THYROXINE AND ANTITHYROID DRUGS

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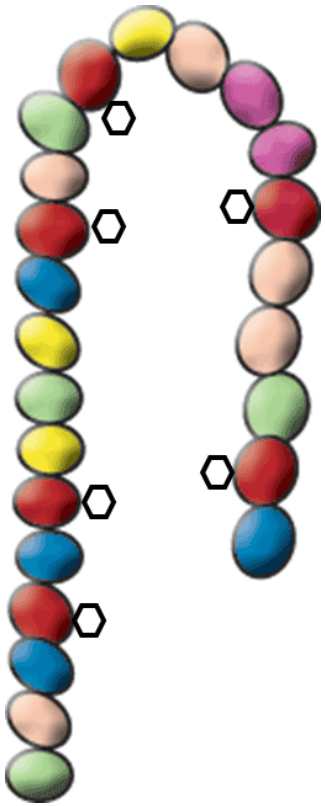
LEARNING OUTCOMES

- By the end of the lecture, students will be able to…
  I. Explain the mechanism of action of antithyroid drugs in relation to thyroid hormone synthesis and secretion
  II. Describe adverse drug reactions of antithyroid drugs
  III. Explain the rationale of using thyroxine in replacement and suppressive therapy
  IV. Describe pharmacokinetics of thyroxine

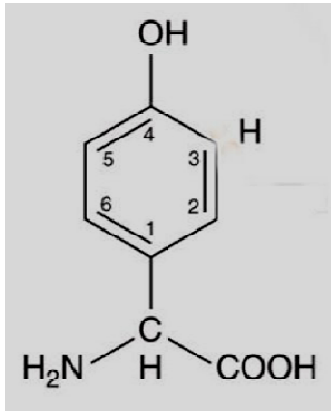
OUTLINE....

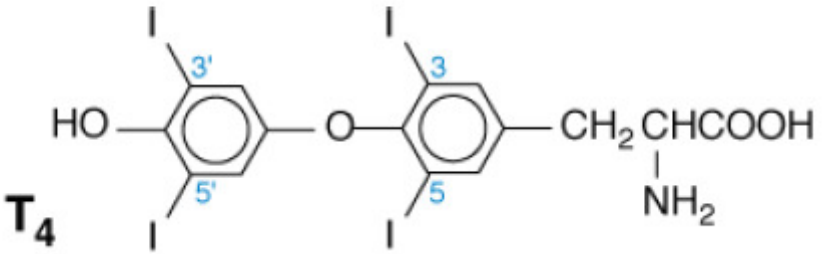
A. Physiology
B. Mode of action and clinical effects of thyroid hormones
C. Antithyroid drugs – mode of action, pharmacokinetics and ADRs
D. Thyroxine – mode of action, kinetics and therapeutic use

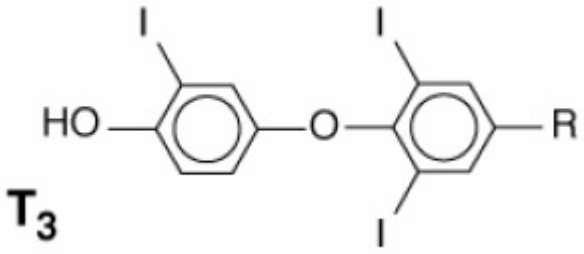
SYNTHESIS AND SECRETION OF THYROID HORMONES



Thyroglobulin







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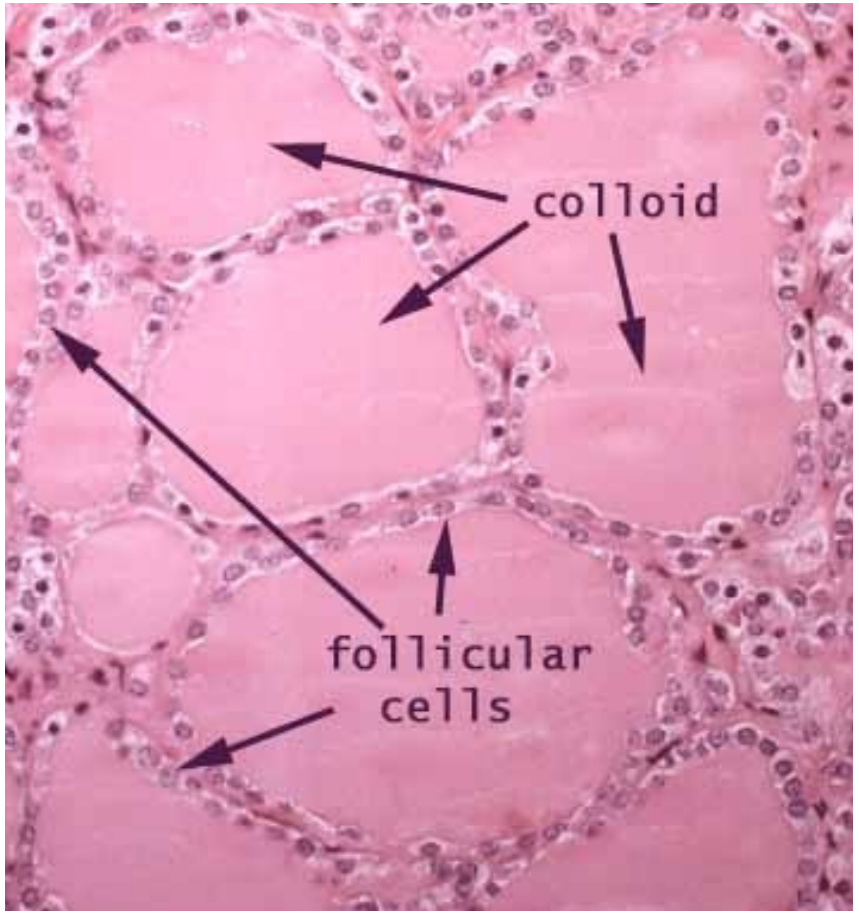

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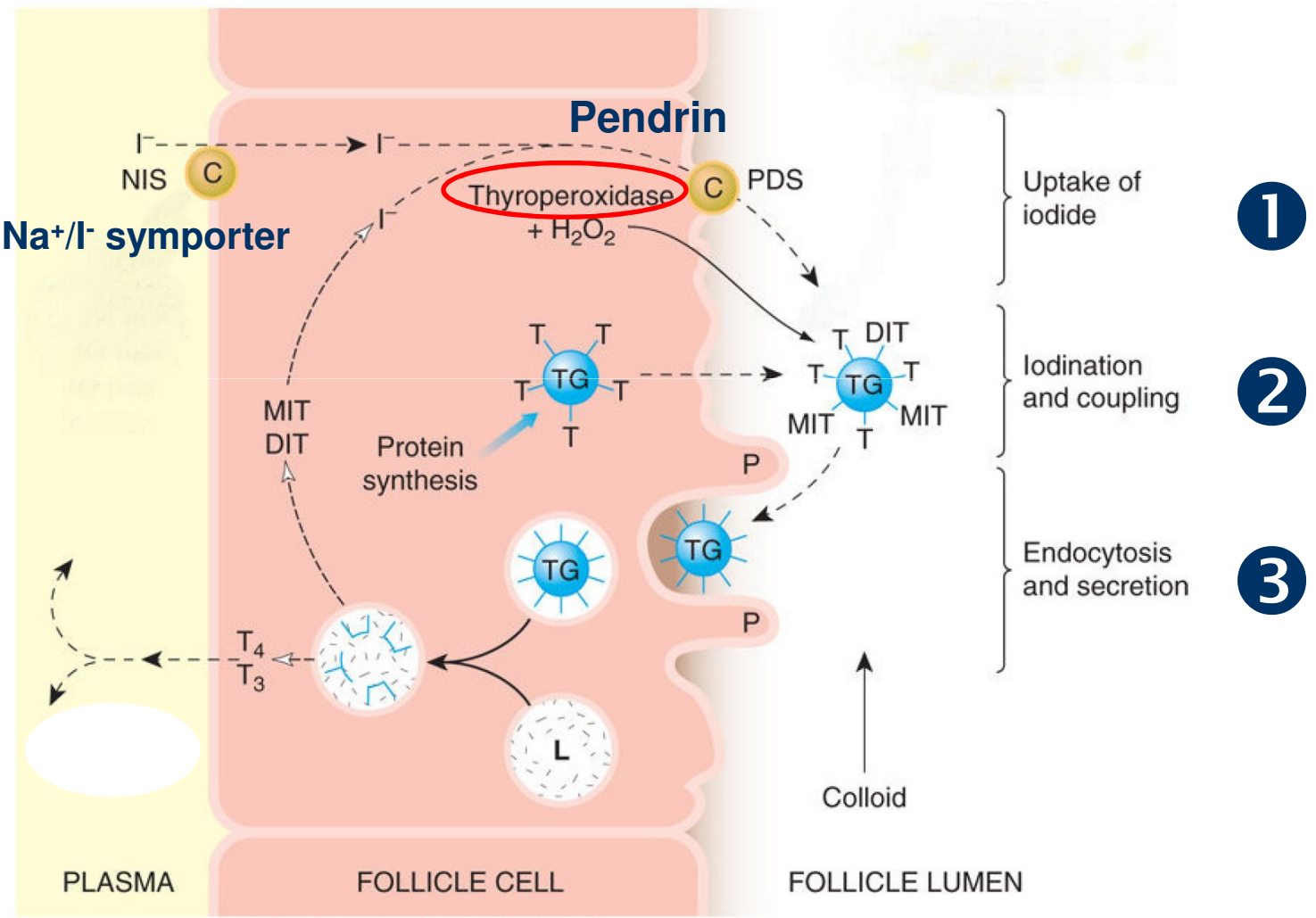
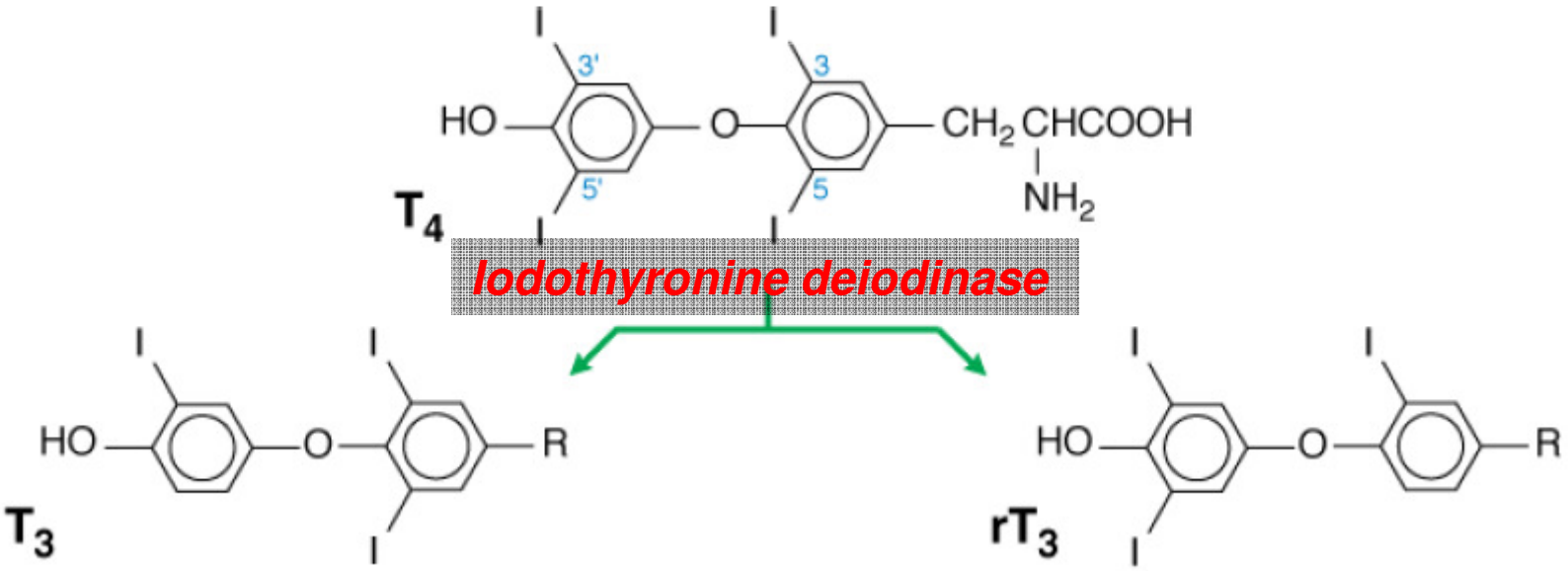
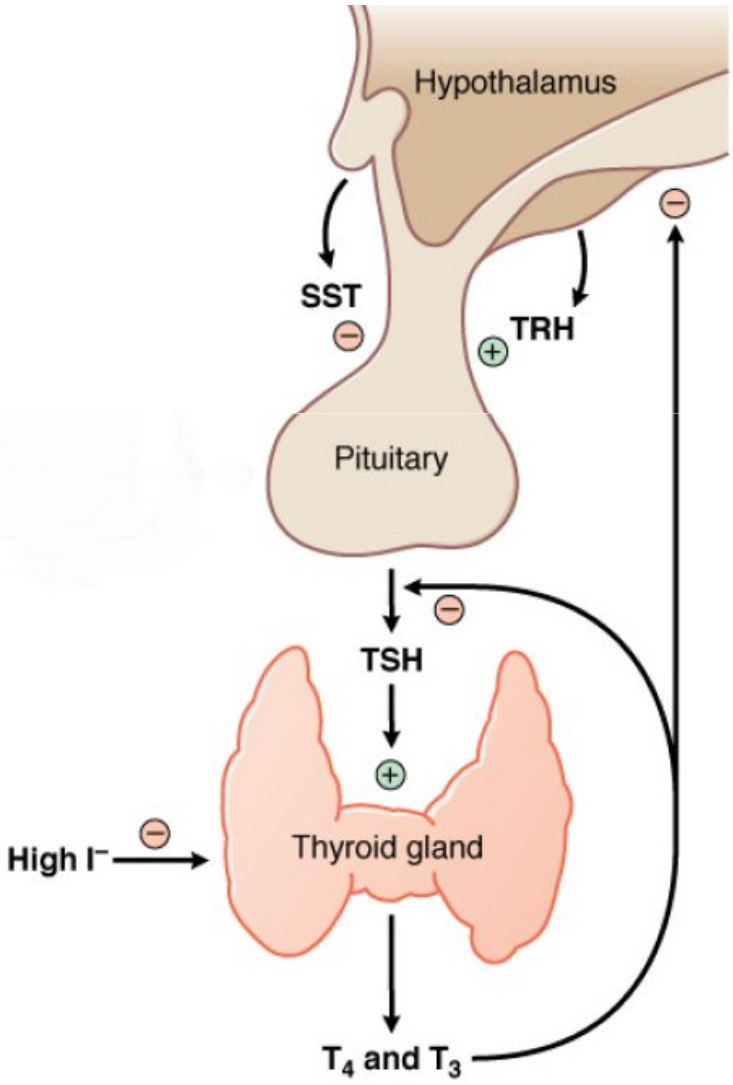


CONVERSION OF T_4 TO T_3 IN PERIPHERAL TISSUES

- Source of ~80% of circulating triiodothyronine(T_3)



REGULATION OF THYROID FUNCTION



MECHANISM OF ACTION OF THYROID HORMONES

- Act mainly by the binding of T_3 to a specific nuclear receptor
- T_4 is not biologically active in normal physiology
- When T_3 is bound, the gene transcription is activated, resulting in generation of mRNA and protein synthesis

CLINICAL EFFECTS OF THYROID HORMONES

- Regulation of growth and brain development
- Necessary for thermogenesis
- Increase in the metabolism of carbohydrates, fats and proteins
- Increased heart rate and cardiac output

ANTITHYROID DRUGS

- THIOUREYLENES:
  1. **Carbimazole**
  2. **Methimazole**
  3. **Propylthiouracil**

MODE OF ACTION - THIOUREYLENES

Inhibit thyroperoxidase

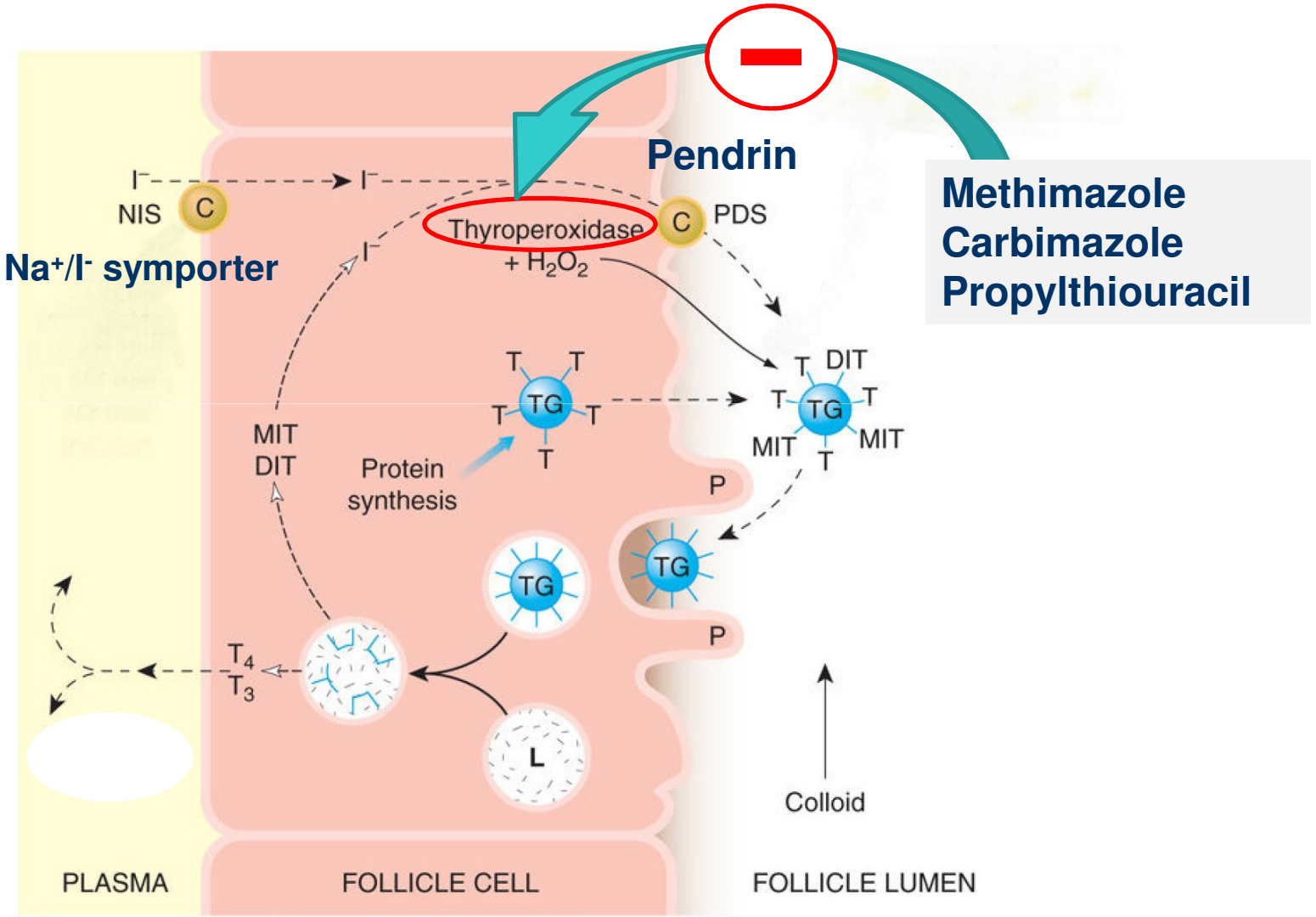
Inhibit,

1. the iodination of tyrosyl residues in thyroglobulin
2. the coupling of these iodotyrosyl residues to form iodothyronines

Depletion of stores of iodinated thyroglobulin

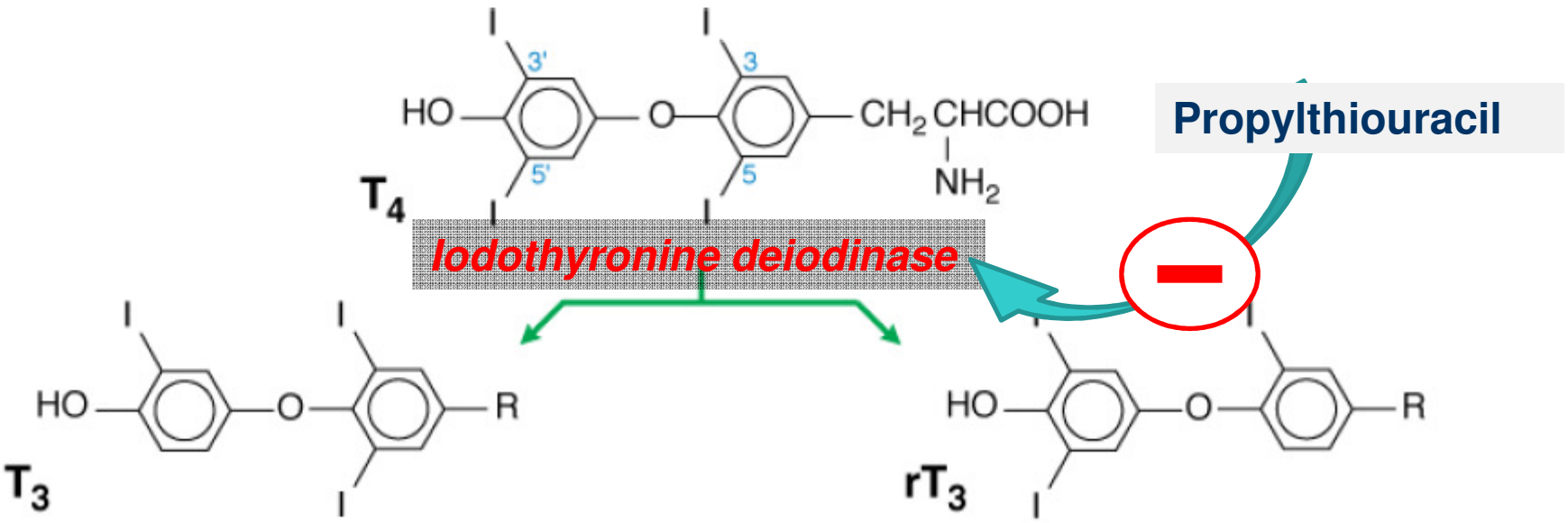
Gradual reduction in the signs and symptoms of thyrotoxicosis

MODE OF ACTION - THIOUREYLENES



MODE OF ACTION - PROPYLTHIOURACIL

- Partially inhibits the deiodination of T4 to T_3 in peripheral tissues



PHARMACOKINETICS

- Carbimazole is rapidly converted to its active metabolite methimazole

Drug	Half-life
Carbimazole	6-15 h
Propylthiouracil	75 minutes

- Cross the placenta and appear in the milk
- Concentrated in the thyroid

ADVERSE DRUG REACTIONS

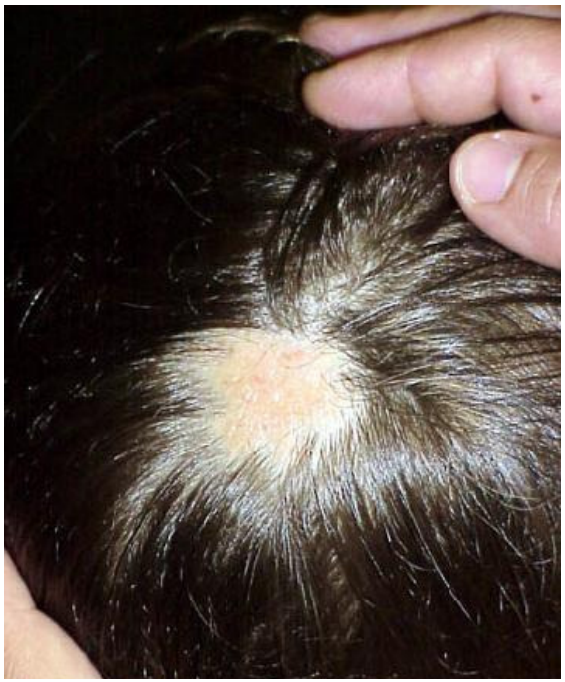
- Agranulocytosis:
  - Agranulocytosis develops rapidly ∴ periodic white cell counts not helpful
  - Reversible on discontinuation of the drug
  - Patients should be instructed to immediately report symptoms of leucopoenia i.e. sore throat or fever
  - If these signs or symptoms occur, patients should discontinue their anti-thyroid drug and obtain a white cell count

ADVERSE DRUG REACTIONS

- Propylthiouracil induced hepatotoxicity:
  - More common among children and adolescents
  - Third drug after paracetamol and isoniazid that requires liver transplantation due to hepatotoxicity
  - Mildly altered liver function tests ⟷ Death
- The most common reaction - purpuric, urticarial papular rash

ADVERSE DRUG REACTIONS

- Teratogenicity:
  - With carbimazole/methimazole," **aplasia cutis congenita** "



- Reserve propylthiouracil use for patients who are in their first trimester of pregnancy, or who are allergic to or intolerant of methimazole

- Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of methimazole, and there are no other treatment options available

RADIOIODINE

- When taken orally incorporated into thyroglobulin in a similar way to iodide
- The isotope used is ^{131}I
- Emits both β and γ radiation. B rays are destructive to tissues
- ^{131}I has a half-life of 8 days ∴ its radioactivity lasts ~2 months
- Cytotoxic effect on the gland is delayed for 1-2 months and maximum effect reached in 4 months

THYROID HORMONES

- Two types:
  1. Thyroxine (levothyroxine)
  2. Tri-iodothyronine (liothyronine)

- Synthetic compounds identical to the natural hormones

- Liothyronine has a faster onset but a shorter duration of action($t_{1/2}$ = 0.75 days) ∴ Used only in acute emergencies e.g.myxoedema coma

LEVOTHYROXINE

- Drug absorption:
  - ~ 80% absorbed
  - Reduced by food, aluminum-containing antacids ,cholestyramine, calcium carbonate ,proton pump inhibitors and raloxifene
  - ∴ Should be taken on an empty stomach

LEVOTHYROXINE

- Drug metabolism:
  - Metabolized mainly in the liver
  - Hepatic CYP3A4 induction reduces the plasma concentration of the medicine

    e.g. phenytoin, carbamazepine, Rifampicin

LEVOTHYROXINE

- Drug excretion:
  - Excreted partly in the bile and partly in the urine
  - Binding strongly to plasma proteins protect the drug from metabolism an excretion there by increasing $t_{1/2}$
  - Due to the long $t_{1/2}$ (7 days) takes long for clinical effects to be noticed and minimal effect on missing a dose

CLINICAL USE

1. Thyroid hormone replacement therapy in hypothyroidism – to replenish thyroid hormone lost due to illness(e.g. Autoimmune thyroiditis) or iatrogenic causes (e.g. Radioiodine or surgery)
2. Suppression of TSH after thyroidectomy and radioiodine in thyroid carcinoma, as TSH is a growth factor for thyroid carcinomas

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