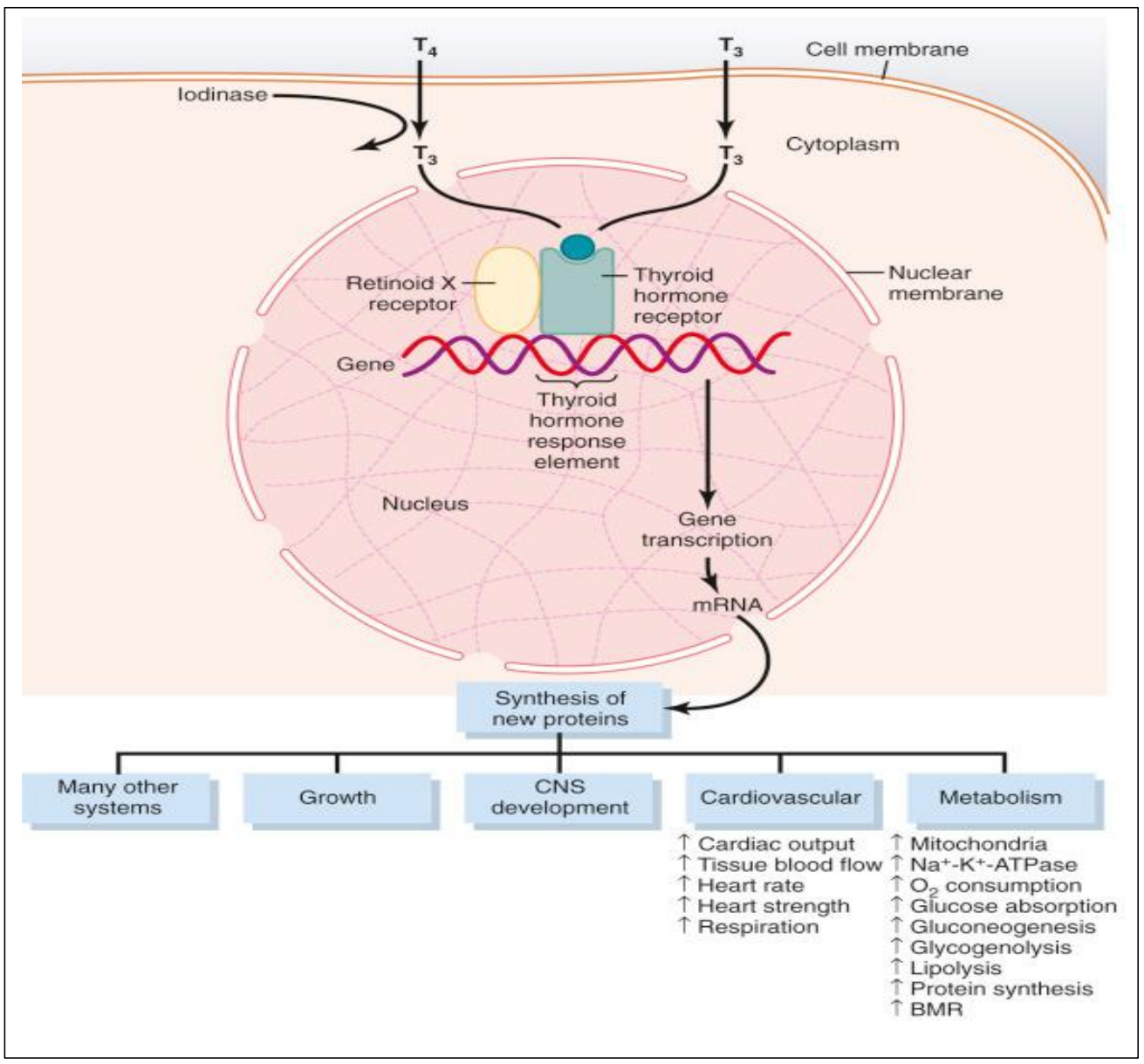
Inc production of ATP

Inc synthesis of ATPases

⏬

Inc depletion of ATP stores

(**Inc ATP consumption**)



Physiological Effects of Thyroid Hormones

- Acceleration of rate of food utilization for energy .
- Inc of protein synthesis as well as rate of protein catabolism .
- Inc # of mitochondria and size & total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate.
- ***Growth and development of the brain during fetal life and for the first few years of postnatal life require thyroid hormones***.

▪Inc oxygen consumption and heat production .

▪ +ve chronotropic and +ve inotropic effects on the heart .

▪Up-regulates β-adrenergic receptors ⏭ increase sensitivity to adrenergic effectors .

▪Inc gut motility. ▪Inc bone turnover ▪Inc reflex response ▪Inc hepatic glycogenolysis and gluconeogenesis

▪ Stimulates lipolysis ▪**Developmental effects ➡Growth & Brain development**

▪Inc # of LDL receptors on the liver cells ⏭ rapid removal of LDL from the plasma.

▪Inc significantly the rate of cholesterol secretion in the bile and consequent loss in the feces ➡dec the concentrations of cholesterol .

▪***Inc the strength of the heart when only a slight excess of thyroid hormone is secreted ➡when thyroid hormone is increased markedly, the heart muscle strength becomes depressed because of long-term excessive protein catabolism***.

▪The increased rate of metabolism inc the utilization of oxygen and formation of carbon dioxide ➡ activate all the mechanisms that inc the rate and depth of respiration.

▪Increases the rates of secretion of most other endocrine glands ➡***Insulin &PTH***

▪Lack of thyroid hormone is likely to cause loss of libido in both males and females.

▪***In females lack or excess can cause menstrual irregularities***.

✔CNS effects :

▪Excitatory effects on the CNS, including cognition.

▪Slight increase in thyroid hormone usually makes the muscles react with vigor, but when the quantity of hormone becomes excessive, the muscles become weakened because of excess protein catabolism.

▪***One of the most characteristic signs of hyperthyroidism is a fine muscle tremor***.

▪Because of the excitable effects of thyroid hormone on the synapses, it is difficult to sleep(insomnia), in case of excess.