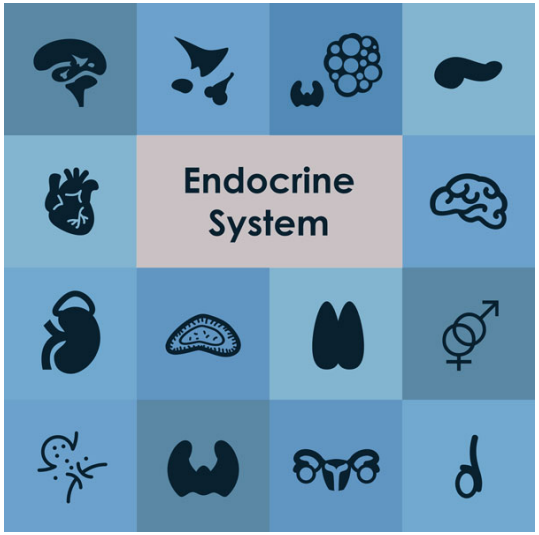
VIGUS ACADEMIC TEAM

BAU-Medicine



Sheet no. 2
Lecture Date: 30/12/2020
Lecture Title: Thyroid Hormones
Written by: Rahmeh Adel

Note: Every picture in this sheet is included and is explained by the doctor

دعاء لزميلنا رشيد
اللهم اغفر له وارحمه وعافه واعف عنه وأكرم نزله ووسع مدخله واغسله بالماء والثلج والبرد ونقه من الخطايا، كما نقيت الثوب الأبيض من الدنس وأبدله دارًا خيرًا من داره وأهلًا خيرا من أهله، وأدخله الجنة، واعذه من عذاب القبر ومن عذاب النار

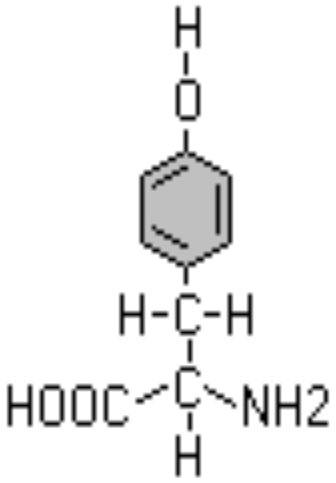
If you come by any mistake (whether it be spelling, grammatical or scientific) while browsing this sheet, kindly report it to the Academic team Facebook account.

Thyroid Hormones

OBJECTIVES

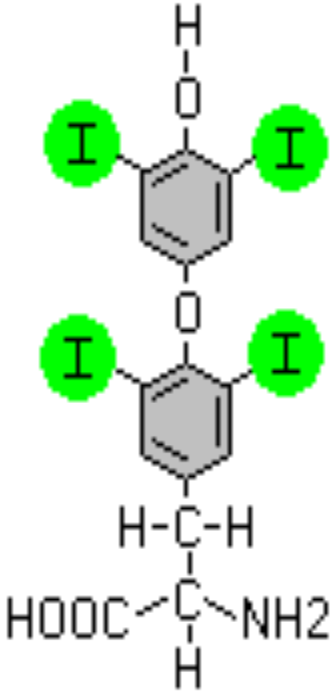
- Chemical nature of the thyroid hormones
- How different enzymes play a role in thyroid hormone formation? And what drugs affect them?
- Describe Function & Metabolism of thyroid hormones.
- Understand the types of thyroid diseases.

Thyroid hormones derived from two iodinated tyrosine molecules



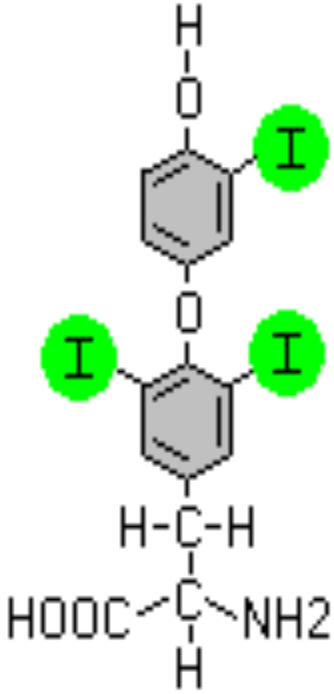
Tyrosine

وهو الأصل



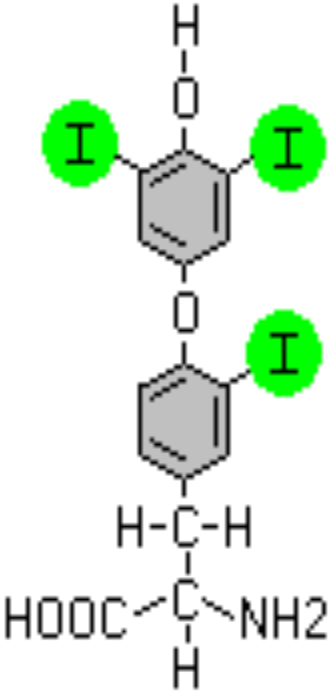
Thyroxine (T4)

Contains 4 iodine molecules



Triiodothyronine (T3)

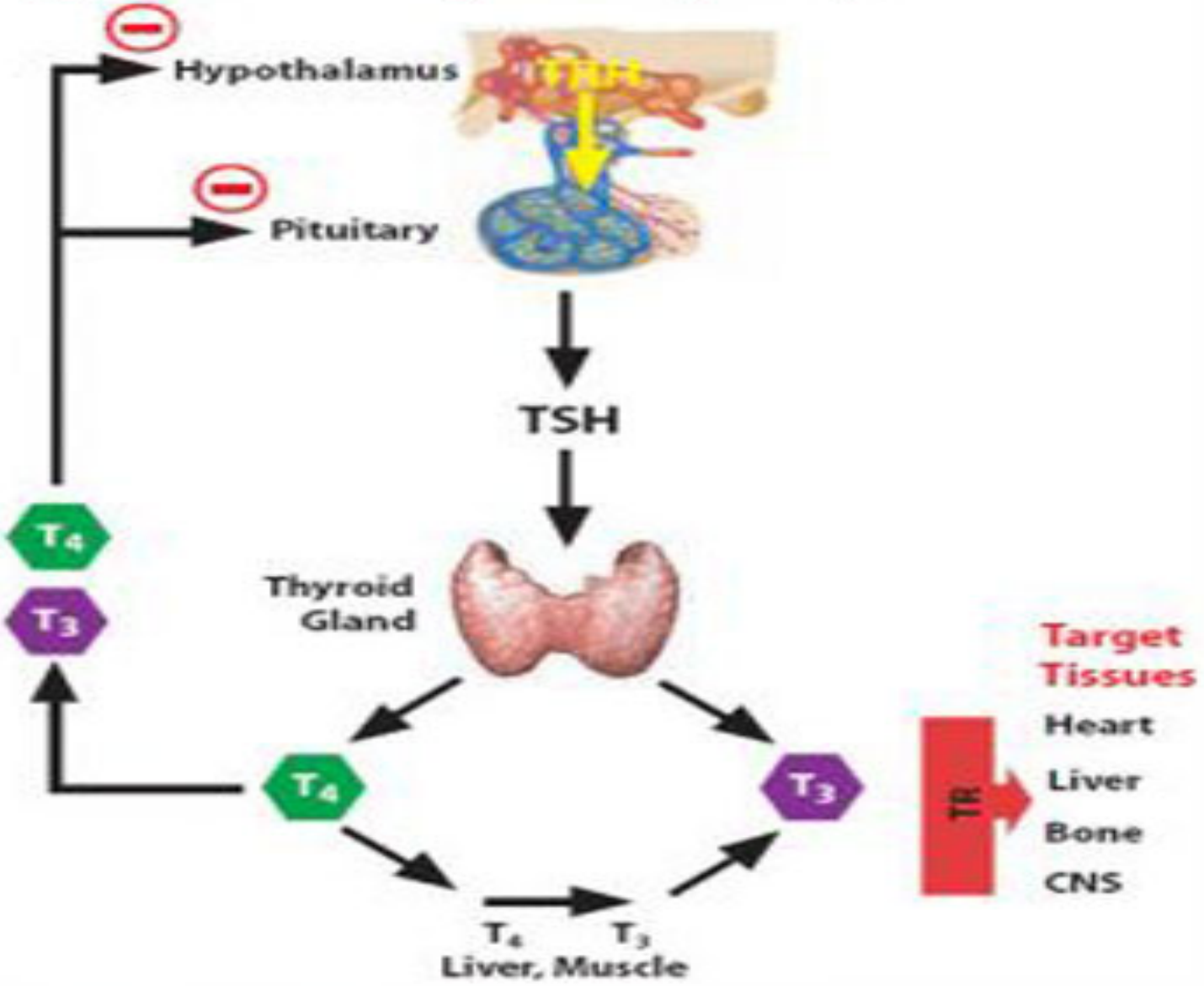
Contains 3 iodine molecules



"Reverse T3" (inactive)

The order of the 3 iodine molecules is different from T3

Hypothalamo- pituitary-Thyroid Axis

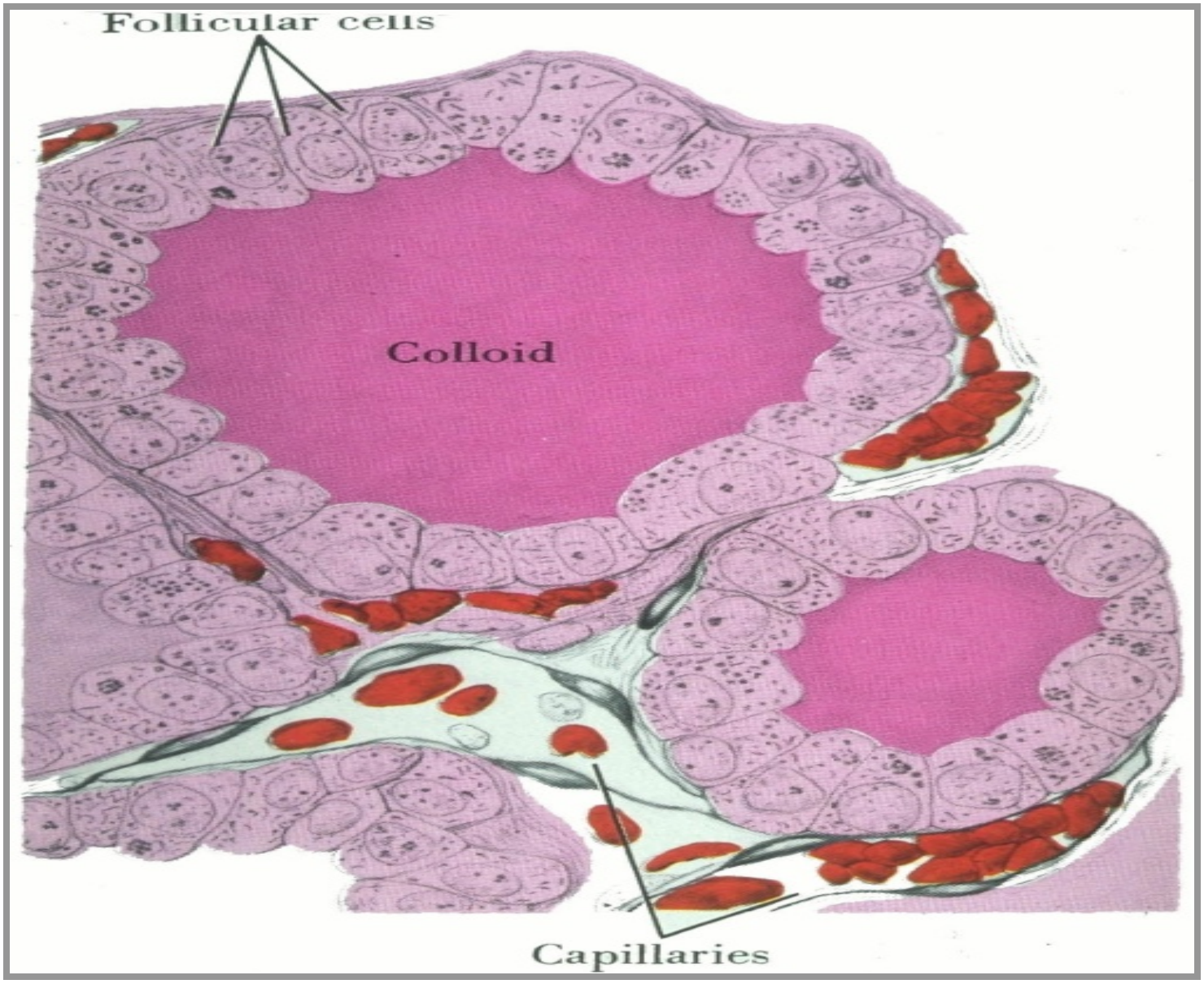


Sheet #1

- Hypothalamus release thyroid releasing hormone (TRH) >> that stimulates pituitary gland to release TSH (thyrotropin-stimulating hormone) >> that stimulates thyroid gland to release T3 & T4
- T4 in peripheral tissues stimulates liver and muscle to release T3 and T3 goes to the target tissues like heart, CNS and bone
- Of course there's feedback inhibition on pituitary gland (inhibit the release of TSH) and hypothalamus (inhibit the release of thyroid releasing hormone)

Thyroid Hormone Synthesis

- Large numbers of closed *follicles (*100 to 300 micrometers in diameter) are filled with a secretory substance called *colloid*.
- The major constituent of colloid is the large glycoprotein *thyroglobulin*, with a molecular weight of about 335,000 per subunit. Each Tg exists as a homodimer with a molecular weight of 660,000 .
- The endoplasmic reticulum and Golgi apparatus synthesize and secrete the thyroglobulin into the follicles
- Thyroglobulin contains the thyroid hormones, T_3 and T_4, within its molecule.


Follicular cells
Colloid
Capillaries

Thyroid Hormone Synthesis

- Each molecule of thyroglobulin contains about 130 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form *within* the thyroglobulin molecule.
- Each thyroglobulin molecule contains up to 30 iodinated tyrosine molecules, but only 3 T4 and even fewer T3.
- In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months.

Iodine

- 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.
- The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell, using a pump called the sodium-iodide symporter (**NIS**). This is called ***iodide trapping***. In a normal gland, the iodide pump concentrates the iodide to about **30** times its concentration in the blood.

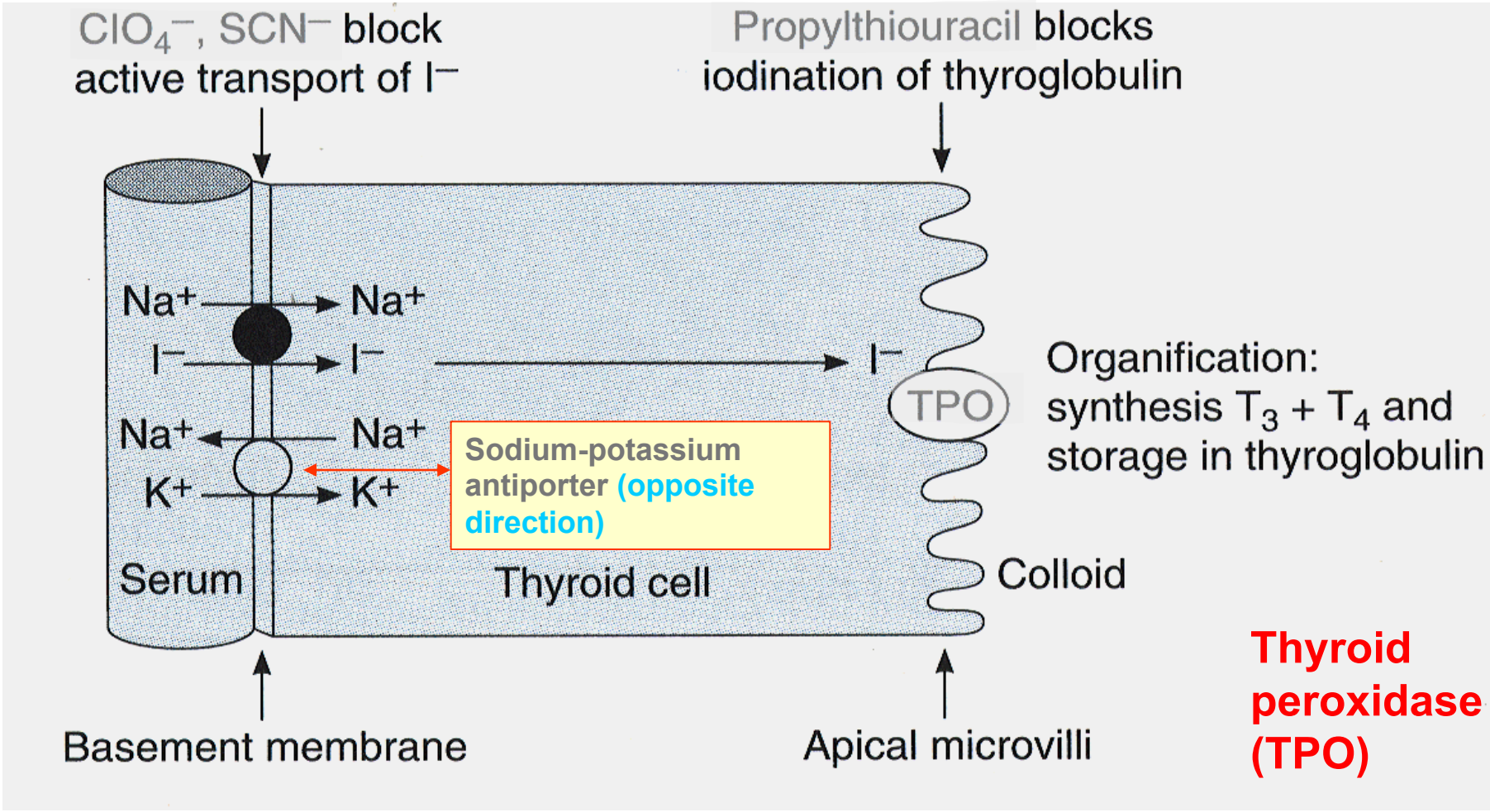
Sodium-iodide symporter; transport both sodium and iodide ion to the interior of the cell (same direction)

There were trends to add iron to the salts beside iodine but iron will stain it red which will decrease the customer's desire.

Synthesis of thyroid hormones

- Active uptake of iodide into follicular cell
- Iodide → Iodine - H_2O_2 (catalysed by TPO)
- Active uptake of iodine at follicular/ colloid interface
- Incorporation of iodine onto tyrosine residues of thyroglobulin
- Coupling of iodinated tyrosines
- Storage of T_3 and T_4

Active transport of iodine (ATPase dependent) against electrical and chemical gradient - concentration of iodine 30-50 times that of the circulation



Iodine metabolism

Concentration of Iodide (I^-)

- **ACTIVE TRANSPORT BY THYROIDAL (I^-) TRANSPORTER LINKED WITH Na^+/I^+ ATPase**
- **Inhibitiors : Perchlorate (ClO^-_4)**
  - **Thiocyanate (SCN^-)**

Oxidation of iodide ($I^- \rightarrow I$)

- **Iodide** ⟶ **Iodine**

Thyroid peroxidase & H_2O_2

Inhibitor : Propylthiouracil

Iodination of tyrosine (Organification)

- **Oxidized Iodine + tyrosine residues**

(thyroglobulin) → **MIT and DIT**

Peroxidase

Inhibitor

Thioureas

Coupling of Iodotyrosyls

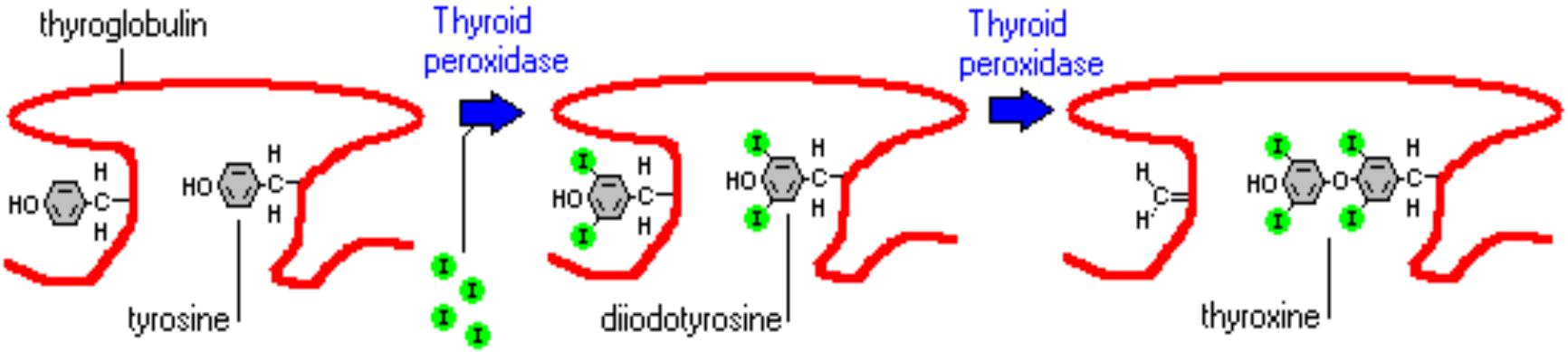
DIT + DIT $\xrightarrow[\text{Thyroperoxidase}]{}$ Thyroxine (T_4)

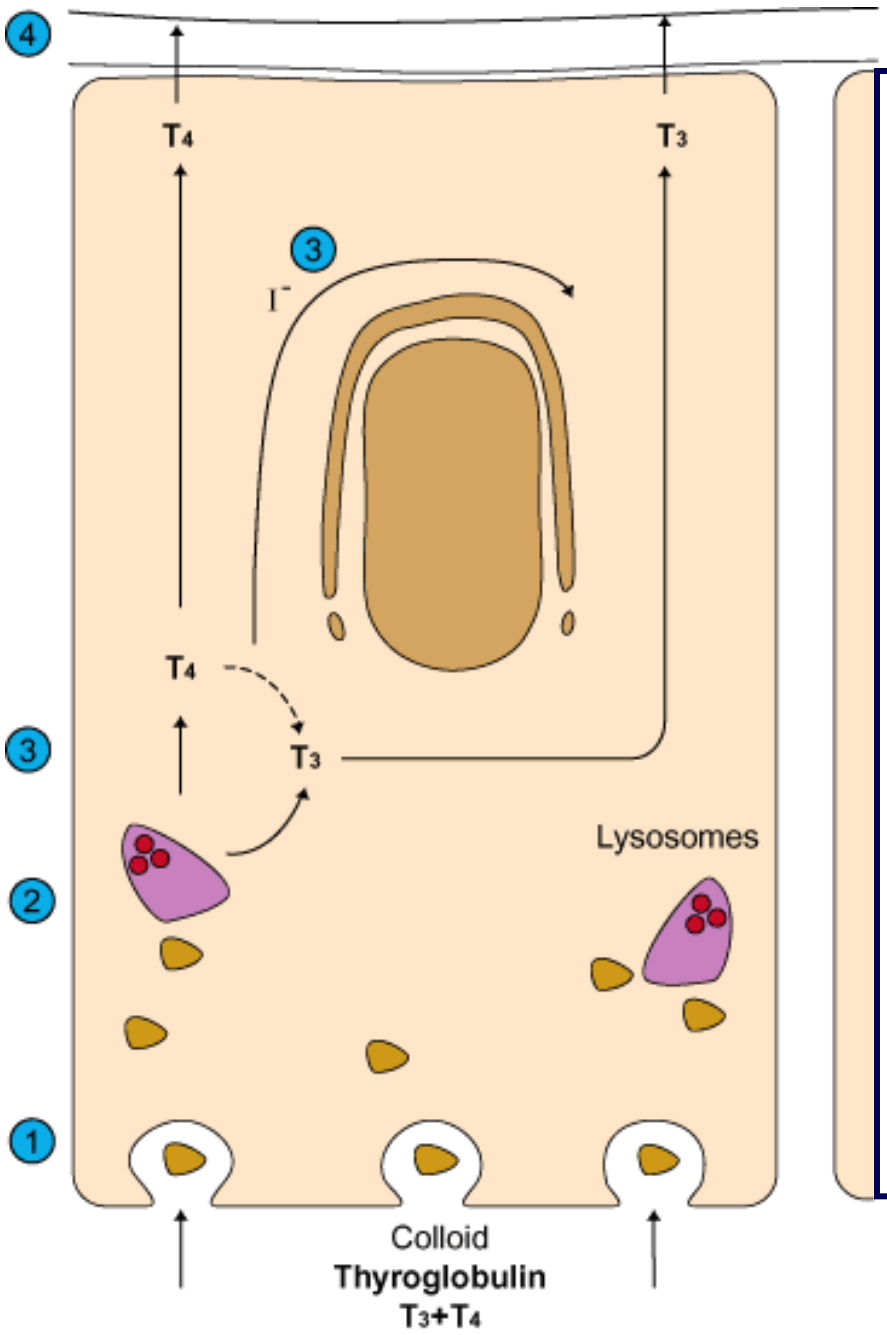
DIT + MIT $\xrightarrow[\text{Thyroperoxidase}]{}$ Triiodothyronines (T_3)

- **Inhibitor**
  Propylthiouracil

DIT: Di-iodotyrosine
MIT: Mono-iodotyrosine

Incorporation of iodine onto tyrosine residues on the thyroglobulin molecule





1) Release of T_4 and T_3 into circulation -

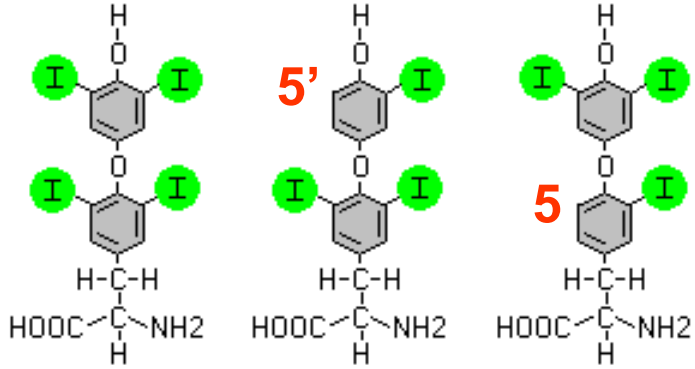
100µg T_4 & 10µg T_3/day

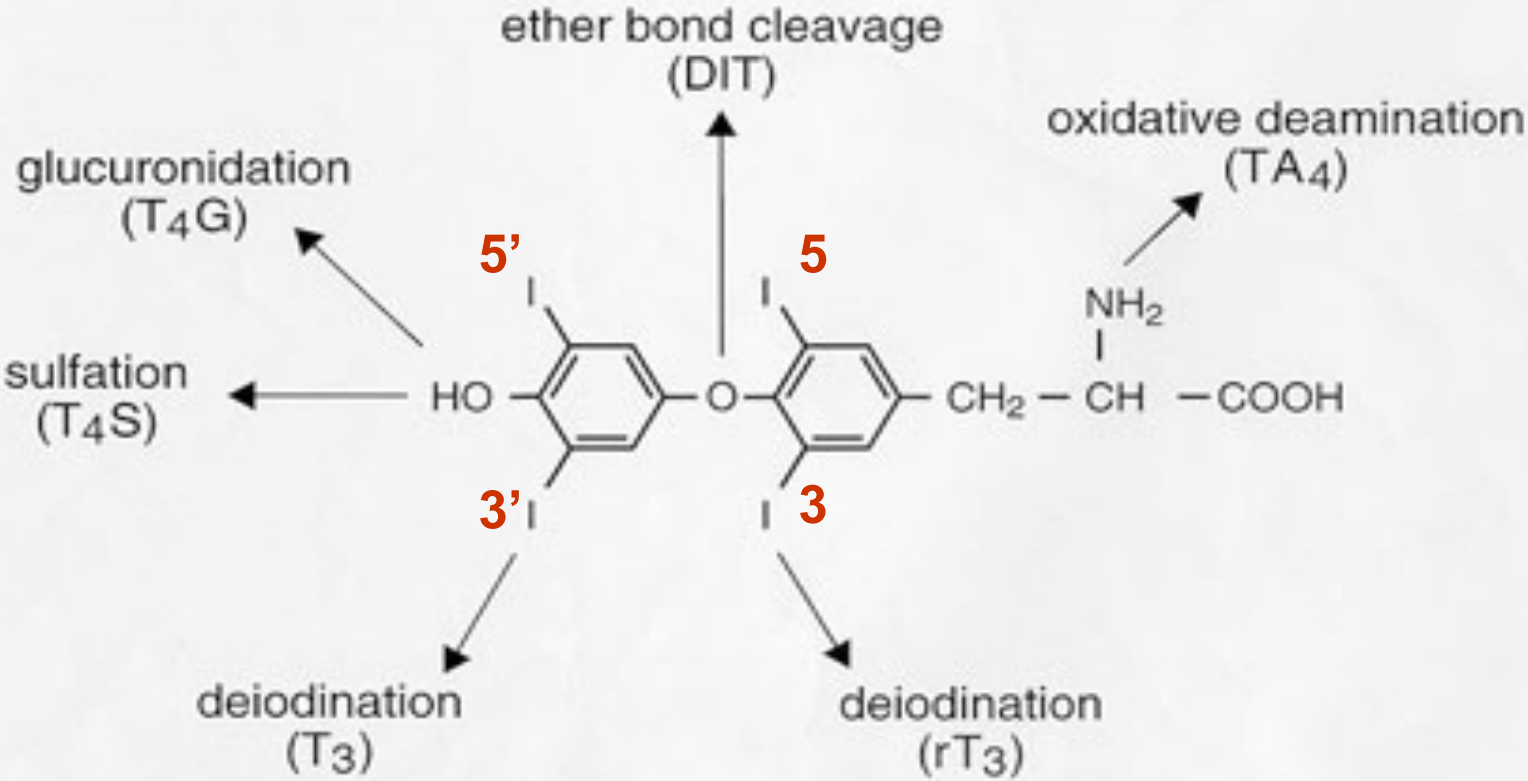
2) ~ 10% T_4 undergoes mono-deiodination to T_3 before secretion

3) Fusion of colloid droplets with lysosomes --> hydrolysis and release of thyroid hormones

4) Stimulated by TSH colloid droplets with the bound thyroid hormones are taken back into follicular cells by pinocytosis

Thyroid hormone metabolism





Sheet #2

- What you should know from previous slide is:

Pathways of thyroid hormone metabolism:

1. **Glucuronidation**: addition of glucuronic acid
2. **sulfation**: addition of sulfur group

Both sulfation and glucuronidation occur in the OH group

3. **deiodination**: removal of iodine group to become T3 or rT3
4. **ether bond cleavage**; to become DIT.
5. **oxidative deamination**.

Thyroid Hormone Release

- 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.

Thyroid hormone transport

To be transported in blood

- Thyroid binding globulin (TBG)
  - –Highest affinity
- Thyroid binding prealbumin binds 15 %
  - –Intermediate affinity
- Albumin binds 10 %
  - –Low affinity, High capacity

Thyroid Hormone transport

- **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**

Biologically active portion is free portion not bound one

Metabolism of thyroid hormones

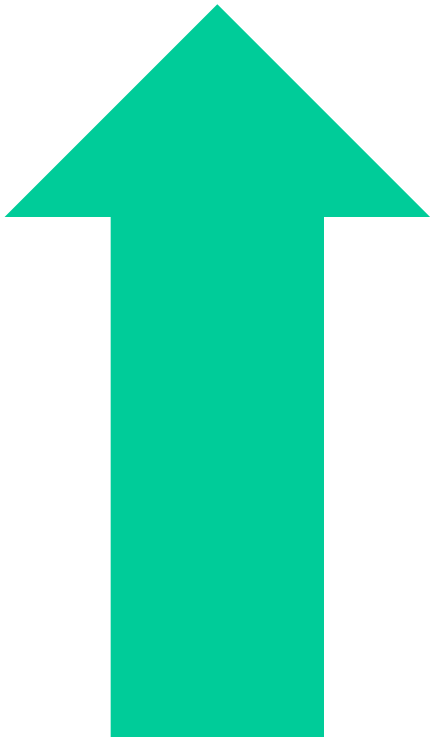
Series of deiodinations by deiodinases

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

Other metabolic pathways: sulphation, decarboxylation, conjugated with glucuronide

Factors affecting Thyroxine binding Globulin level (TBG)-Increase level

- **Hereditary**
- **Pregnancy**
- **Estrogen therapy**
- **Hypothyroidism**
- **Phenothiazines**
- **Acute viral hepatitis**



Factors that decrease (TBG)

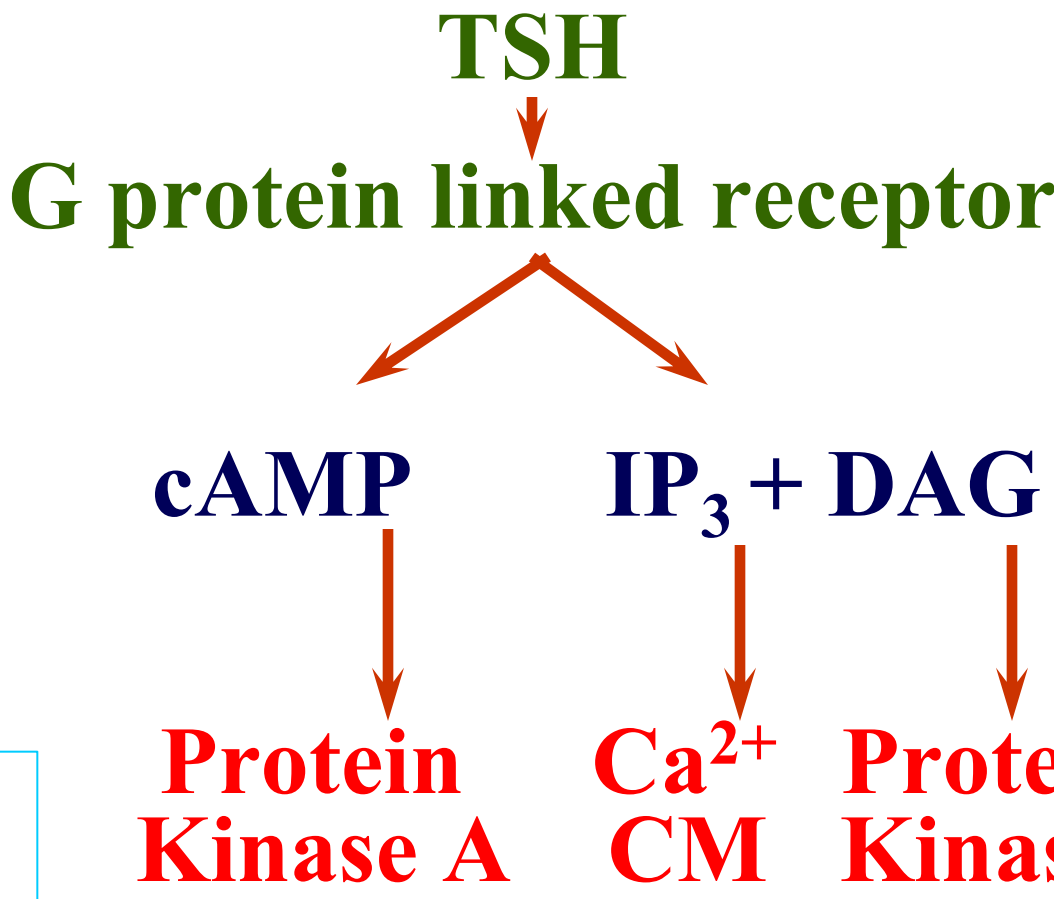
- Hereditary
- Androgens
- Corticosteroids
- Thyrotoxicosis
- Nephrotic syndrome
- Malnutrition
- ’major illness

Thyroid function in pregnancy

- Rise in Total Binding globulin (due to estrogen) →inc. total T4 and T3, due to estrogen
- Free T4 and T3 are normal
- HCG has weak TSH agonist activity, and responsible for the slight thyroid enlargement during pregnancy
- Anti thyroid drugs like Carbimazole and Propylthiouracil (**PTU**) is a medication used to treat hyperthyroidism cross the placenta to varying degrees.

That's why In pregnancy there's increase in temperature, anxiety and restlessness and so on

TSH Receptors



Calmodulin (CaM) (an abbreviation for calcium-modulated protein) is an intermediate calcium-binding messenger protein (**EXTRA from internet)**

Regulation of Thyroid Hormone Secretion

- TSH binds with specific TSH receptors on the basal membrane surfaces of the thyroid cell.
- **Most, if not all, of its effects result from activation of the "second messenger" *cyclic adenosine monophosphate (cAMP)* system of the cell.**

Actions of TSH

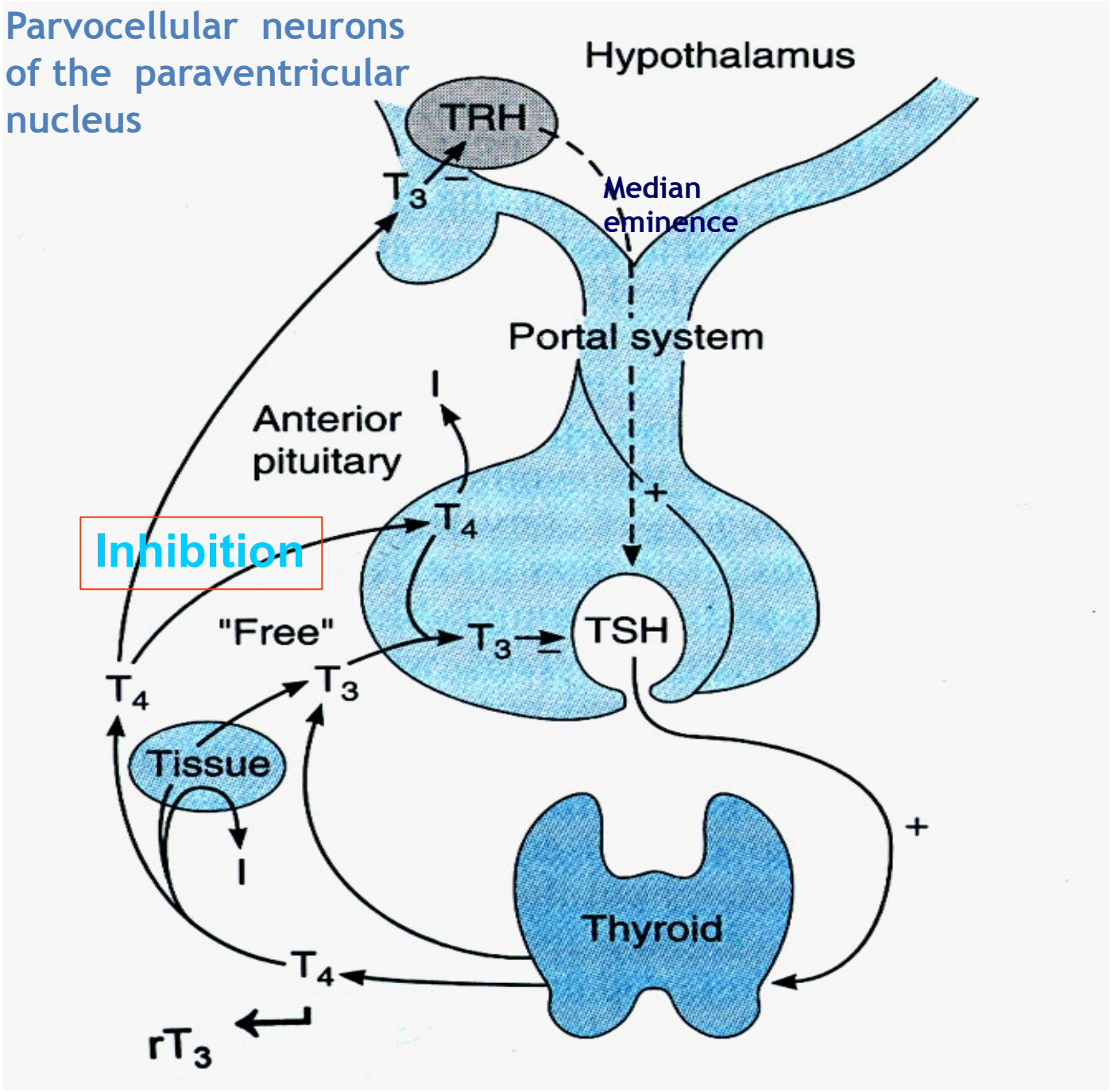
- Active uptake of iodine Stimulates other reactions involved in thyroid hormone synthesis
- Stimulates the uptake of colloid
- Induces growth of the thyroid gland

So TSH enlarges thyroid gland

Thyroid Hormone Regulation

- **Four mechanisms**
  1. **Classic hypothalamic-pituitary-thyroid axis.**
  2. **Pituitary and peripheral deiodinases.**
  3. **Thyroid autoregulation, response to iodine.**
  4. **TSH receptor antibodies.**

Thyroid Axis



TRH

The smallest hormone structure is TRH

- Tripeptide; regulates TSH secretion and synthesis
- The TRH receptor is G-protein coupled
  - Activation of phospholipase C
  - Hydrolysis of PIP2 to IP3 and diacylglycerol
  - IP3 stimulates release of intracellular Ca++
  - Ca++ stimulates TSH release
  - Diacylglycerol simultaneously activates PKC
  - PKC stimulates TSH α and β subunit gene transcription
  - TRH also regulates TSH glycosylation
- TRH ↑ by a decrease in serum T_3 or T_4
- TRH ↓ by an increase in serum T_3 or T_4
  >> Feedback inhibition

PKC; Protein kinase C

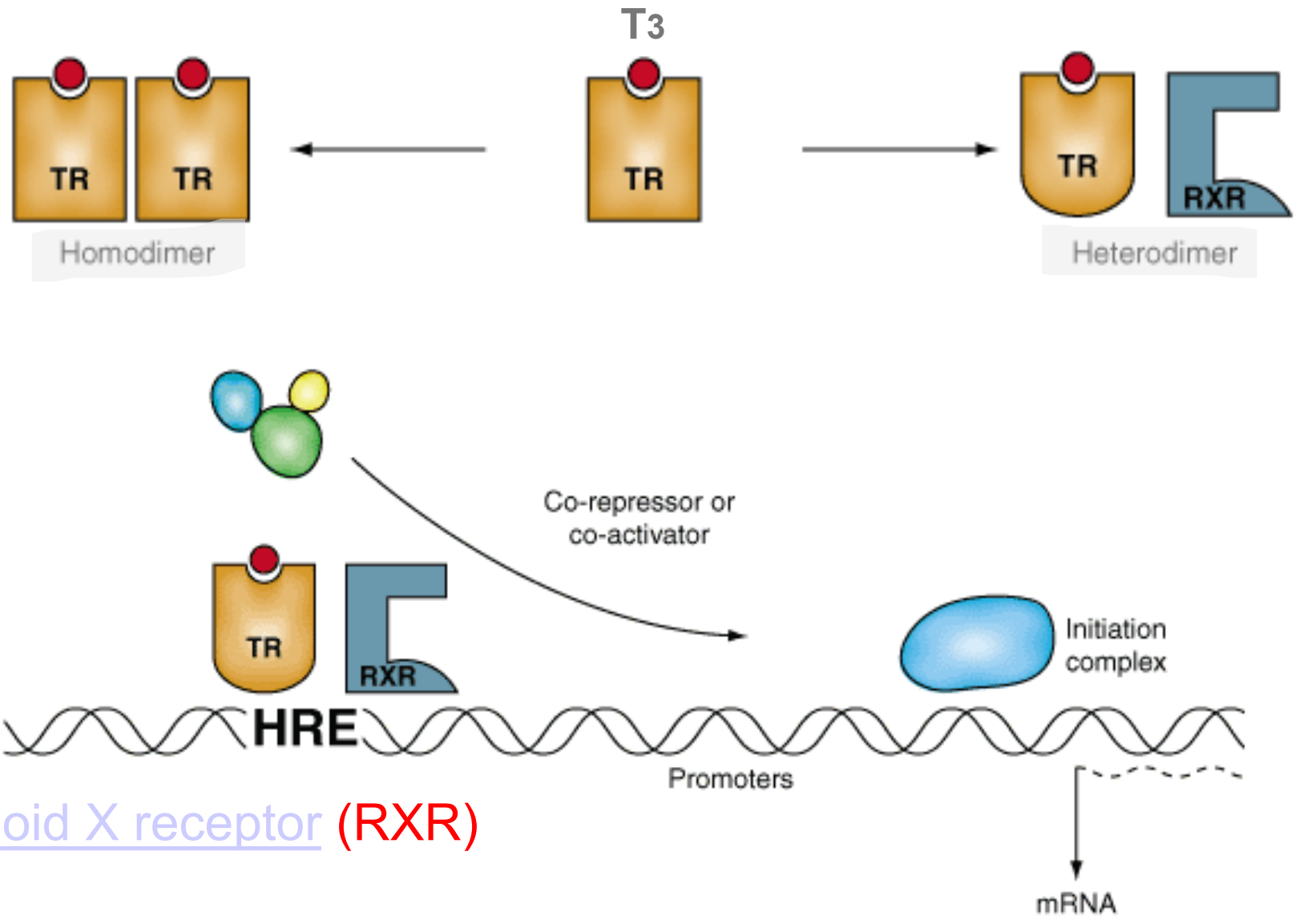
Alpha subunits are similar and beta subunits are different in structure

Thyroid hormone receptors

- **Type 2 receptors in nucleus - high affinity for T_3**
- **Dimerize with another T_3 receptor (homodimer) or retinoic acid receptor (heterodimer)**
- **Dimerized receptor + other transcription factors → gene transcription**
- **Membrane receptors? Ion movements**
- The thyroid hormones increase the metabolic activities of almost all the tissues of the body.

*Thyroid hormone and steroid hormones work intracellularly

Dimerization of thyroid hormone receptors and gene activation/inactivation



retinoid X receptor (RXR)

Mechanism of thyroid hormone action

- Receptors for thyroid hormones are nuclear and its affinity is ten times higher for T_3 than T_4
- Four variants of nuclear receptor were observed and mitochondrial receptor for T_3 was also described
- Free thyroid hormone receptor (TR) without bound hormone is bound to hormone response element of DNA (HRE) and corepressor (CoR)

Increased expression of proteins by thyroid hormones

- **Glycerol 3-phosphate dehydrogenase** – main component of glycerol 3-phosphate shuttle in mitochondria (one of transport systems for NADH into mitochondria)
- **Cytochrome c oxidase** – the complex mitochondrial enzyme in the electron transport chain (from cytochrome c to oxygen)
- **ATPases** – (eg. Ca ATPase of muscle cells)
- **Carbamyl phosphate synthase I** – enzyme of urea cycle
- **Growth hormone**

They are important because hormones work on these enzymes

There're two shuttle mechanisms:
1- Glycerol 3-phosphate dehydrogenase shuttle
2- Malate-aspartate shuttle.

Increased respiration during hyperthyroidism

Increased synthesis of ATP – increased synthesis of cytochrome c oxidase – increased oxidative phosphorylation (it means the increased consumption of oxygen) – increased production of ATP

Increased consumption of ATP – increased synthesis of various ATPase (eg. Ca dependent in muscles) – increased depletion of store of ATP **So there's production of heat**

Mechanisms increasing body temperature during hyperthyroidism

Reducing efficiency of ATP synthesis - increased synthesis of glycerol 3-phosphate dehydrogenase – increased transport NADH by this shuttle than malate/aspartate shuttle

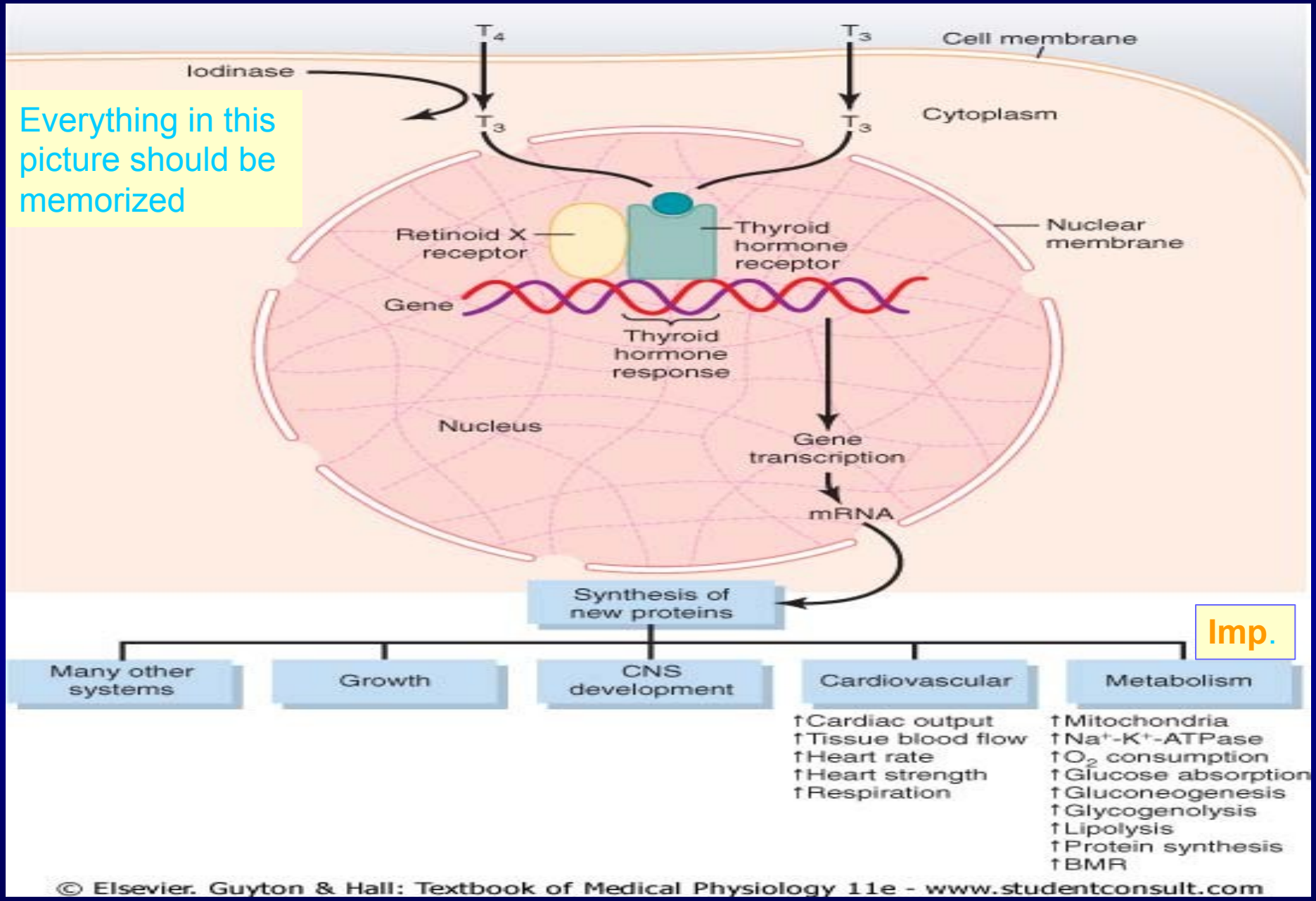
Increased synthesis of ATP

Increased consumption of ATP

Uncoupling of phosphorylation and oxidation in mitochondria **All of this increase energy production**

Thyroid hormone activation of target cells.

Everything in this picture should be memorized



Physiological Effects of Thyroid Hormones

Appetite increases

- The rate of utilization of foods for energy is greatly accelerated.
- Protein synthesis is greatly increased as well as the rate of protein catabolism.
- The mitochondria in most cells of the animal's body increase in size as well as number. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate of the whole animal.

in **newborn screening Test** we do test thyroid hormones
We test Phenylketonuria, TSH(for thyroid function), and GPDH

Physiological Effects of Thyroid Hormones

- The growth rate of young people is greatly accelerated.
- Growth and development of the brain during fetal life and for the first few years of postnatal life require thyroid hormones.

Physiological effects of thyroid hormone

- Increases oxygen consumption and heat production
- Positive chronotropic (the heart rate)and inotropic effects (affect the force of cardiac contraction) on heart.
- Increase sensitivity to adrenergic effectors
  - Up-regulates β-adrenergic receptors
- Increase gut motility.
- Increase bone turnover.

Physiological effects of thyroid hormone

- Increases reflex response
- Increase hepatic glycogenolysis and gluconeogenesis
- Stimulates lipolysis
- Developmental effects
  - Growth
  - Brain development

Physiological Effects of Thyroid Hormones

- *Decreases* the concentrations of cholesterol, phospholipids, and triglycerides.
- Increases numbers of low-density lipoprotein receptors on the liver cells, leading to rapid removal of low-density lipoproteins from the plasma.
- Increases significantly the rate of cholesterol secretion in the bile and consequent loss in the feces.

Factors that Affect Thyroid Function

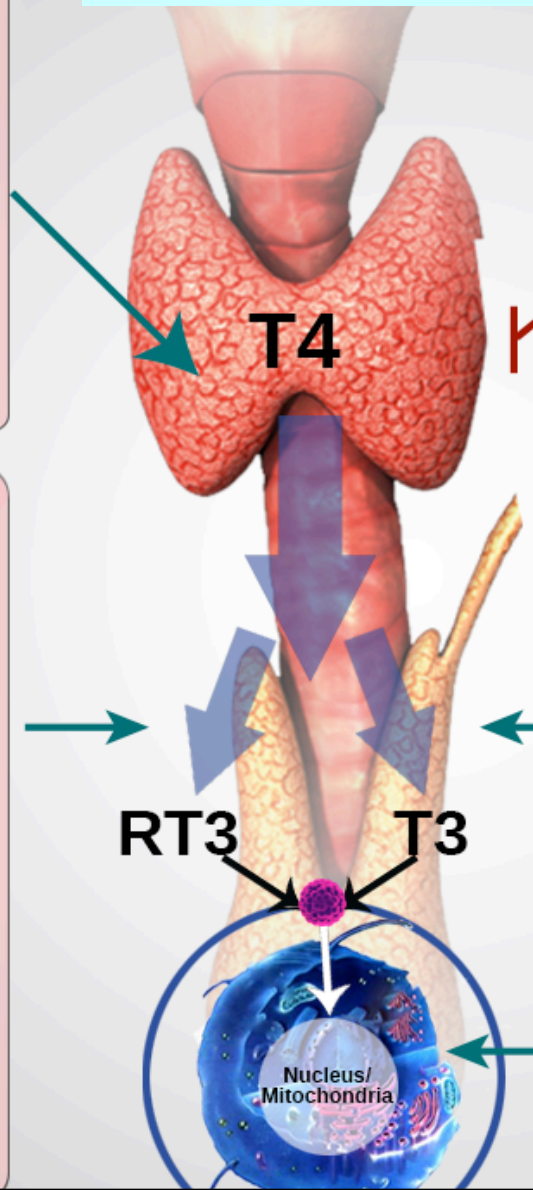
** Everything in this slide is included and should be memorized

Factors that contribute to proper production of thyroid hormones

- **Nutrients:** Iron, iodine, tyrosine, zinc, selenium, vitamin E, B2, B3, B6, C, D

Factors that increase conversion of T4 to RT3

- Stress
- Trauma
- Low-calorie diet
- Inflammation(cytokines, etc.)
- Toxins
- Infections
- Liver/kidney dysfunction
- Certain medications



Factors that inhibit proper production of thyroid hormone

- Stress
- Infection, trauma, radiation, medications
- Fluoride (antagonist to Iodine)
- Toxins: pesticides, mercury, cadmium, lead
- AutoImmune disease: Celiac

Factors that increase conversion of T4 to T3

- Selenium
- Zinc

RT3 and T3 compete for binding sites

Factors that improve cellular sensitivity to thyroid hormones

- Vitamin A
- Exercise
- Zinc

Sheet #3

- Iodine are found in: **Salts and seafood.**
- **Zinc and selenium are found in nuts , meet, vegetables**
- **Zinc are now taken orally with vitamin C and D (OTC) for protection from COVID-19**

CNS Effects of ThyroidHormones

- Excitatory effects on the central nervous system, 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, in case of excess.

Effects of Thyroid Hormones

- Increases both the rates of secretion of the digestive juices and the motility of the GIT.
- 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.

- END PART I
- >>>>>>>>>>>>>>>>>>>>To Be Continued