PHARM.D • YEAR 3

Medicinal Chemistry

CHAPTER 9

Thyroid and Antithyroid Agents

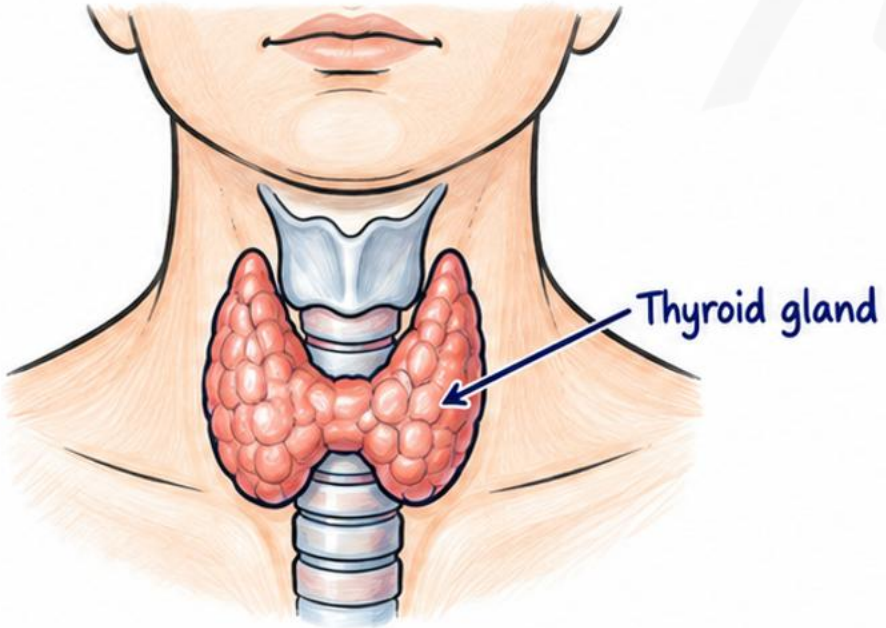
PPT CHAPTER COVER



THYROID HORMONES & CONTROL

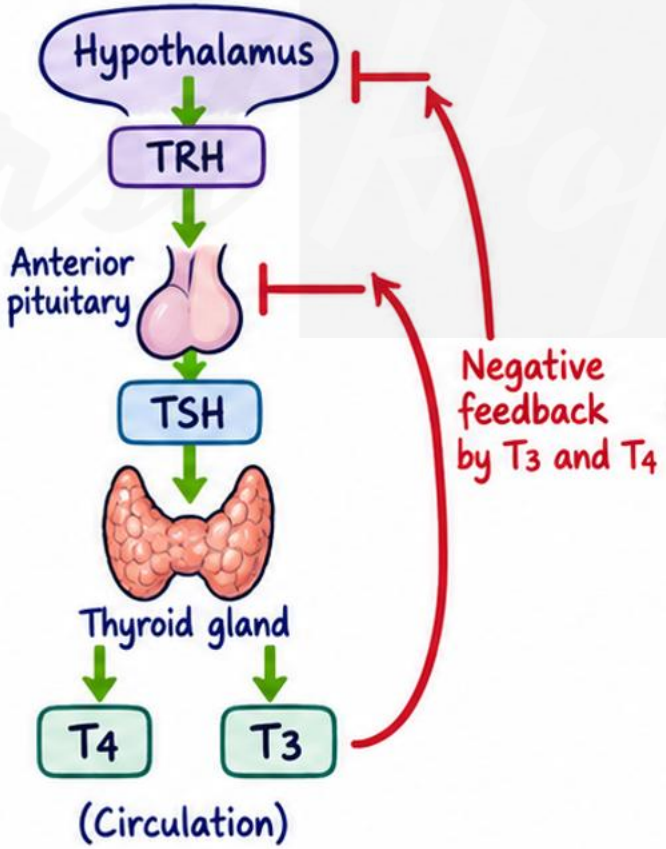
THE GLAND

Follicular cells make thyroxine (T4) and triiodothyronine (T3). These regulate metabolism, growth and neurological development.



CONTROL AXIS

Hypothalamic TRH stimulates pituitary TSH. TSH stimulates thyroid hormone synthesis and release. T3 and T4 provide negative feedback.



LOW HORMONE



Hypothyroidism may produce fatigue, cold intolerance and weight gain.



EXCESS HORMONE



Hyperthyroidism may produce tremor, heat intolerance, weight loss and tachycardia.



DISTINGUISH

Calcitonin comes from thyroid C cells. It is a peptide involved in calcium regulation, not an iodothyronine.

THYROID HORMONE BIOSYNTHESIS

1 IODIDE TRAPPING

Iodide enters follicular cells and is transported into colloid.

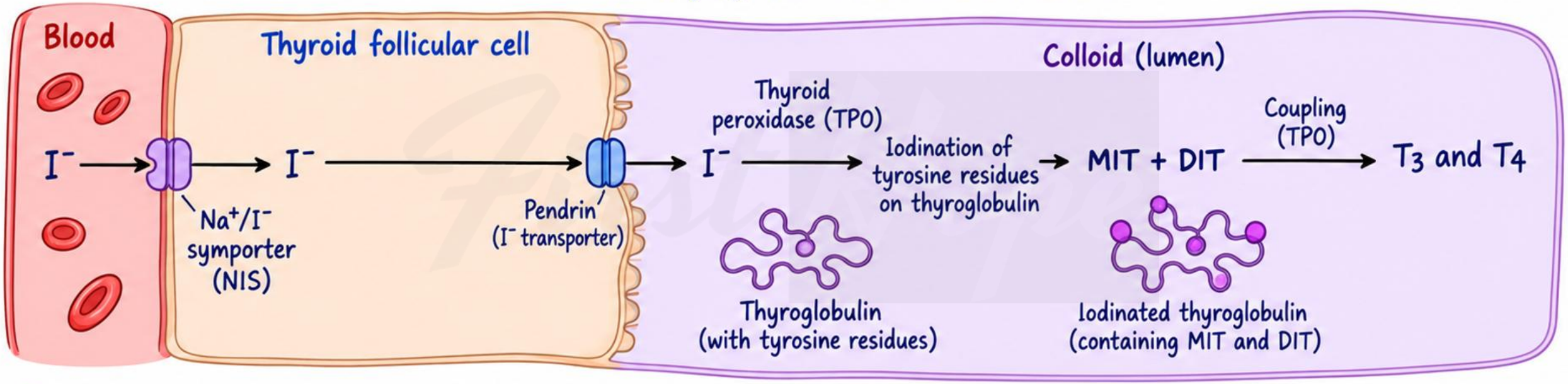
2 ORGANIFICATION

Thyroid peroxidase helps oxidise iodide and iodinate tyrosine residues on thyroglobulin. MIT and DIT form.

3 COUPLING

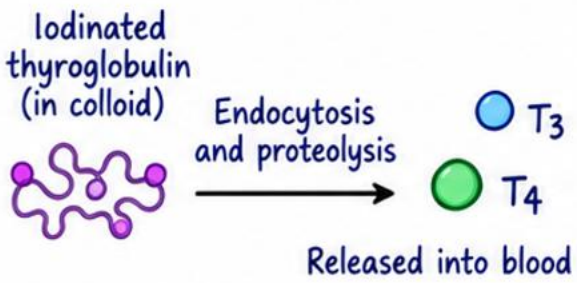
MIT + DIT gives T_3.

DIT + DIT gives T_4.



4 STORAGE & RELEASE

Hormones remain bound to thyroglobulin in colloid. Endocytosis and proteolysis release T_3 and T_4.



5 PERIPHERAL CONVERSION

Deiodinases convert much of T_4 into more active T_3.



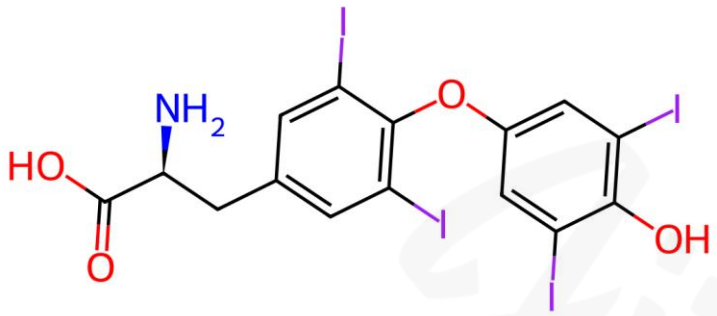
DRUG TARGET

Thionamides inhibit organification and coupling.

T4 & T3: CHEMISTRY

LEVOTHYROXINE: T4

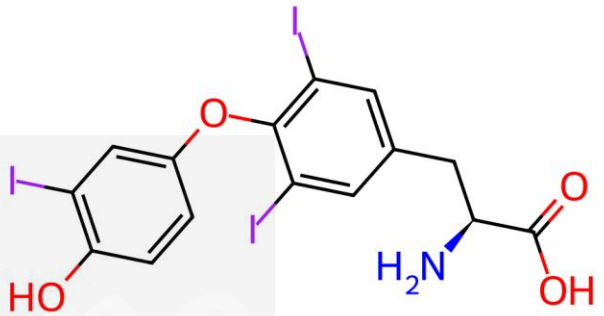
$C_{15}H_{11}I_4NO_4$



Four iodine atoms on an L-iodothyronine DIPHENYL ETHER scaffold.
Main replacement hormone for hypothyroidism.

LIOTHYRONINE: T3

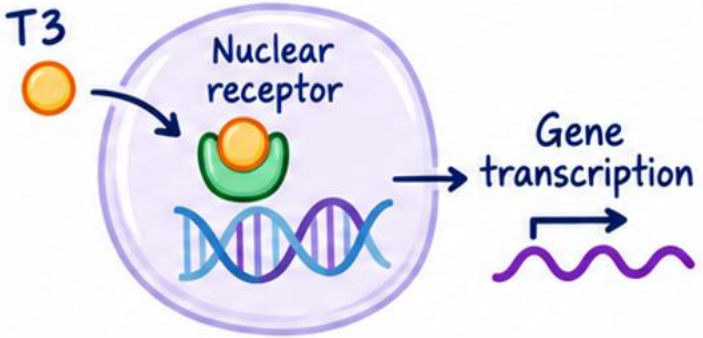
$C_{15}H_{12}I_3NO_4$



Three iodine atoms on the same scaffold.
More active, with faster onset and shorter action.

COMMON ACTION

T3 binds nuclear thyroid-hormone receptors and regulates gene transcription.
T4 supplies a longer-lasting reservoir.



CAUTION

Excess replacement can cause thyrotoxic symptoms and cardiac effects. These agents are not weight-loss medicines.

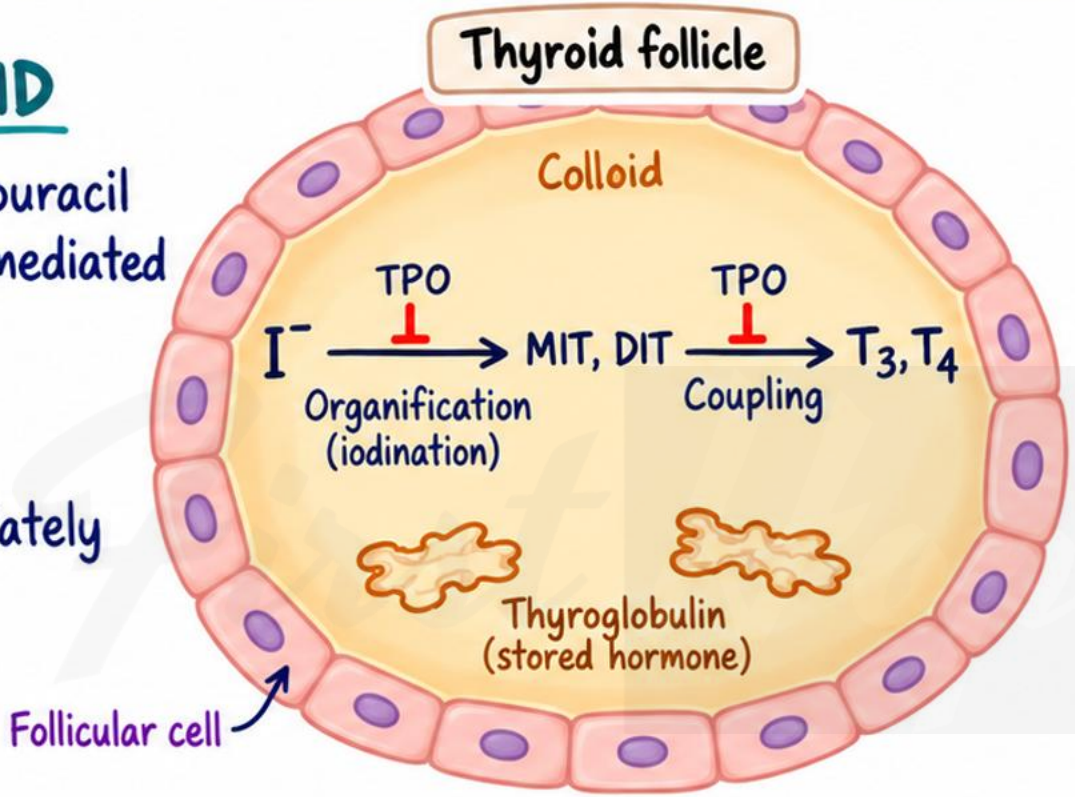


THIONAMIDES: DRUG TARGETS

WITHIN THE THYROID

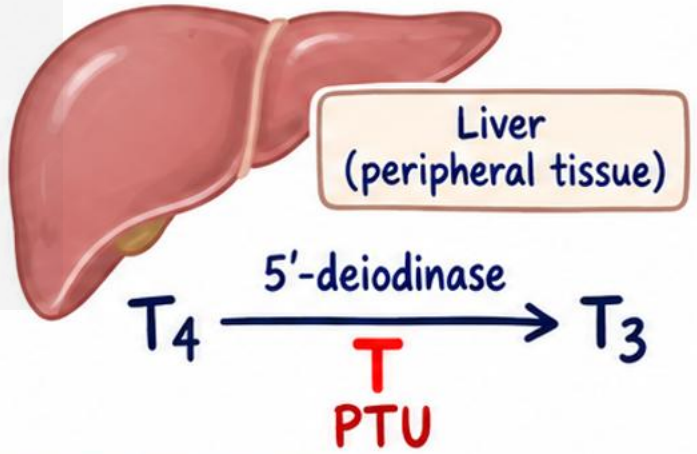
Methimazole and propylthiouracil inhibit thyroid-peroxidase-mediated iodination and coupling.

They reduce NEW hormone synthesis but do not immediately remove stored hormone.



OUTSIDE THE THYROID

PTU also inhibits peripheral T4-to-T3 conversion.
This is not a major methimazole action.



USE

Control of hormone overproduction, especially Graves disease.

LIMITATION

Destructive thyroiditis releases stored hormone; thionamides are generally not effective for that mechanism.

SHARED RISK

Rare agranulocytosis. Fever or sore throat during treatment needs urgent clinical assessment.

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