THYROID HORMONE INHIBITORS - 2

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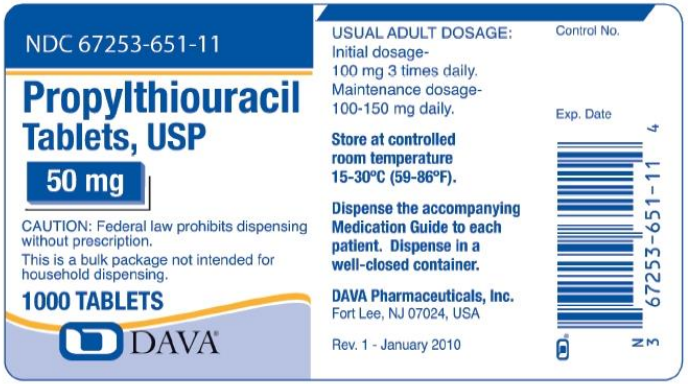
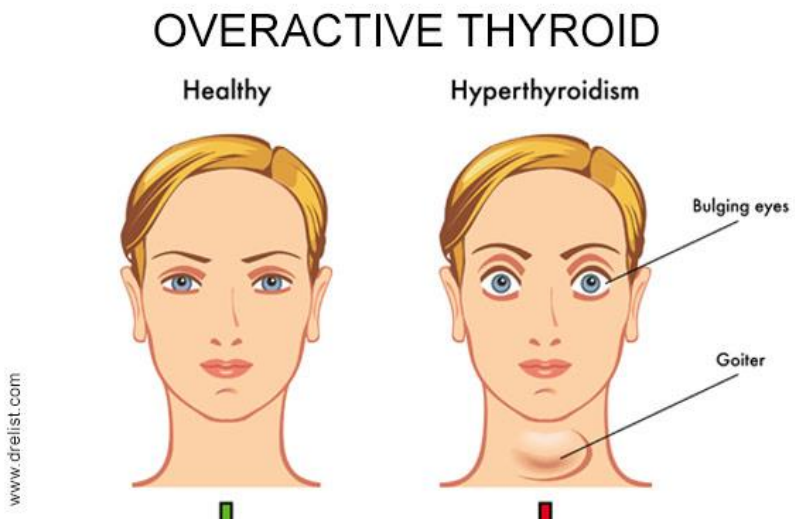


Thyrotoxicosis

- "Thyrotoxicosis" refers to the clinical manifestations associated with serum levels of T4 or T3 that are excessive for an individual (Hyper- thyroidism)



HYPERTHYROIDISM (THYROTOXICOSIS)

ESSENTIALS OF DIAGNOSIS

- Sweating, weight loss or gain, anxiety, palpitations, loose stools, heat intolerance, irritability, fatigue, weakness, menstrual irregularity.
- Tachycardia; warm, moist skin; stare; tremor.
- In Graves disease: goiter (often with bruit); ophthalmopathy.
- Suppressed TSH in primary hyperthyroidism; increased T_4, FT_4, T_3, FT_3.

Source : **CMDT**

Goal of the treatment

- The goal of therapy is to decrease synthesis & release of additional thyroxine hormone

METHODS

- 1) Partial/local destruction of the thyroid tissue (Surgery/ Radio active Iodine)

- 2) By inhibiting synthesis of the hormones, or by blocking release of the hormones from the thryoid follicle (Anti-thyroid Drugs)

Thyroid Hormone Inhibitors

CPM-Radio

- Drugs that are used to lower the functional capacity of the hyperactive thyroid gland.

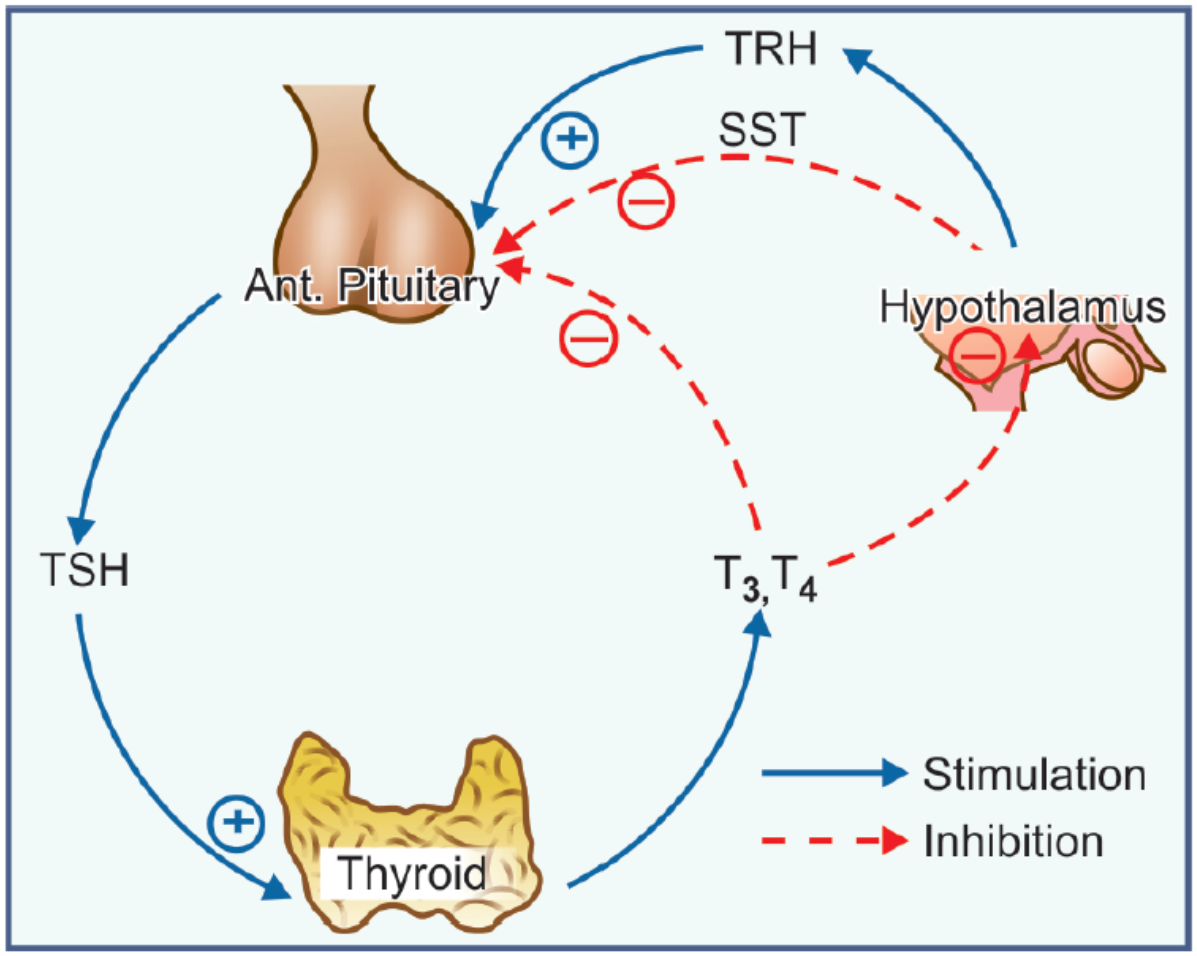
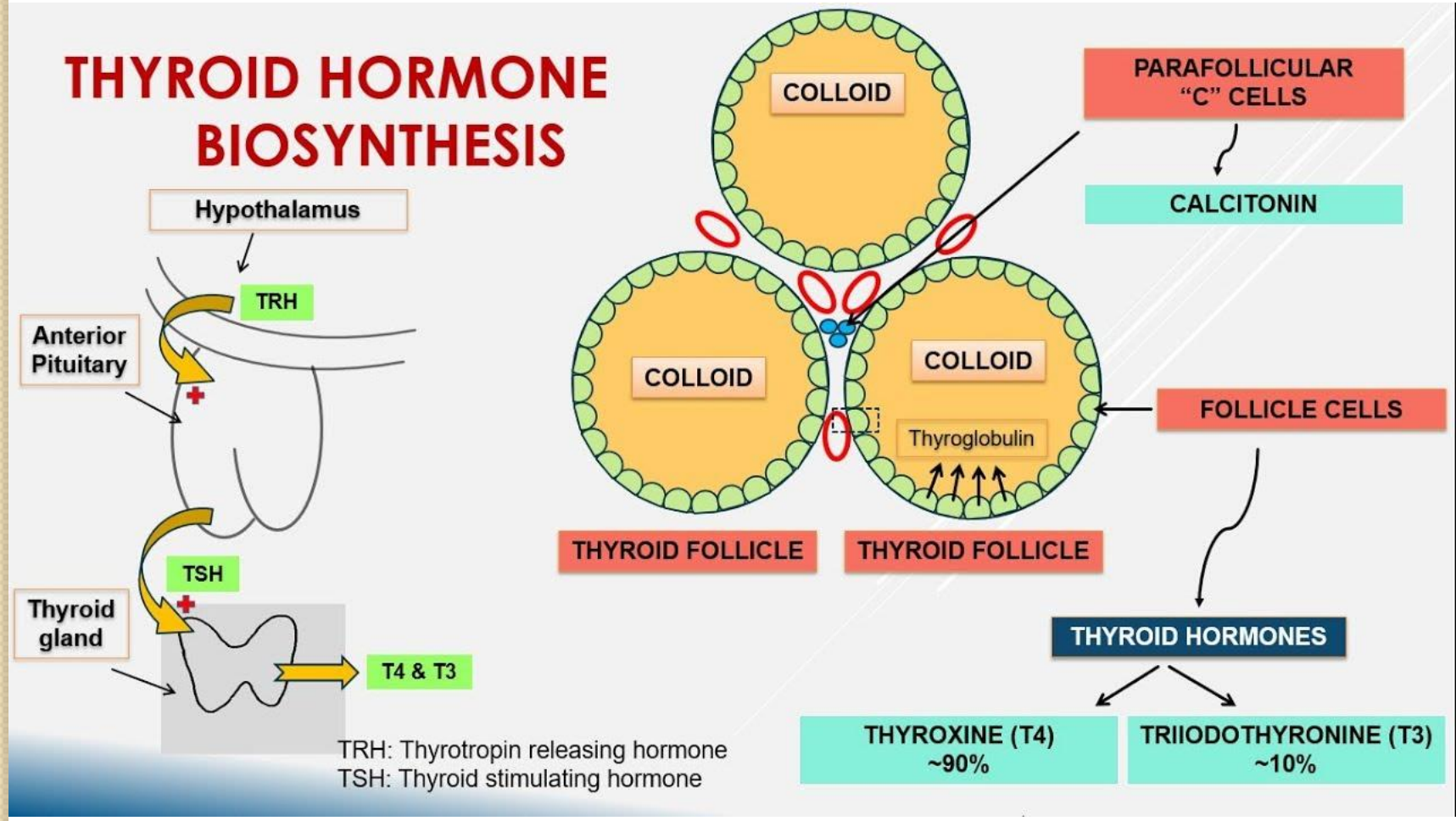
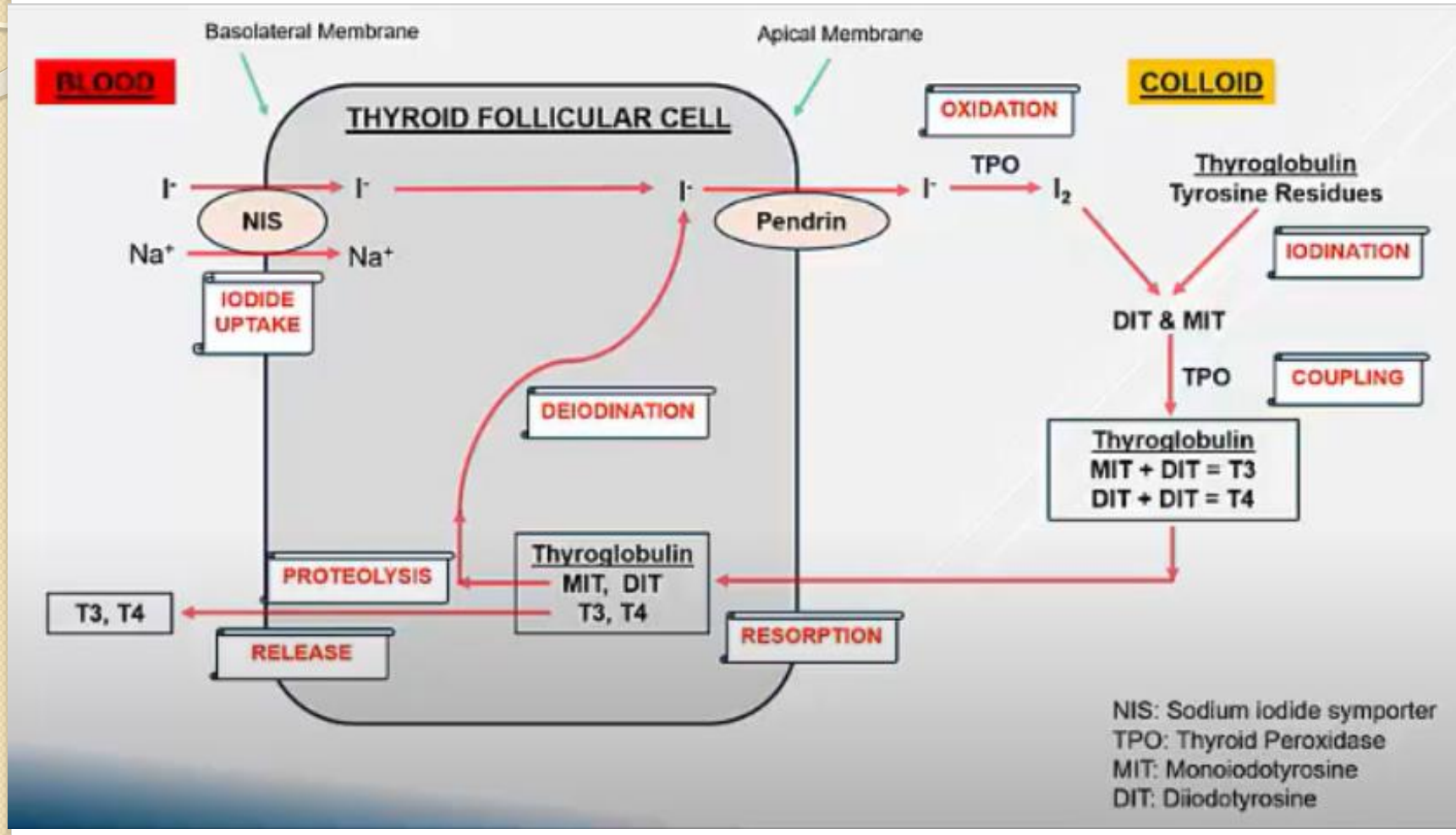


Fig. 18.3: Regulation of thyroid function
TSH—Thyroid stimulating hormone; TRH—Thyrotropin releasing hormone; T_3—Triiodothyronine; T_4—Thyroxine; SST—Somatostatin

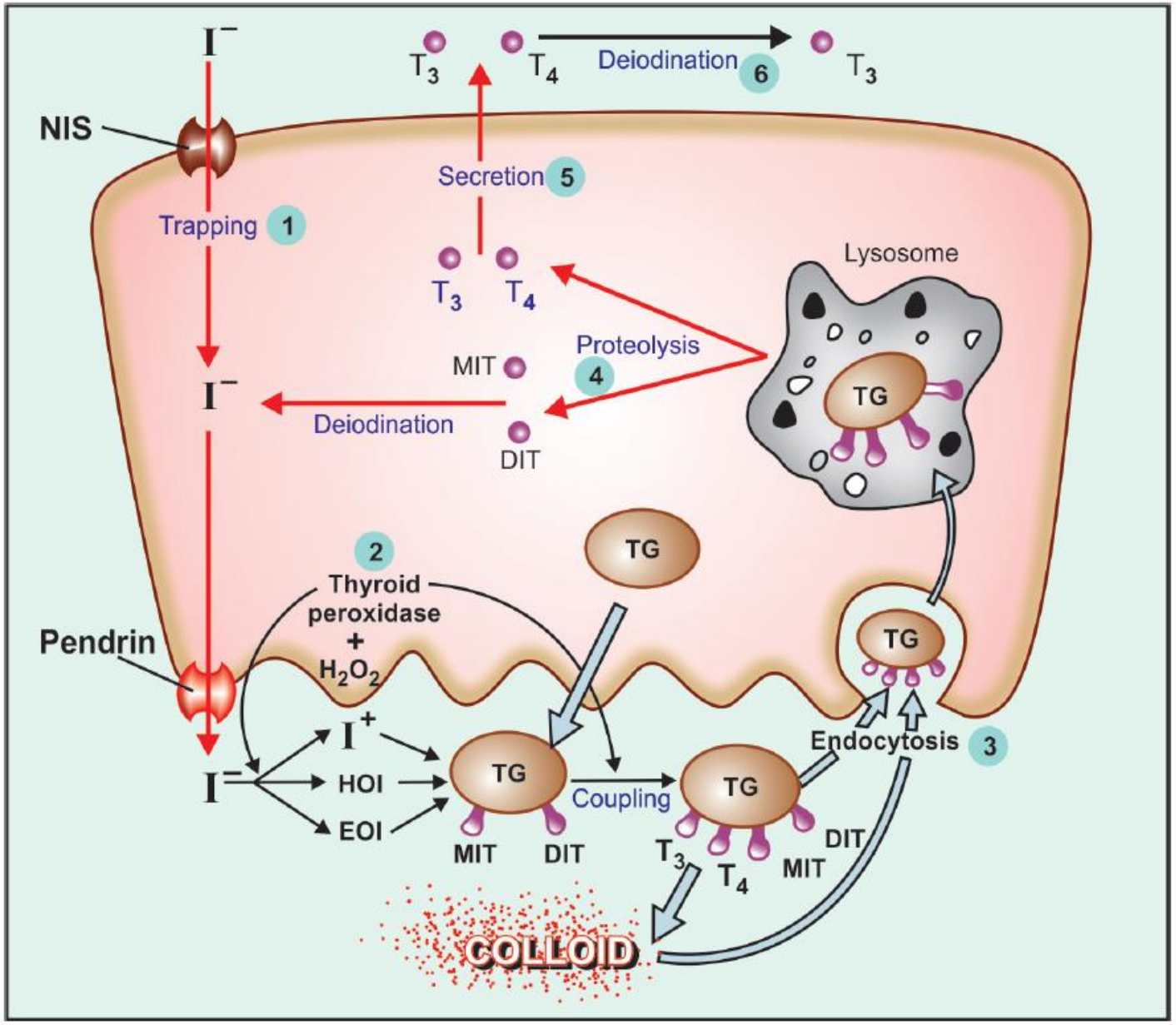

THYROID HORMONE BIOSYNTHESIS
Hypothalamus
TRH
Anterior Pituitary
TSH
Thyroid gland
T4 & T3
TRH: Thyrotropin releasing hormone
TSH: Thyroid stimulating hormone
COLLOID
COLLOID
COLLOID
Thyroglobulin
THYROID FOLLICLE
THYROID FOLLICLE
PARAFOLLICULAR "C" CELLS
CALCITONIN
FOLLICLE CELLS
THYROID HORMONES
THYROXINE (T4) ~90%
TRIIODOTHYRONINE (T3) ~10%

Biosynthesis & Anti-thyroid Drugs site of Action

Let's re-collect ... Steps involved in the synthesis of Thyroid Hormone



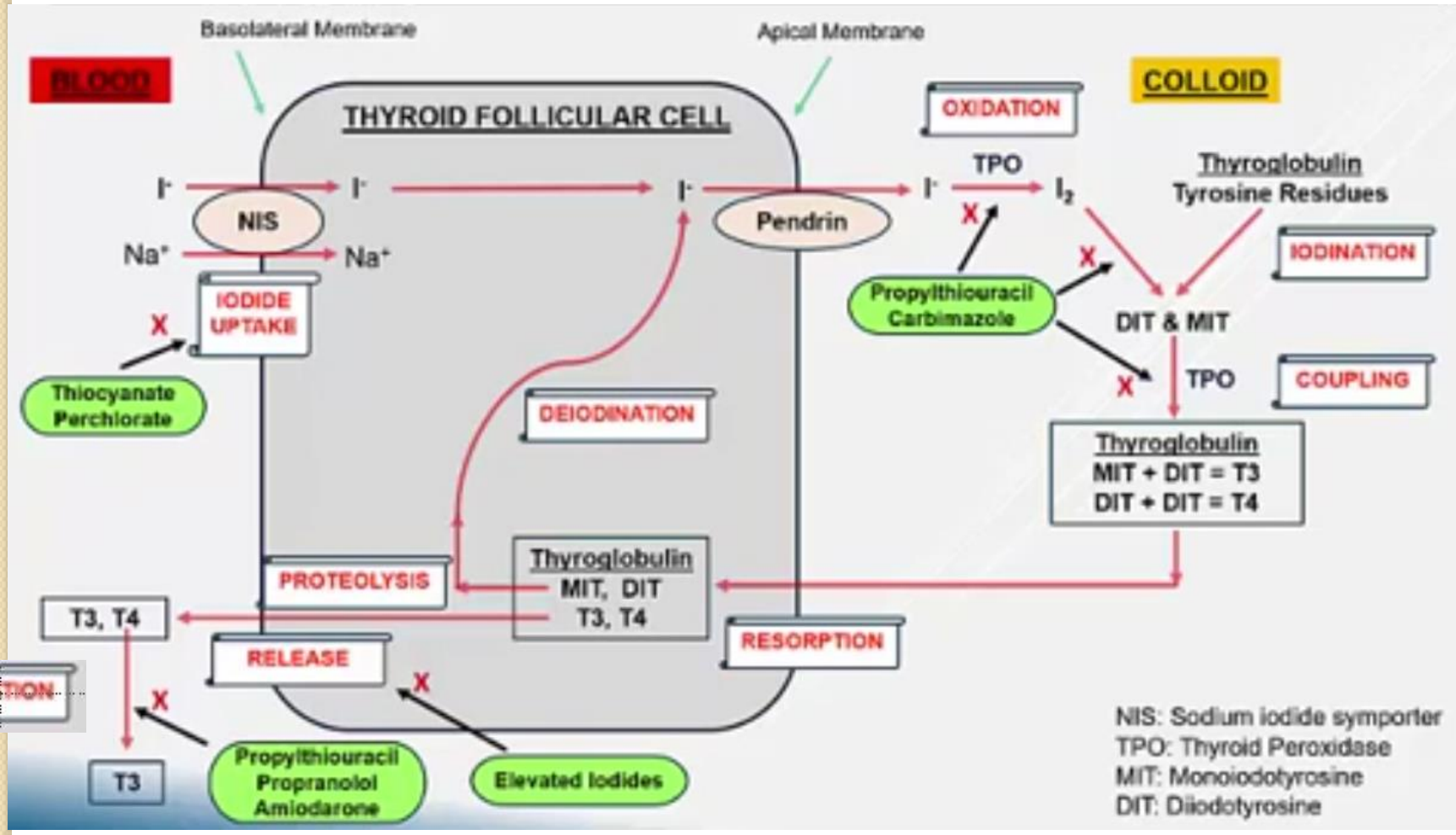
Bio-synthesis of Thyroid Hormone …. KD Tripathi



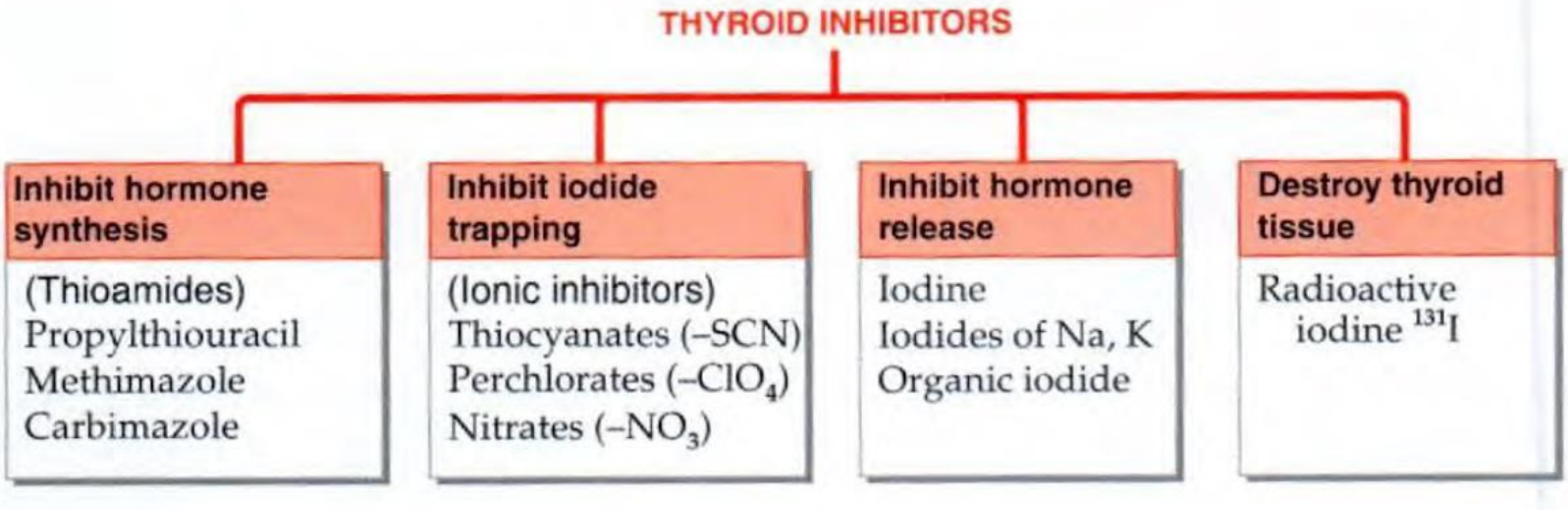
Relation between T_4 and T_3

- Thyroid secretes more T_4 than T_3, but in iodine deficient state this difference is reduced.
- T_4 is the major circulating hormone because it is 15 times more tightly bound to plasma proteins.
- T_3 is 5 times more potent than T_4 and acts faster. Peak effect of T_3 comes in 1–2 days while that of T_4 takes 6–8 days.

Thyroid Hormone Inhibitors – Site of Action



CLASSIFICATION



2) TPO Inhibitors
(Colloid level & Peripheral t4 to T3

eg : CPM

1) Iodide Uptake Inhibitors
(Entry level-Thyroid Follicle)

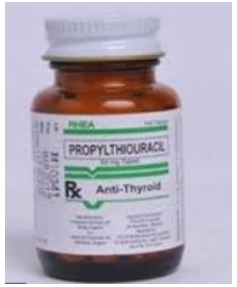
Eg : TPN

3) Thyroid Constipating Agents
(Exit level-Thyroid Follicle)

Eg : Na, K Iodides

THIO-AMIDES

- Anti-thyroid drugs



Carbamizole (prodrug)—Degraded to Methimazole in the body.

Propyl-thio-uracil

Methimazole

Antithyroid drugs bind to the thyroid peroxidase and prevent oxidation of iodide/ iodotyrosyl residues, thereby;

(i) Inhibit iodination of tyrosine residues in thyroglobulin

(ii) Inhibit coupling of iodotyrosine residues to form T_3 and T_4.

THIO-AMIDES

Suitable for …

- Methimazole or Propylthiouracil is generally used for young adults or patients with mild thyrotoxicosis, small goiters

- It also useful for preparing hyper-thyroid patients for surgery and elderly patients for RAI treatment.


NDC 0143-1480-01
Propylthiouracil
Tablets, USP
50 mg
℞ Only
100 TABLETS
propylthiouracil
anti-thyroid drug

Propylthiouracil (PTU)

- **MOA** : It **inhibits** **PTU**

Propylthiouracil Inhibits

- **P**eroxidase (binds to the **thyroid peroxidase**)
- **P**eripheral conversion of T4 to T3
- **T**yrosine iodination
- **U**nion (coupling to form T4 & T3)

* Can be used in **P**REGNANCY

Thioamides (Anti-thyroid drugs)

- Decrease thyroid hormones output from the gland

<u>Causes a gradual reduction</u>

- Signs and symptoms of thyrotoxicosis
- BMR
- Pulse normal over a period of 3-4 weeks

Thioamides … P/K

- All anti-thyroid drugs are quickly absorbed orally, widely distributed in the body, enter milk and cross placenta
- metabolized in liver and excreted in urine
- Carbimazole acts largely by getting converted to methimazole in the body and is longer acting than propythiouracil

TABLE 18.1 **Differences between propylthiouracil and carbimazole**

	Propylthiouracil	*Carbimazole*
1.	Dose to dose less potent	About 5 × more potent
2.	Highly plasma protein bound	Less bound
3.	Less transferred across placenta and in milk	Larger amounts cross to foetus and in milk
4.	Plasma t½ 1–2 hours	6–10 hours
5.	Single dose acts for 4–8 hours	12–24 hours
6.	No active metabolite	Produces active metabolite—methimazole
7.	Multiple (2–3) daily doses needed	Mostly single daily dose
8.	Inhibits peripheral conversion of T_4 to T_3	Does not inhibit T_4 to T_3 conversion

PTU :ADR

- Hypothyroidism and goiter can occur due to overtreatment, but is reversible on stopping the drug.
- g.i. intolerance, skin rashes and joint pain.
- Agranulocytosis (rare)

PTU – Uses

- Graves' disease
- Toxic nodular goiter
- Preoperatively used before the Surgery/Radio-active Iodine usage
- Thyroid storm

Safe in Pregnancy & DOC during Breastfeeding

Carbamizole

Carbimazole is more commonly used in India.

Advantages of Methimazole over PTU

- Methimazole is more convenient and does not cause hepatic necrosis

RAI - Radioactive iodine (I_{131})

- An excellent method of <u>destroying overactive thyroid tissue</u> (either diffuse or toxic nodular goiter
- ^{131}I is the preferred treatment for most patients over 21 years of age.
- 6 to 12 weeks following the administration of radioiodine, the gland will shrink in size and the patient will usually become euthyroid or hypothyroid.

Radio active Iodine

- Hypothyroidism occurs in about 80% of patients following radioiodine therapy.
- Serum T_4 and TSH levels should be monitored regularly.
- When hypothyroidism develops, prompt replacement with oral levothyroxine, 50–150 mcg daily, should be instituted.

RIA

- It is used as sodium salt form which is dissolved in water and taken orally.
- Average dose : 3-6 milli curie
- Response start after 2 weeks and take 2-3 months to see the peak action.

Limitations

- There is a high incidence of hypothyroidism and hyperparathyroidism (childhood)
- Due to fetal radiation <u>not suitable in Pregnancy</u>

A word about - Lugol's iodine

- **Lugol's iodine**, also known as **Lugol's solution**, first made in 1829 (solution of elemental iodine and potassium iodide in water)
- French physician Genes Lugol

Lugol's iodine

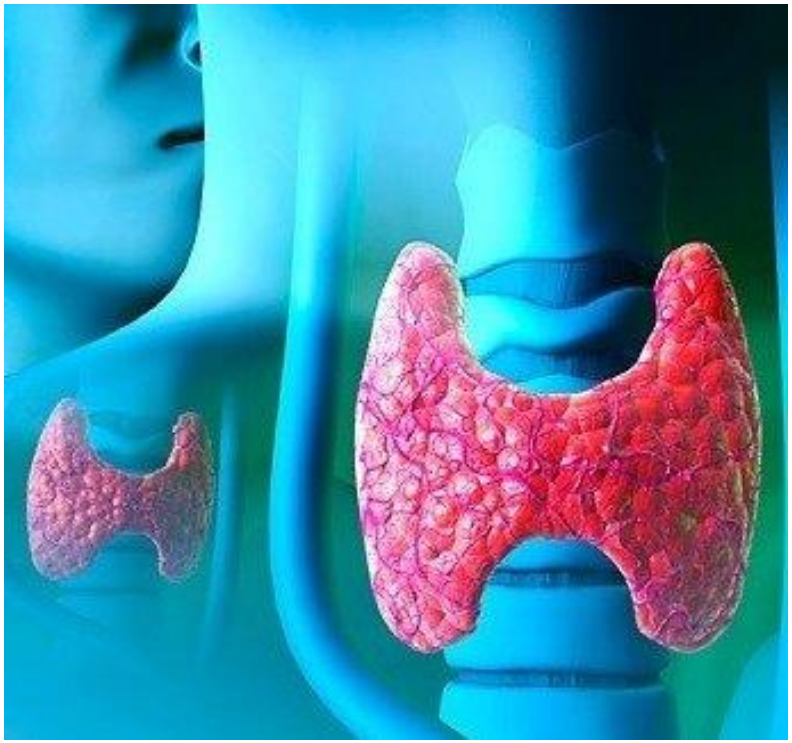
- Composition : (5% iodine in 10% Pot. iodide solution) Dose : 5- 10 drops /day
- Use :

1. Preoperative preparation before thyroidectomy
2. Thyroid storm
3. Prophylaxis of endemic goiter
4. Antiseptic (Povidine Iodine – topically)

Role of Beta-blockers in Thyrotoxicosis

- **Propranolol :** effectively relieves the tachycardia, tremor, diaphoresis, and anxiety
- It is the initial treatment of choice for thyroid storm
- Propranolol ER 60 mg orally once or twice daily, with dosage increases every 2–3 days to a maximum daily dose of 320 mg.

THYROID STORM



Causes : Thyroid Storm

- It is an medical emergency due to decompensated hyperthyroidism.
- sudden acute exacerbation of all of the symptoms of thyrotoxicosis
  - Fever
  - Mental Status Changes
  - Cardiovascular Collapse
- Precipitants By
  - surgery
  - Sepsis
  - Iodine loads
  - Post-partum

Thyroid Storm - Treatment

- Non-selective Beta blockers : Propranolol 1-2 mg slow i.v. may be followed by 20-120 mg oral 4- 6th hours .
- Propylthiouracil 150 – 250 mg oral 6 hourly: reduces hormone synthesis as well as peripheral conversion of T4 to T3 (or) Methimazole 15–25 mg orally every 6 hours

Thyroid Storm - Treatment

- Hydrocortisone 50 mg orally 6th hourly
- It helps to tide over crisis, cover any adrenal insufficiency and inhibit conversion of T4 to T3 in periphery.
- Rehydration, anxiolylics, external cooling and appropriate antibiotics are the other measures.