ENDOCRINE SYSTEM

Pharmacology

Lec. 5

WRITER: Sara Omar

CORRECTOR: Abdallah Aburoman

DOCTOR: Suheil Zmeili

سُورَةُ الحَشْر

لَا يُقَٰتِلُونَكُمْ جَمِيعًا إِلَّا فِى قُرًى مُّحَصَّنَةٍ أَوْ مِن وَرَآءِ جُدُرٍ ۚ
بَأْسُهُم بَيْنَهُمْ شَدِيدٌ ۚ تَحْسَبُهُمْ جَمِيعًا وَقُلُوبُهُمْ شَتَّىٰ ۚ ذَٰلِكَ
بِأَنَّهُمْ قَوْمٌ لَّا يَعْقِلُونَ ﴿١٤﴾

Golden Quran | المصحف الذهبي

ما ينطق به الدكتور من شرح سيكون باللون الاحمر
وما يكون مهم في شرح الدكتور يكون باللون البنفسجي
المعلومات الإضافية ستكون باللون الأزرق داخل مستطيل رمادي
ما يكون مهم في السلايدات يكون بخطين أو بخط

Thyroid Gland Hormones

The thyroid gland synthesizes and secretes three major hormones,

1. **T3(triiodothyronine(,**
2. **T4 (thyroxine(**
3. **Calcitonin.**

T3 and T4 are synthesized in thyroid molecules ,and calcitonin is synthesized by C-cells ,or parafollicular cells .

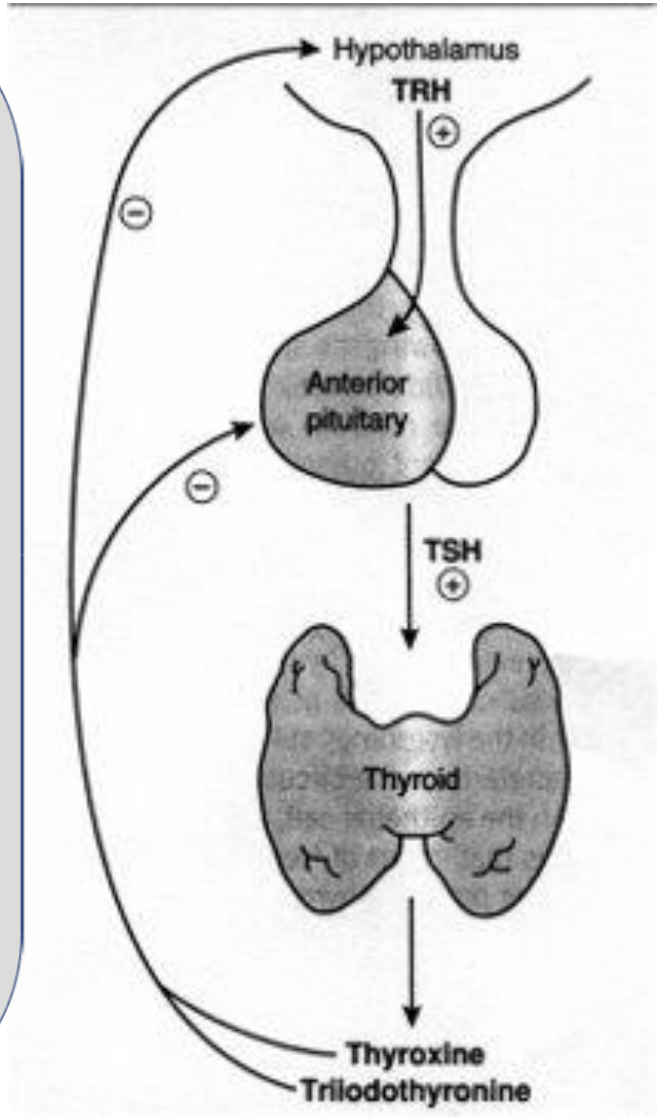
In this lecture ,we will discuss T3 and T4, and calcitonin will be discussed along with para thyroid hormone ,which is involved in calcium metabolism.

Recall physiology

Axis of regulation of thyroid hormone synthesis and release

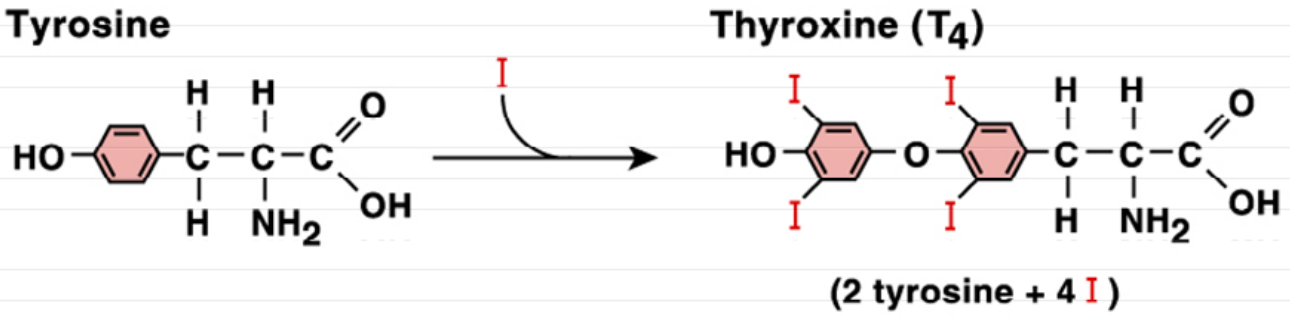
1. hypothalamic releases TRH, 3-aminoacid peptide ,reaches the anterior pituitary .
2. TRH interacts with surface membrane receptors leading to stimulat of synthesis and release of TSH .
3. TSH ,in turn ,reaches the anterior pituitary, interacts with surface membrane receptor leading ultimately to increased synthesis and release of T3 and T4 by the thyroid gland .

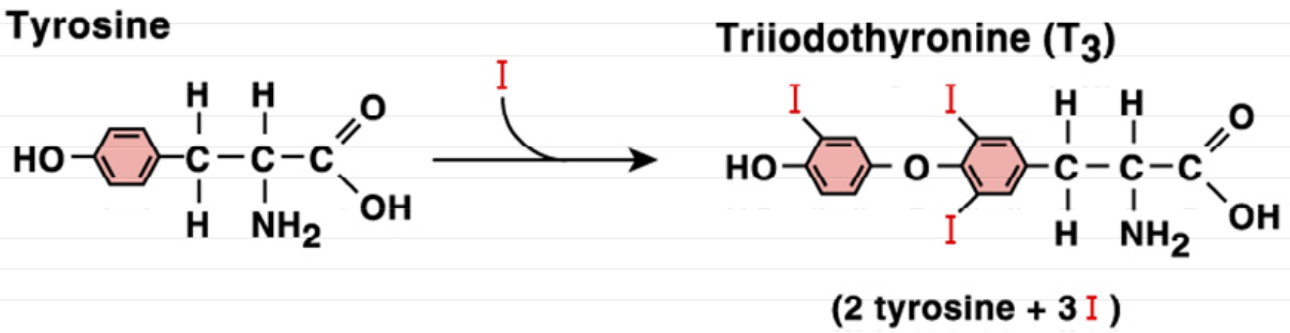
4. This system is highly regulated after thyroxine and T3 produce their desired actions or response. T3 and T4 negatively feedback at the level of the pituitary ,as well as the hypothalamus ,regulating the whole system.



Recall Biocemistry

- The major precursor of T3 and T4 is tyrosine.
- T4 is two tyrosines and four iodines.
- T3 is two tyrosines and three iodines.

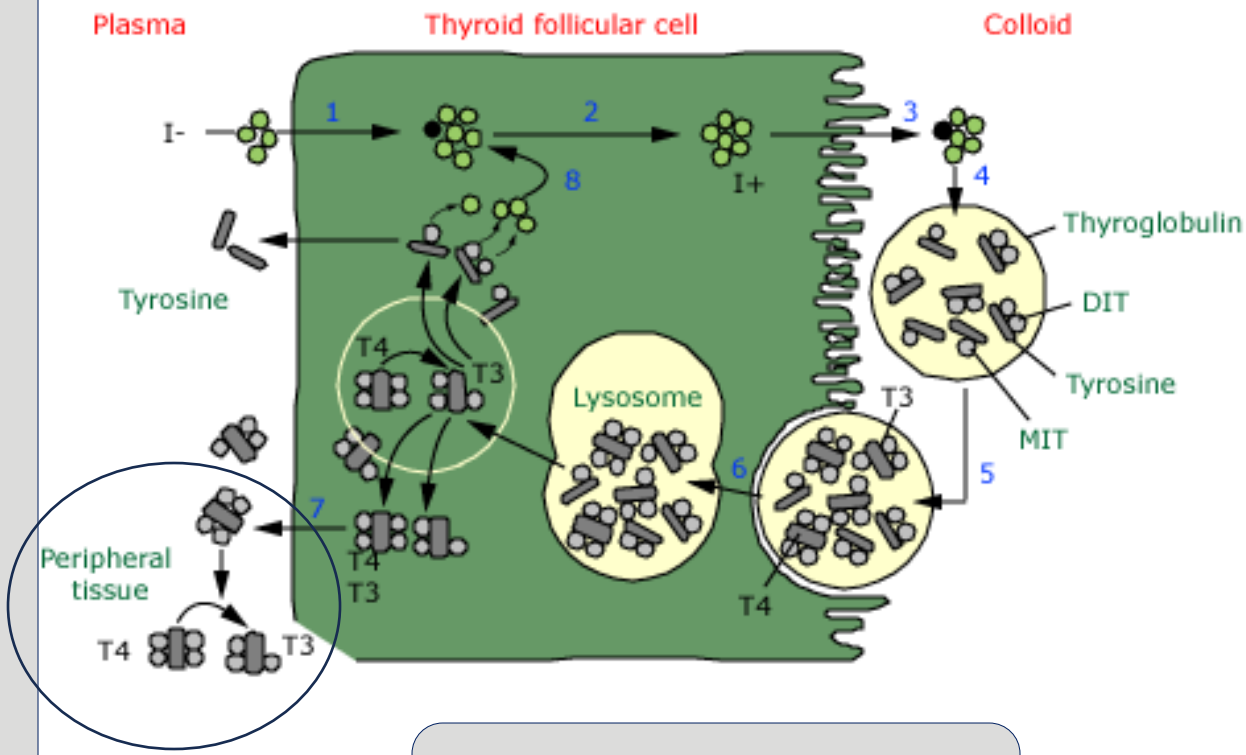




1.iodide trapping or uptake
2.oxidation of iodide into iodine (Activation, oxidation)
3. Then iodine is added to tyrosine residue which are present on storage protein to thyroid hormone known as thyroglobulin (TG).
4.tyrosine residues on thyroglobulin forming mono-iodotyrosine, di-iodotyrosines
5. coupling reaction to form T4 and T3
6. hydrolysis of thyroglobulin by lysosomal enzymes.
7. releasing T3, T4.
8. some of T3, T4 are recycled to reserve iodine

- storage of such hormones before being released into the bloodstream.

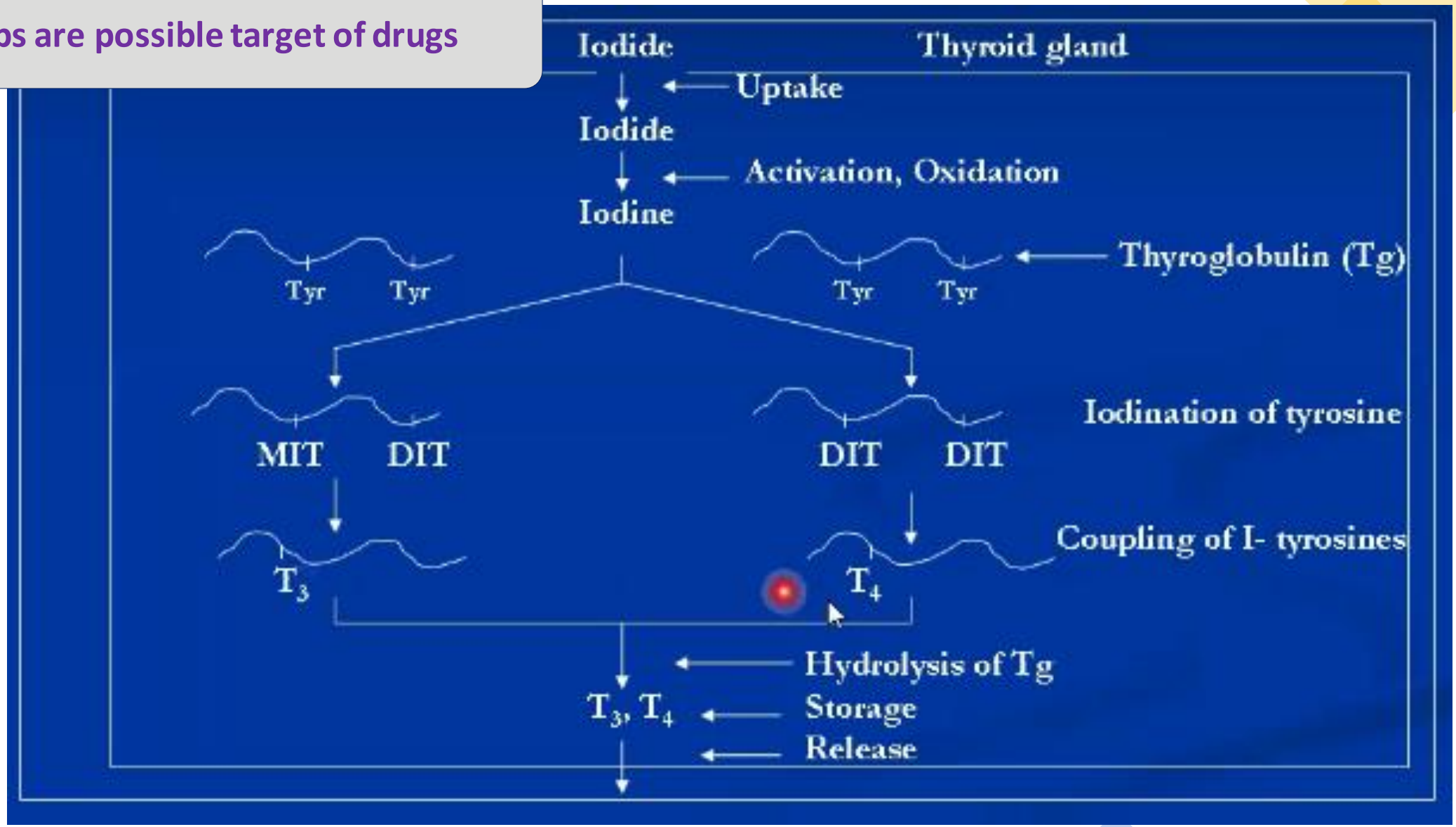
Recall physiology
the synthetic pathway of T3, T4:



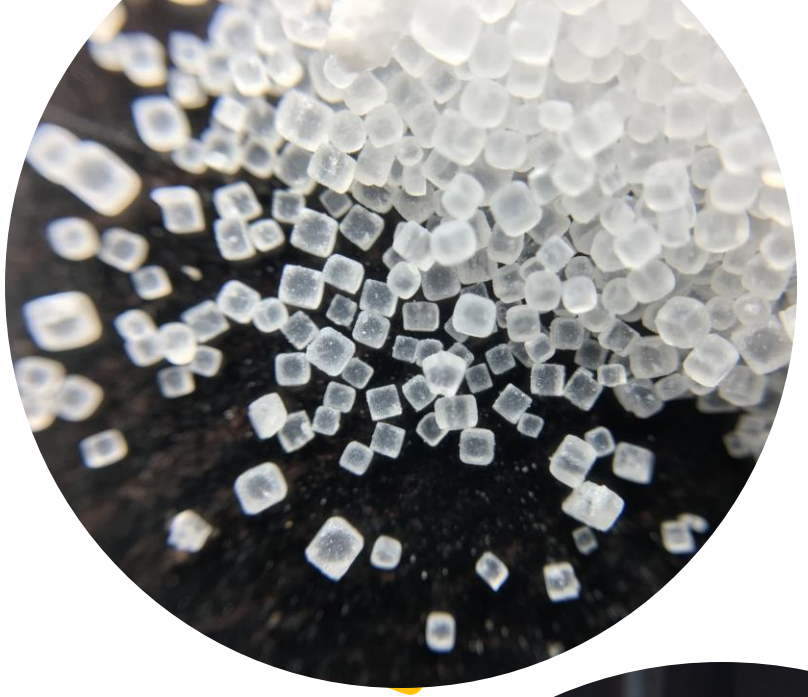
MIT+DIT= T3
DIT+DIT= T4

de-iodination reaction or conversion of T4 to T3 empirically. So T4 in peripheral tissues usually is converted to T3.This is one iodide in peripheral tissues is removed by deiodinase enzyme to form T3. We are seeing that the major effects of thyroid hormones are those for T3 rather than T4.

these steps are possible target of drugs



Iodide



Needed for synthesis of thyroid hormones

Sources:

- Iodized salt
- Iodated bread
- Dairy products

Daily requirement: 75 micrograms which is about 10g of iodized salt

Nowadays we don't have any condition of hypothyroidism due to iodine deficiency because iodide is usually added to our salt.

This Photo by Unknown author is licensed under CC BY.

Recall physiology

The oxidation, iodination , and coupling reactions are catalyzed by	**iodine or *thyroid peroxidase enzyme***
hydrolyze thyroglobulin	***Lysosomal enzymes***
Most of released T_4 is converted in periphery to T_3 by	***deiodinase enzyme***
• **Thyroid hormones travel in blood bound to a specific**	***thyroxine binding globulin (TBG)***

Comparison between T3 & T4

Thyroid content:	T_4 (Thyroxine) > T_3 (4:1)
Source	T_4 = thyroid gland; T_3= deiodination reaction of T_4 (80% of T3 is formed by deiodination of T_4 in peripheral tissues)
Potency	T_3 > T_4 (Free T_3 is 3-5 times more active than free T_4)
Protein binding To specific globulin:	T_4 > T_3 (T_4 99.97% bound; T_3 99.5% bound)
• Half-life:	T_4 > T_3 T_4 = 1 week; T_3 = 1 day

Thyroid hormones MOA

- Thyroxine reaches target cells by the aid of the carrier protein. Thyroxine easily passes plasma membrane (highly lipophilic)

- Most of T_4 is converted to T_3 in target cells

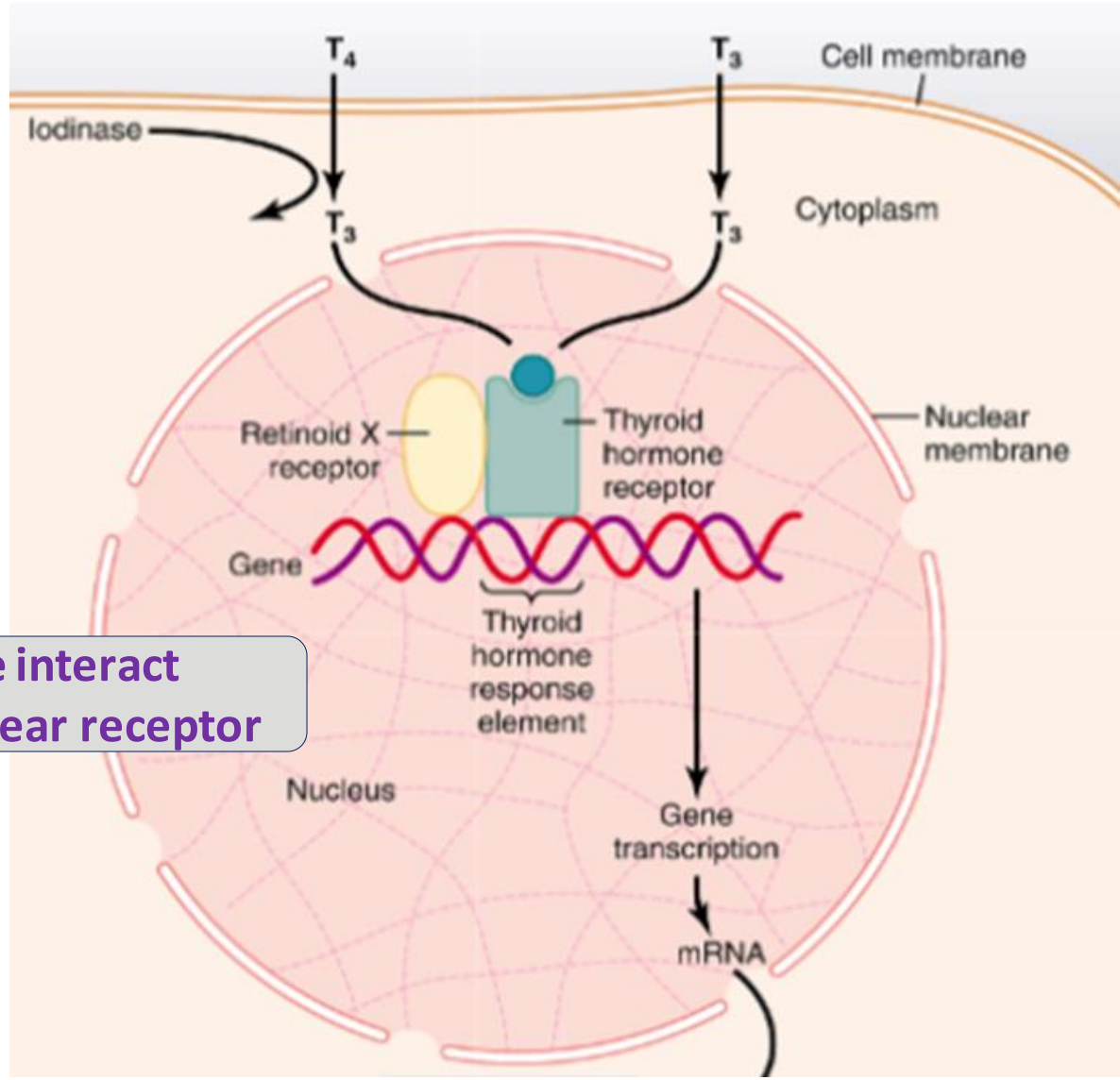
- Only the T_3 form enters the nucleus and binds nuclear receptor protein

Thyroid hormone interact with specific nuclear receptor

- The hormone-receptor protein complex binds specific response elements on DNA leading to a direct effect on the level of transcription

- The mRNA produced then codes for specific proteins that mediate effects of thyroid hormones

Recall physiology
Additional image



Recall physiology

- **General effects of thyroid hormones:**

- Promote growth & development (essential for growth in childhood)

It is essential in neural development during fetal life

- Calorigenic effect:

↑ BMR ; ↑ O_2 consumption; ↑ general metabolism; ↑ CHO metabolism

BMR (basic metabolic rate), CHO (carbohydrate)

- ↑ lipolysis; ↑ lipid breakdown

- ↓ Cholesterol blood level

- ↑ β-adrenergic receptors in most tissues

specially in cardiovascular system important effect!!

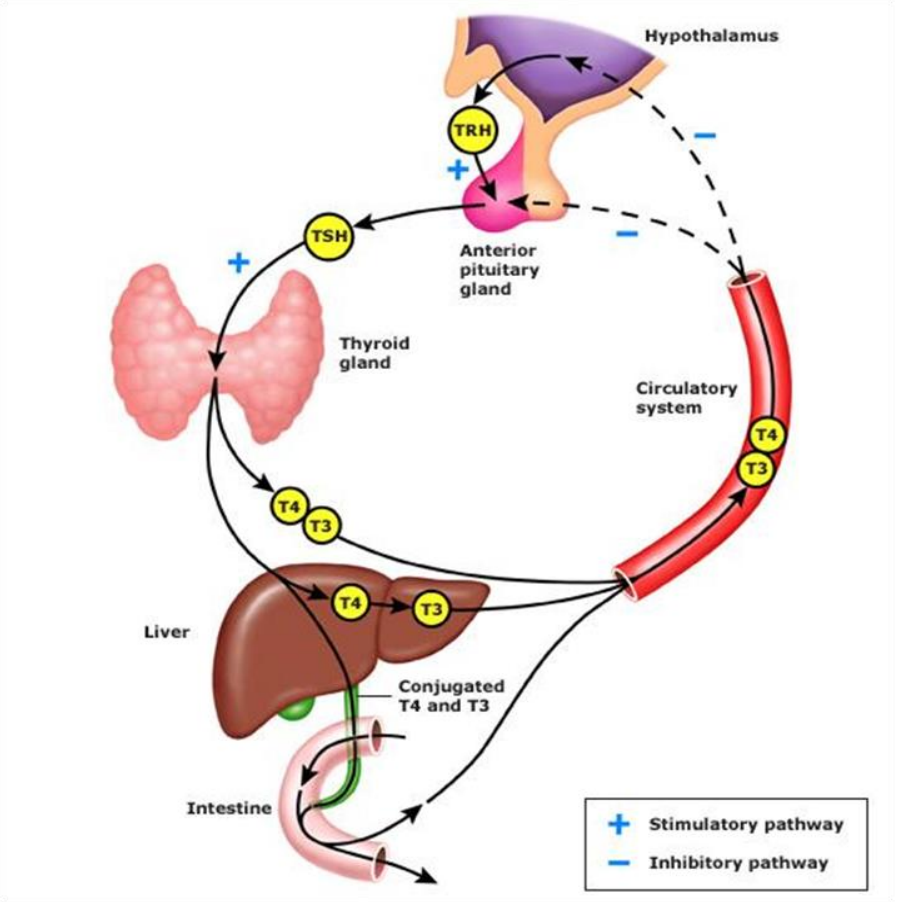
- ↑ GIT motility…

leading to diarhea

• Pathways of thyroid hormone metabolism

After thyroid hormone performs its biological pharmacological effect ,its action terminated by:

1. **negative feedback mechanism at the level hypothalamus and pituitary gland**
2. **metabolised by the liver through conjugation pathway II and excreted with bile.**



In pharmacology, liver metabolism of drugs is generally categorized into two phases: Phase I and Phase II. Pathway 2 refers to Phase II metabolism.
Phase II Metabolism (Conjugation Reactions)
Phase II reactions involve the conjugation of a drug or its Phase I metabolites with an endogenous substrate, making the compound more water-soluble and therefore easier to excrete

• Disorders affecting the thyroid gland:

Hypothyroidism and Hyperthyroidism

1.Hypothyroidism

In Children → Cretinism

In adults → Myxedema

Recall Pathology

- **Causes:**

- Surgical removal of thyroid

- Thyroiditis

(Hashimoto's= chronic lymphocytic thyroiditis= an Autoimmune inflammatory disease causing atrophy of thyroid, infectious, transient, postpartum hemorrhage…)

- Severe deficiency or excess of iodine

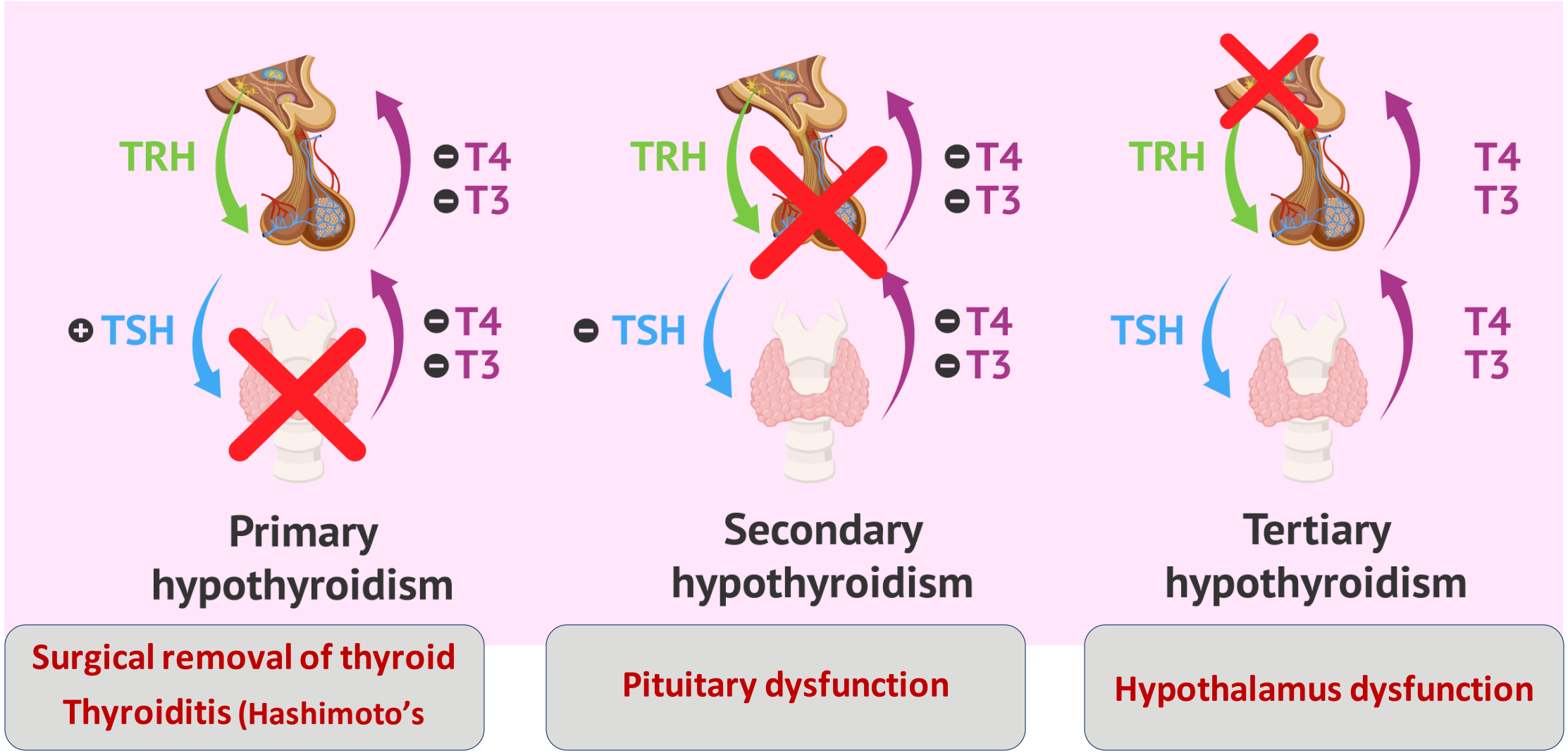
- Severe deficiency of one or more of the synthesis enzymes

Which are involved in the synthesis of thyroid hormone

- Severe pituitary or hypothalamic dysfunction

- Drug induced… These drugs are known as antithyroid drugs

Recall Pathology
Additional image



Surgical removal of thyroid
Thyroiditis (Hashimoto's

Pituitary dysfunction

Hypothalamus dysfunction

Recall Pathology

- **Hypothyroidism-symptoms**

Hypothyroidism is diagnosed by its symptoms

Cold intolerance, lethargy, constipation

Slowing of mental function and motor activity

Weight gain but appetite decreased, abnormal menses, dry/thick skin, hair loss, and hoarsevoice

Stroke volume and heart rate decreased; non pitting edema

- **R_x : HRT**

Treatment by hormone replacement therapy

• Thyroid hormones preparations:

- Thyroid USP (bovine, ovine, porcine) oral

- Thyroid USP (United States Pharmacopeia)
- derived from desiccated (dried) animal thyroid glands, typically from pigs.
- very Cheap product

- Thyroid extract (Thyroglobulin) oral

- Clean product compared to thyroid USP
- Extract the storage protein thyroglobulin from the thyroid gland of such animals, which contains T3, T4

animal sources since the animal hormone has similar structure to human hormone

- ℓ- thyroxine sodium; synthetic T_4, oral

- Liothyronine sodium, synthetic T_3, oral & I.V

- Liotrix, synthetic T_4 & T_3 (4:1), oral

- Contains both T3, T4 in the same ratio as the normal thyroid gland

Synthetic drugs since thyroide hormone is an amino acid derivitive; make it easily to synthesized

- All have $t_{1/2}$ of 1 week because they contains T4 except liothyronine which contains only T3
- Allergies more with animal preparations

Clinical uses to thyroid hormones:

- **Hypothyroidism**
- **Thyroid cancer**

Which is dependent on TSH in their growth , so when T3, T4 are given exogenously, they could supress by negative feedback mechanism TSH production by Ant pituitary gland.

- **Weight reduction (abuse!!!)**

It was used to in weight loss since ,It decreases cholesterol levels in blood, however now it`s considered an abuse due to its serious side effects

- ***d*- isomer as compared to *L*- isomer:**

***d*- is equipotent to the *L*- with respect to its effects on blood cholesterol levels, but has ¼ the potency with respect to other effects (e.g. growth and development, calorigenic effect…etc)**

D-isomer was commonly used in weight and cholesterol reduction, now it is not due to its side effects

- **Side effects to thyroid hormones:**

- Hyperthyroidism

- Allergic reactions (more frequent with animal preparations)

2.Hyperthyroidism

Thyrotoxicosis

Grave's disease

→ Hyperthyroidism

→ Hyperplasia of thyroid

→ Exophthalmos

To diagnose patient with Grave's disease, patient should full fill 3 criteria

- **Hyperthyroidism-symptoms**
- **Heat intolerance**
- **Nervousness, irritability, emotional instability**
- **Fatigue**
- **Weight loss but increased food ingestion**
- **Increased bowel movements (diarrhea)**
- **Abnormal menses**
- **Tachycardia and atrial arrhythmias (atrial fibrillation)**

The most important consequence of hyperthyroidism increasing beta receptors of the heart. So, you notice that most of the symptoms of hyperthyroidism are those of increased or overactivity of the sympathetic system.

- **R_x / treatment of hyperthyroidism:**

- Propranolol

- Antithyroid drugs

- Surgery (removal of the thyroid gland)

Propranolol controls the manifestations of thyrotoxicosis

It has no antithyroid activity.

- **Propranolol it is used to control the hyperactivity of sympathetic system associated with hyperthyroidism.**
- **Propranolol: beta blockers**
- **Antithyroid drugs defined as drugs interfere with thyroid hormone synthetic machinery.**
- **Such manifestations should be controlled before sending to surgery, as you cannot send irritable nervous patient to surgery.**

Antithyroid drugs:

** Thiourea derivatives (Thionamides)

Methimazole, Carbimazole, Propylthiouracil

Carbimazole (pro-drug) is converted to Methimazole

- **Potency:**

Methi. > Carbi. > Propyl.

All effective orally

- **MOA:**
- **Inhibitors to thyroid perioxidase enzyme**
- **Interfere with oxidation, iodination, and coupling reactions**
- **Propylthiouracil: in addition of the inhibiting oxidation, iodination, and coupling reactions, it is also ↓ peripheral deiodination of T_4 to T_3.**
- **Have no effect on T_4 ,T_3 release,They act on synthetic machinery**

- **Side effects to thionamides:**

- Allergy
- Hepatic dysfunction
- Agranulocytosis(also an absolute contraindication to their use)

Once agranulocytosis is developed , you should stop using thioamides.
Agranulocytosis severe and dangerous lowered white blood cell count (leukopenia, most commonly of neutrophils) and thus causing neutropenia in the circulating blood.

- Methimazole is teratogenic (aplasia cutis congenita); propyltiouracil is not teratogenic

contraindicated during pregnancy,
aplasia cutis congenita: focal or extensive absence of skin.

- **Disadvantages:**

- Delayed onset of action (12-18 hrs)
- Prolong R_x (12-18 months)
- Side effects
- High relapse rate

Delayed onset because they work on synthetic machinery; they need more time to start action compared to drugs which inhibit releasing process

Treatment is used for a prolonged period of 1 to 1.5 years, and once stopped, there is a high relapse rate, so the drug may need to be given for the rest of the patient's life.
The relapse rate specifically indicates how often patients experience a return of hyperthyroid symptoms after completing a course of treatment

** Iodide (K^+ or Na^+): Sodium iodide , Potassium iodide

Solution and oral tab.

- **MOA:**

↓ oxidation ↓ release of T_4, T_3

(the Wolff–Chaikoff effect=an autoregulatory phenomenon, whereby a large amount of ingested iodine acutely inhibits thyroid hormone synthesis within the follicular cells)

- **Major side effects:**

<u>Allergy (test for iodide hypersensitivity)</u>

Widely used before thyroid surgeries to decrease↓ vascularity of the thyroid gland

** Radioactive iodine=RAI (^{131}I):

Rx ; treatment

Sol., Caps.

- **Diagnostic use (small dose)**
- **R_x of hyperthyroidism and Grave's disease (intermediate dose)**
- **R_x of thyroid Cancer (large doses)**

- **In the US, over 60% of endocrinologists select radioiodine as first-line therapy for Grave's disease**
- **It is the preferred therapy for women desiring pregnancy in the near future. After RAI therapy, they must wait 4-6 months before conceiving**

Diagnostic use: (Small dose)
Radioactive iodine (I-123 or I-131) is administered orally in a capsule or liquid form. It is absorbed into the bloodstream and taken up by the thyroid gland, which uses iodine to produce thyroid hormones. The amount of radioactive iodine uptake by the thyroid is measured after 4-6 hours and again at 24 hours using a gamma probe or scanner to diagnose thyroid conditions.

- **Advantages:**

higher remission rates - 10% will fail first treatment and require a second dose of ^{131}I

- **Disadvantage:**
- **hypothyroidism - is dose dependent**
- **Contraindications: pregnancy (absolute), ophthalmopathy (relative- RAI therapy may cause or worsen this condition)**

- **Side effects:**

- Pulmonary fibrosis

- Teratogenicity and carcinogenicity

** Lithium carbonate:

- **Oral and Sustained Released tablet**
- **Has similar MOA to iodide**
- **Has narrow therapeutic window**
- **<u>Also the drug of choice to treat manic depressive psychosis</u>**

Which means that their effective does is closed to toxic does

- **Side effects:**

Nausea, diarrhea, drowsiness, blurred vision

Ataxia, tinnitus and diabetes insipidus

** Iodinated contrast media:

e.g. Ipodate

- **Given orally**
- **Contain iodine +**
- **Inhibit peripheral conversion of T_4 to T_3**
- **Inhibit release of T_4 & T_3**
- **Similar side effects to iodide**
- **Allergic reactions (major side effect)**

Doctor has not discussed this slide but he said that it is required.

Potential T_4, T_3 interactions

- **Drugs reducing thyroid hormone production**

Lithium, Iodine-containing medications, Amiodarone

- **Drugs reducing thyroid hormone absorption**

Sucralfate, Ferrous sulfate, Cholestyramine, Colestipol, Aluminum-containing antacids, Calcium products

- **Drugs increasing metabolism of thyroxine**

Rifampin, Phenobarbital, Carbamazepine,Warfarin, Oral hypoglycemic agents

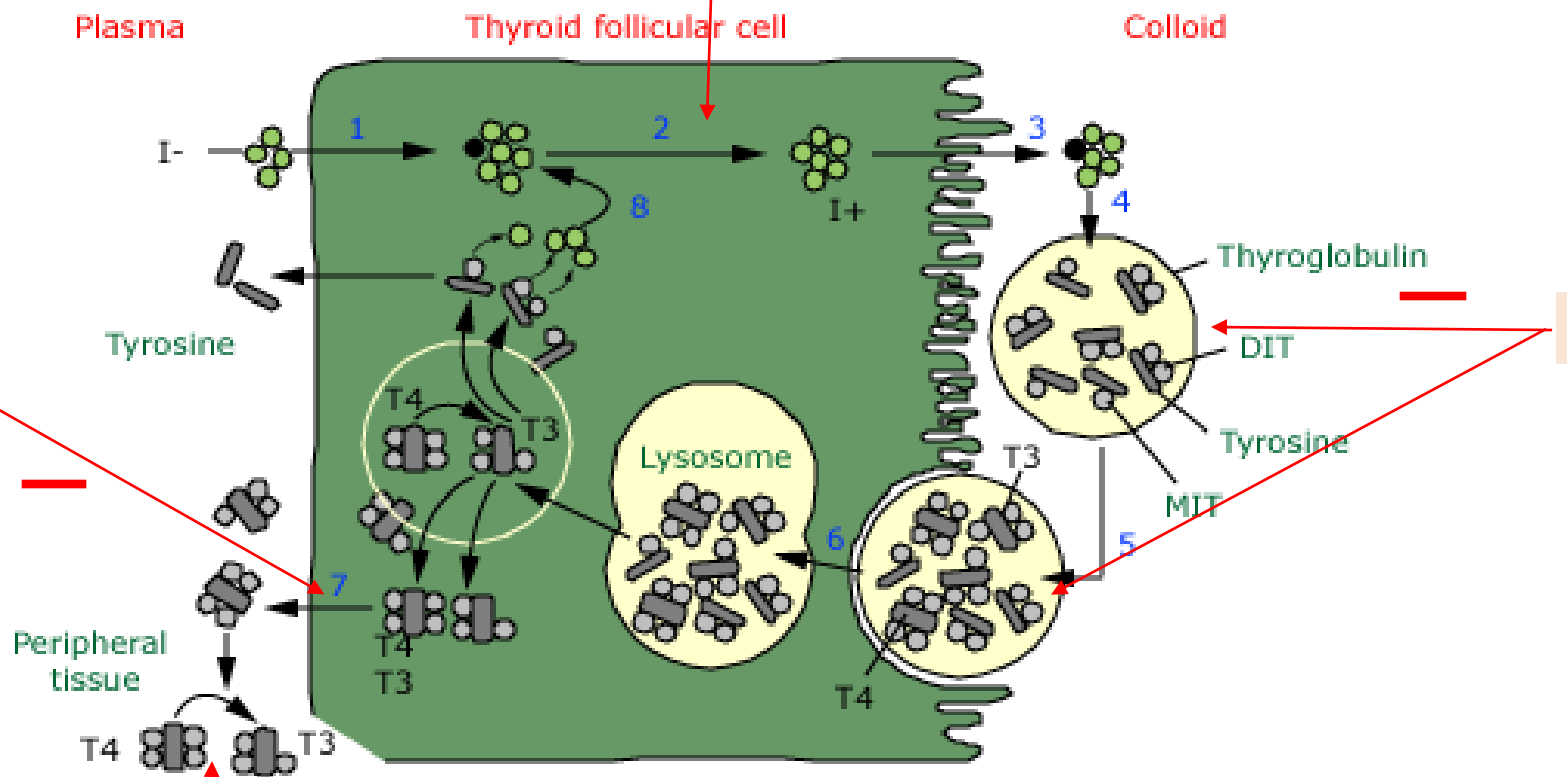
- **Drugs displacing thyroid hormones from protein binding**

Salicylates (Aspirin), Furosemide, Mefenamic acid

Lithium carbonate

iodide

thioamides



Lithium carbonate

Iodide

Ipodate

thioamides

propylthiouracil

Ipodate

اللهم يا من لا يهزم جنده و لا يخلف وعده، ولا إله غيره، كُن لأهل غزة عونًا و نصيرًا ومعينًا وظهيرًا وبدّل خوفهم أمنا، واحرسهم بعينك التي لا تنام . االلهم أنصر ضعفهم فليس لهم سواك ، اللهم اجعل لهم النصرة والعزة والغلبة والقوة . اللهم احفظ ارواحهم وابناءهم من كل من أراد بهم السوء .. اللهم ثبت الارض تحت اقدامهم .

اللهم مُنزل الكتاب، مُجري السحاب، هازم الأحزاب، اللهم اهزِمْ اليهود وزلزِلهم، وأرِنا فيهم عجائب قدرتك، اللهم مَزِّقْهم شرَّ مُمزَّق، اللهم أحصِهم عددا، واقتُلهم بَددا، ولا تُغادر منهم أحدا، اللهم إنا نجعلك في نحورهم ونعوذ بك من شرورهم.

اللهم امين 🤲