THYROID HORMONES

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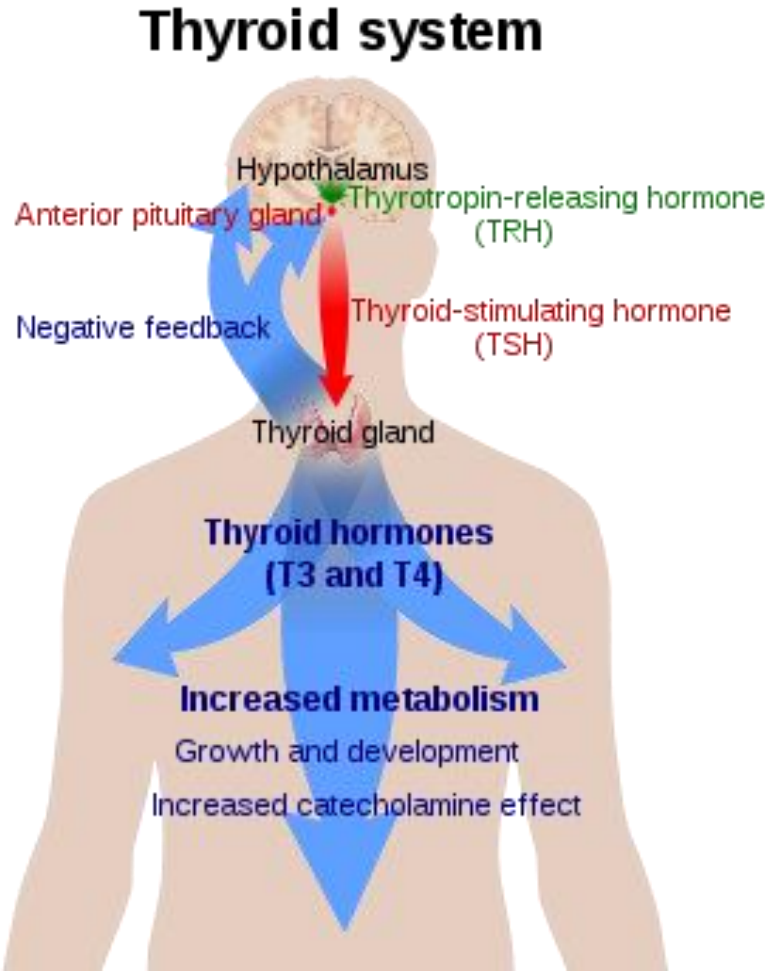
THYROID HORMONES

Regulation & physiological effects



TRIIODOTHYRONINE (T3)

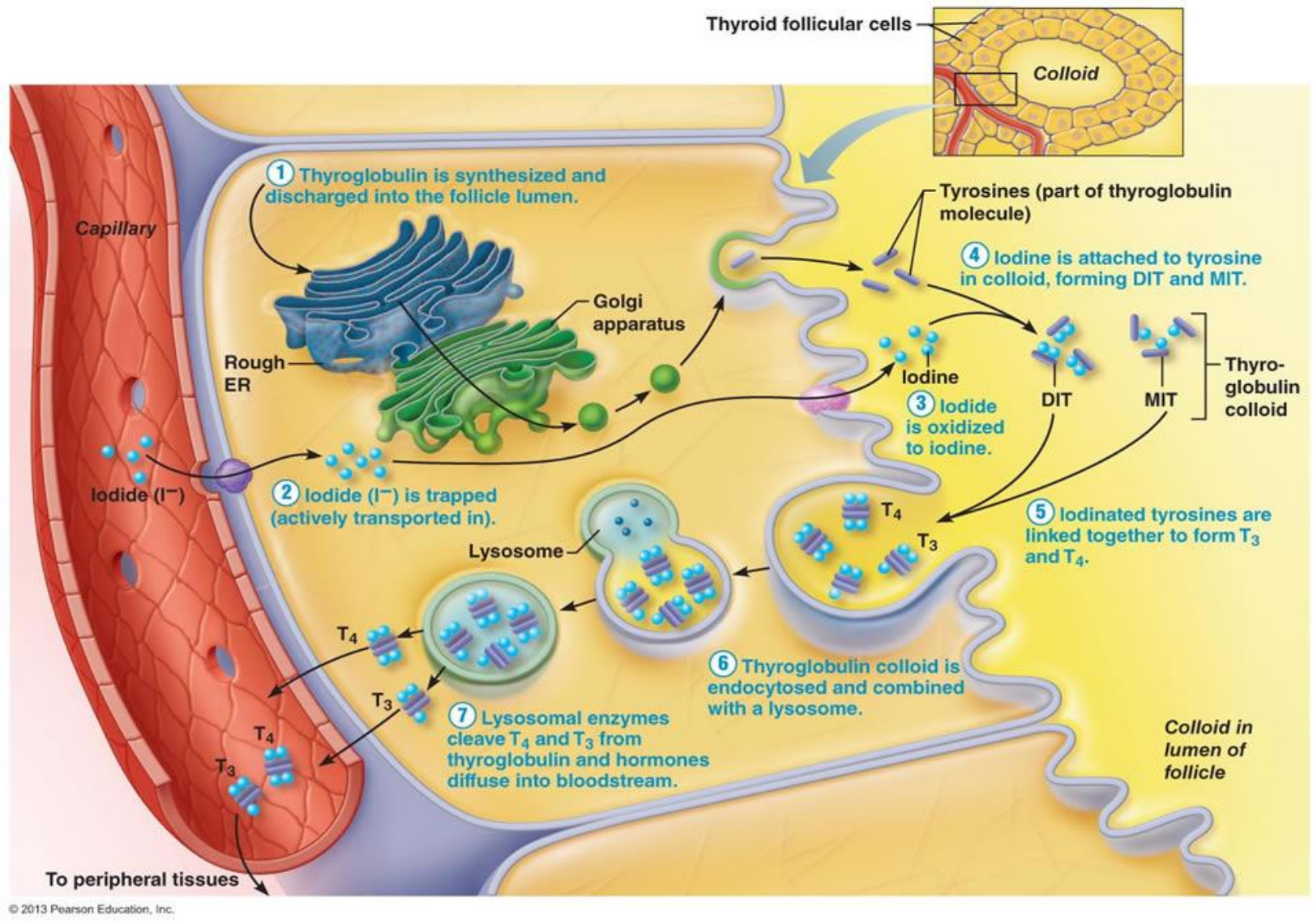
THYROXIN (T4)

1:20 in blood

- influence growth & maturation of the organism
- CNS
- regulation of metabolic activities

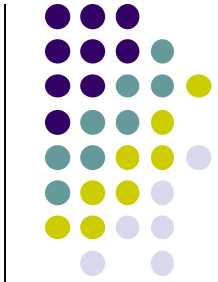
THYROID HORMONES

Thyroxine synthesis



DIT & MIT – di-iodotyrosine & mono-iodotyrosine

HYPOTHYROIDISM



Indications of thyroid hormones:

- **Hypofunction of thyroid gland** (different reasons)

Side effects:

- Each overdose induces the symptoms of hyperthyreosis
- Allergy is very rare
- **Substitution therapy** ⇨ theoreticaly without contraindications

HYPERTHYREOIDISM

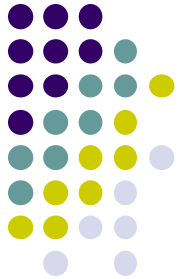
Thyreotoxicosis

- Abundant production of thyroid hormones with subsequent ⇑ of metabolism:

- heat production
- sweating
- nervousness
- tremor
- loss of weight with appetite ⇑

HYPERTHYROIDISM

Therapeutic aims



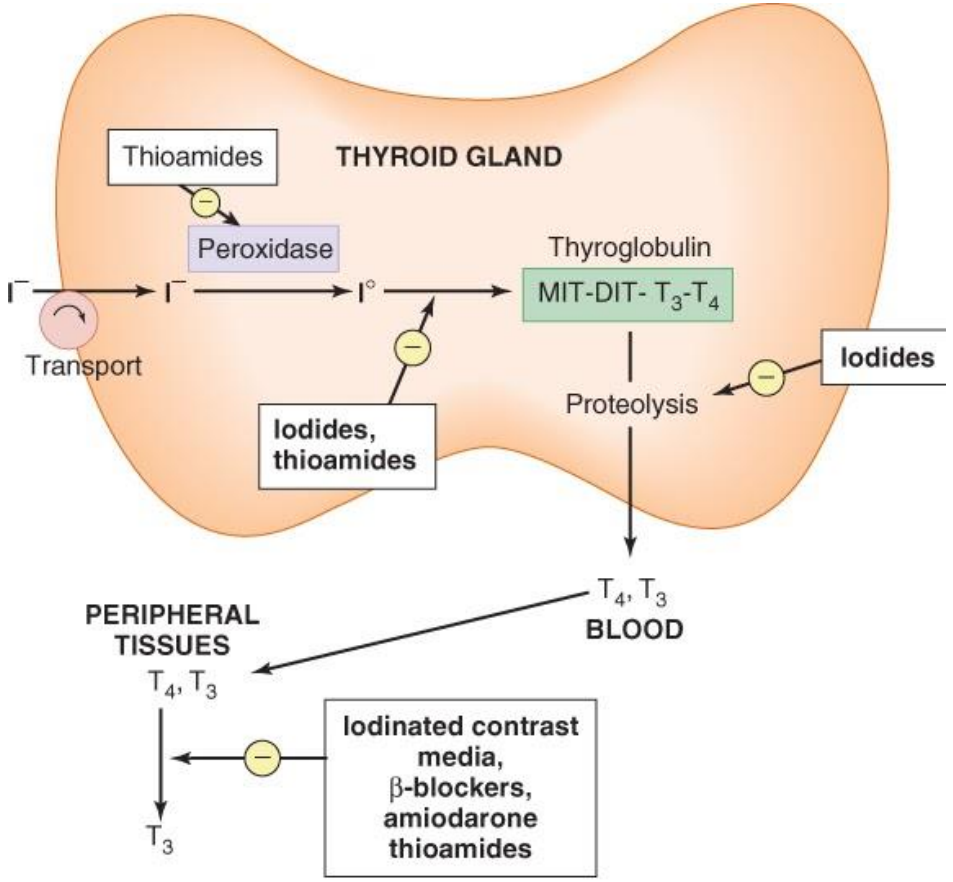
DECREASE SYNTHESIS OR RELEASE OF HORMONE !

- Removal of the part or whole thyroid gland (surgery, radiotherapy)
- **Inhibition of hormone synthesis - *thioamides* *(carbimazol, metimazol, propylthiouracil)***
- **Block of hormone release – *iodides***

ANTITYROID AGENTS

Sites of action

- Iodide ion ⇒ elemental iodine (thyroidal peroxidase)
- Thyroglobulin ⇒ iodinated to:
  - monoiodotyrosine (MIT) or
  - diiodotyrosine (DIT)
- 2 molecules of DIT ⇒ **T4**
- 1 molecule each of MIT & DIT ⇒ **T3**
- Proteolysis of thyroglobulin liberates the T4 & T3
- Transported by thyroxine-binding globulin (from liver)



ANTITYROID AGENTS

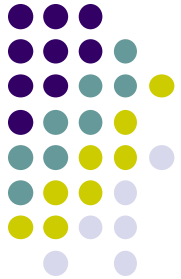
Effect & PK

Carbimazol, metimazol, propylthiouracil

- ⇓ of hormone synthesis after latency
- Rapid absorption after oral application
- Biotransformation in liver, excretion in kidneys
- **High concentration in thyroid gland**
- **Cross placenta** ⇨ block secretion of thyroid hormones in fetal period
- Excreted by breast milk

ANTITYROID AGENTS

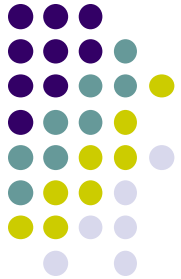
Clinical use



- **They affect all forms of thyroid hormone hypersecretion:**
  - as a short-term treatment in Graves' hyperthyroidism (to prepare for thyroid surgery or radioiodine)
  - as a long-term treatment (approximately 30 % of people with Graves' disease will have a remission after prolonged treatment with antithyroid drugs)
  - to treat hyperthyroidism associated with toxic multinodular goiter or a toxic adenoma ("hot nodule")
  - to treat women with hyperthyroidism during pregnancy

ANTITYROID AGENTS

Mode of use



- ***Methimazole*** is usually preferred over *propylthiouracil* - it reverses hyperthyroidism more quickly & has fewer side effects

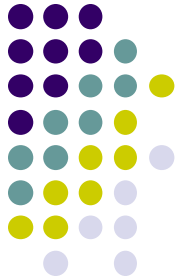
  (it requires an average of 6 weeks to lower T4 levels to normal & is often given before radioactive iodine treatment)

- *Propylthiouracil* does not reverse hyperthyroidism as rapidly as *methimazole* & it has more side effects (because of its potential for **liver damage**, it is used only when *methimazole* or *carbimazole* are not appropriate)

- *Carbimazole* (it is converted into *methimazole* in the body)

ANTITHYROID AGENTS

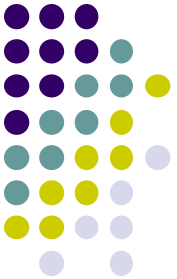
During pregnancy & nursing



- ***Propylthiouracil*** used to be the drug of choice during pregnancy because it has a lower risk of causing birth defects (experts now recommend that *propylthiouracil* be given during the first trimester only - this is because there have been rare cases of liver damage in people taking *propylthiouracil*)
- After the first trimester, women should switch to *methimazole* for the rest of the pregnancy
- For women who are nursing, *methimazole* is probably a better choice than *propylthiouracil* (to avoid liver side effects)

ANTITYROID AGENTS

Minor SE



Minor side effects — up to 15 % of people

- Both *methimazole* & *propylthiouracil* can cause:
  - itching
  - rash
  - hives
  - joint pain & swelling
  - fever
  - changes in taste
  - nausea & vomiting may depend on the dose (spreading large doses out through the day can reduce side effects)

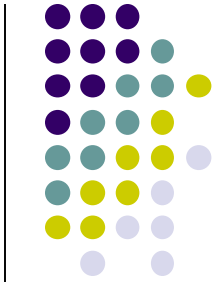
ANTITYROID AGENTS

Major SE

Major side effects are very rare:

- Agranulocytosis (affects only one out of every 200 to 500 people; after discontinuation usually resolves within a week)
- Liver damage (more common with *propylthiouracil)*:
  - typically occurs within 3 months of starting the drug
  - can be serious & potentially life threatening
  - for this reason, *methimazole* is the first choice for treating hyperthyroidism
- Aplastic anemia
- Vasculitis (associated with *propylthiouracil*)

Iodide in thyroid physiology



- The central role of iodide in thyroid physiology is known for many years:

  - the four iodine atoms of thyroxine (T4) constitute 65% of its weight
  - the three iodine atoms of triiodothyronine (T3) constitute 59% of its weight

- Both **iodine deficiency** & **excess** can cause thyroid dysfunction

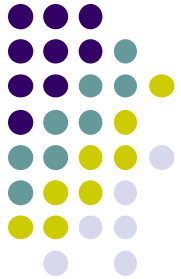
IODIDES

MOA

Lugol´s solution (molecular iodine 5% + potassium iodide 10%):

- **Regulation of activity of transport system, ⇓ thyroid hormones release**
- **Block of synthesis** (Wolff-Chaikoff effect)
- **Inevitable high plasma level of iodine**

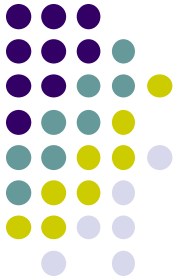
IODIDES
PK



- Iodides are absorbed directly
- Molecular iodine must be reduced to iodide
- Concentrates mainly in thyroid gland & salivary glands
- Crosses placental barrier
- It is excreted in urine

IODIDES

Clinical use

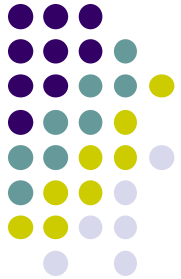


- Patient´s preparation for **subtotal thyroidectomy**

- **Urgent** therapy of the most severe forms of **acute hyperthyroid sypmtoms**

IODIDES

SE



- **Iodine rarely induces SE:**
- hyperproduction of saliva
- metalic taste
- acne
- rhinitis, edema of conjunctiva, allergic reactions
- fetal goiter
- **absolute contraindication is allergy & pregnancy**

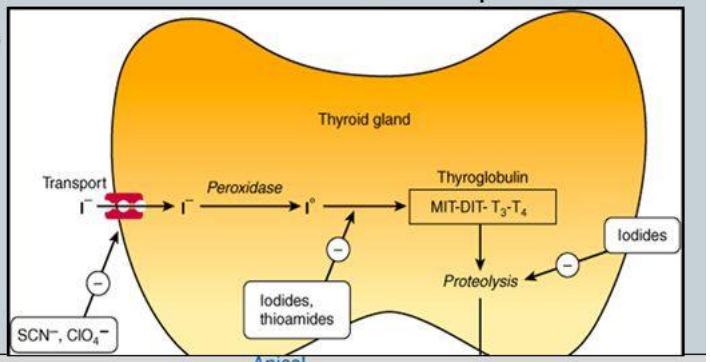
Man with bilobular goiter

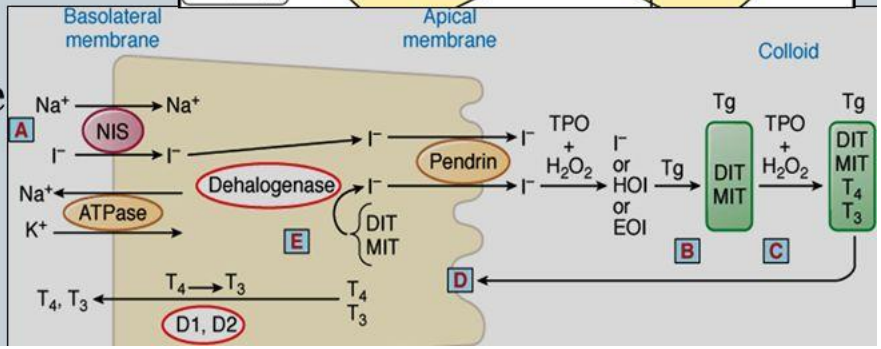
Copy out of *Jusepe de Ribera, Prints and Drawings* Jonathan Brown. Princeton: Trustees of Princeton University, 1973: 182

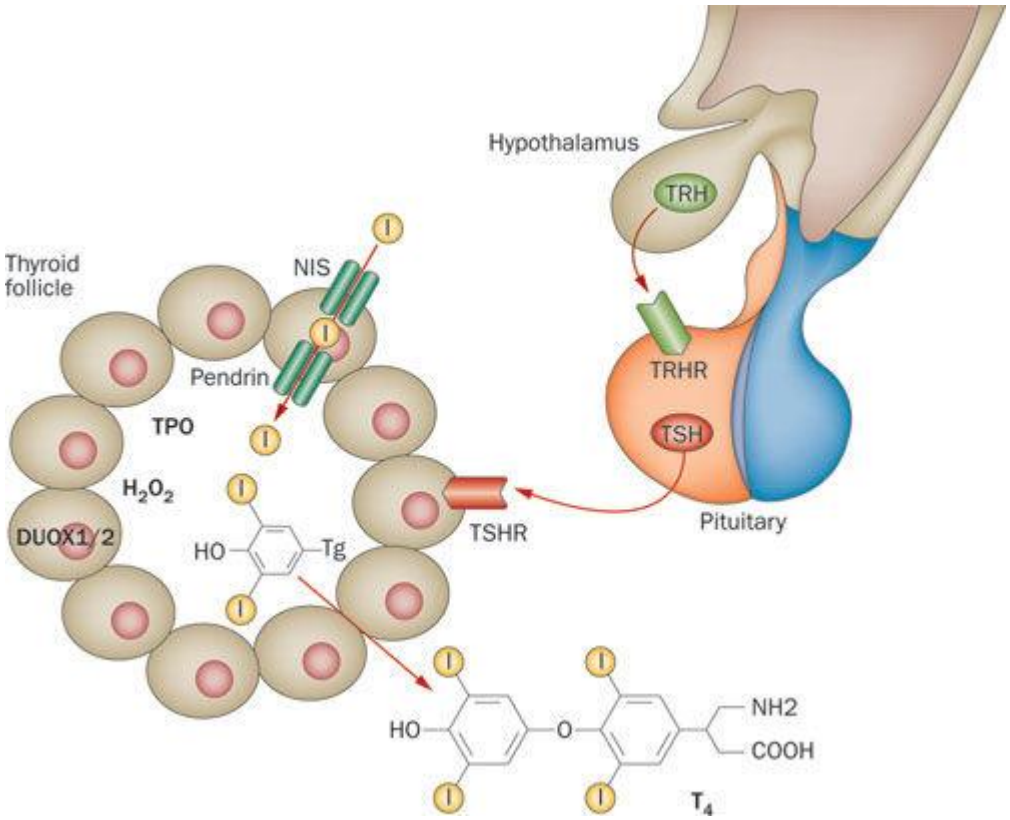
Biosynthesis of Thyroid Hormones

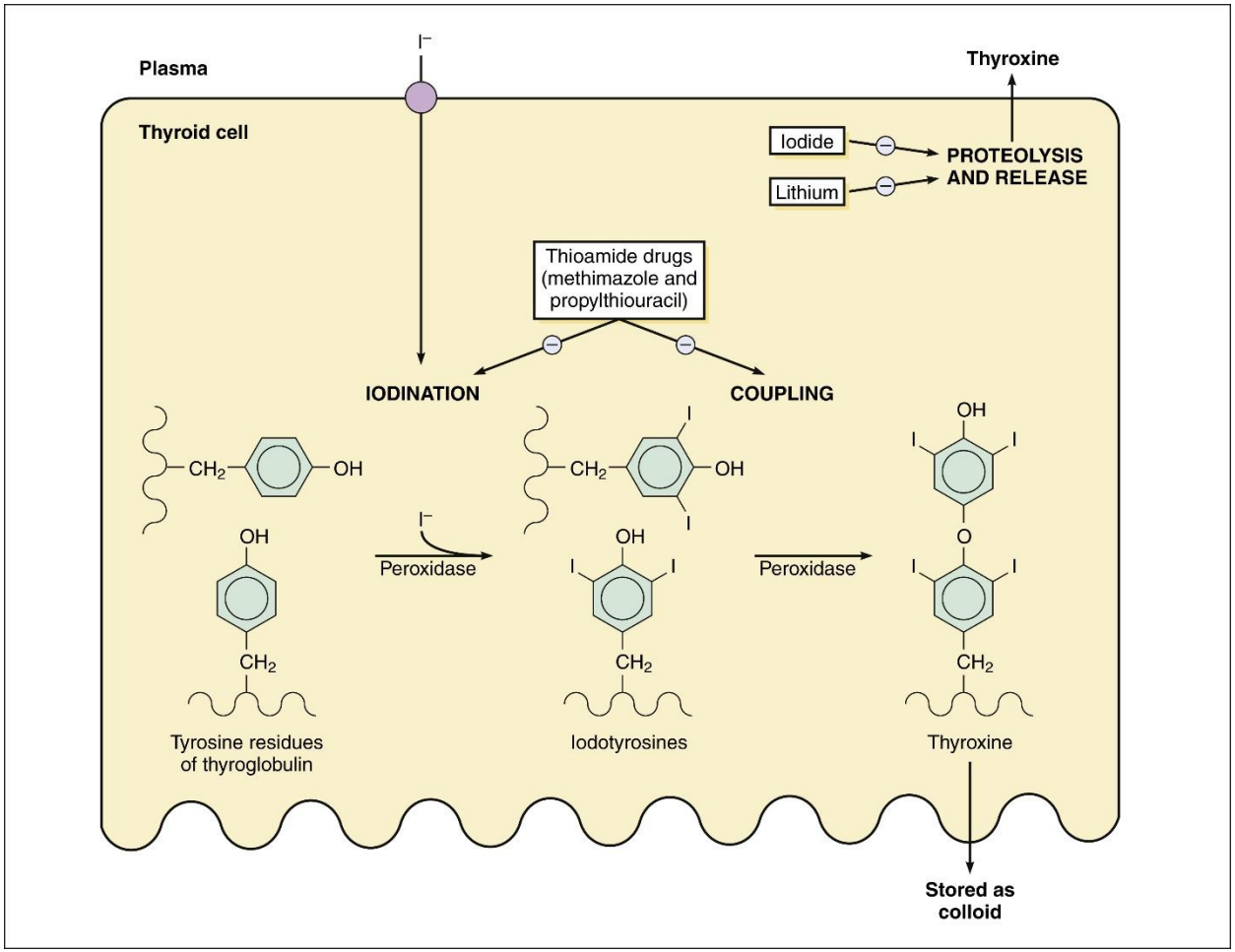
1. **Transport of iodide** into thyroid gland by **Na^+/I^- symporter** ► can be inhibited by anions as **thiocyanate** (SCN^-), **pertechnetate** (TcO_4^-), and **perchlorate** (ClO_4^-).

At the apical cell membrane a second I^- transport enzyme called **pendrin** controls flow of iodide across membrane






Hypothalamus
TRH
TRHR
TSH
Pituitary
Thyroid follicle
NIS
Pendrin
TPO
H_2O_2
DUOX1/2
TSHR
HO
Tg
HO
O
NH2
COOH
T_4


Plasma
I⁻
Thyroxine
Thyroid cell
Iodide
Lithium
PROTEOLYSIS AND RELEASE
Thioamide drugs (methimazole and propylthiouracil)
IODINATION
COUPLING
CH2
OH
I⁻
Peroxidase
Peroxidase
O
Tyrosine residues of thyroglobulin
Iodotyrosines
Thyroxine
Stored as colloid