Thyroid Hormones 1

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Thyroid Hormones

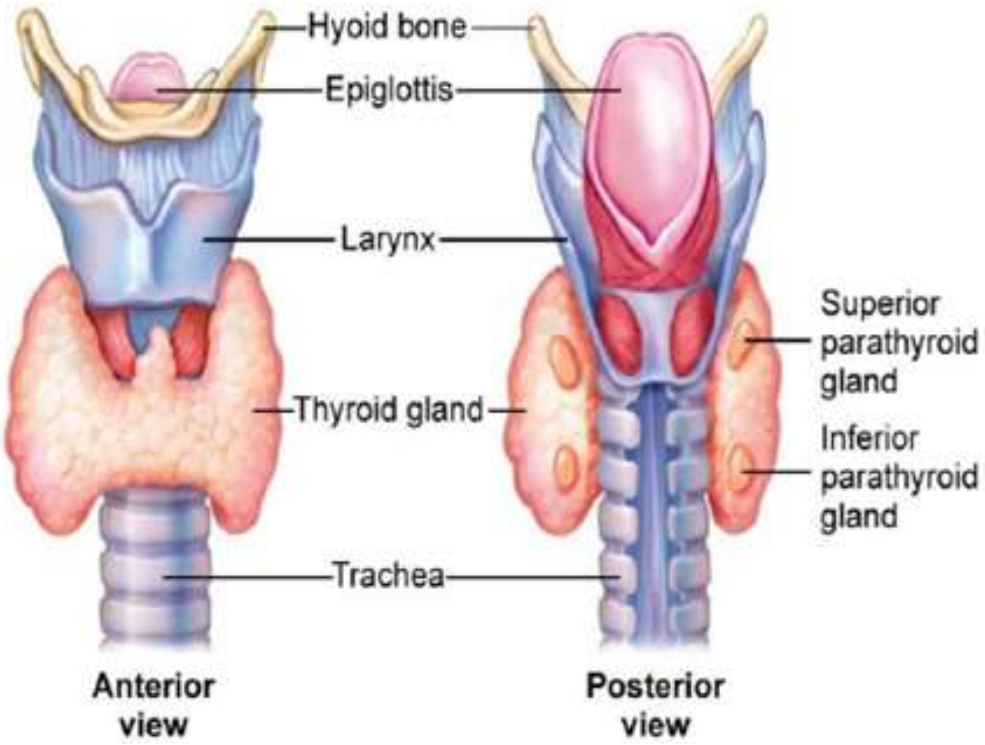
- Thyroid hormones are essential for normal growth and maturation. Therefore, thyroid hormones are major anabolic hormones.

- Thyroid gland synthesizes two kinds of hormones:

1. **Iodine containing hormones**
2. **Calcitonin**

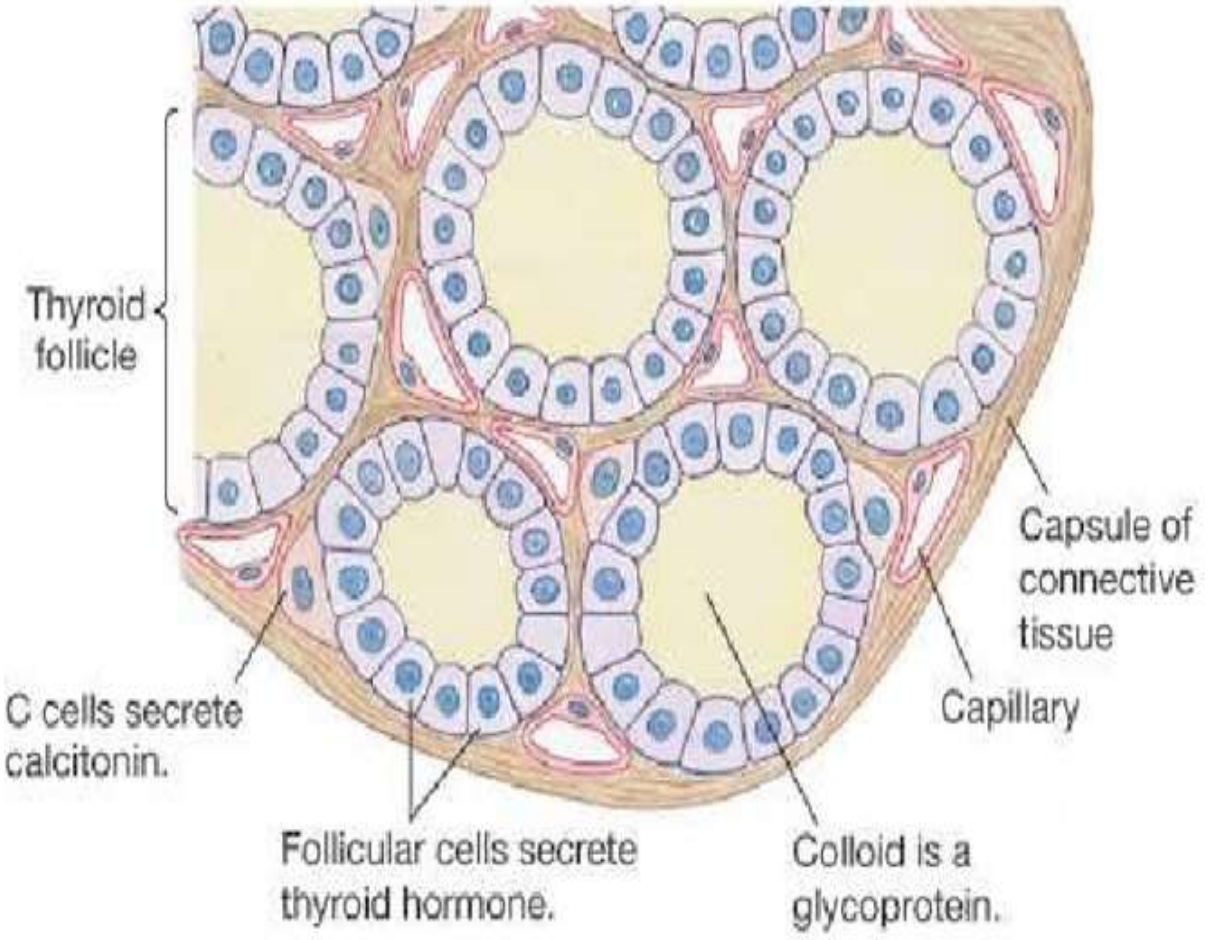
Thyroid Gland

- Largest endocrine gland
- Consists of two lobes one on each side of trachea connected by isthmus



Thyroid Gland

- The functional unit of the thyroid gland is the follicle.
- The lumen is filled with colloid, which consist mainly of a glycoprotein called thyroglobulin.
- Surrounding the lumen are the follicle cells, which function to both synthesize and release thyroglobulin.



Hormones of thyroid gland

1. **Iodine containing Hormones:**
   - **Thyroxine**
   - **Triiodthyronine**
     - Thyroid hormones are unique requiring iodine

2. **Calcitonin** - peptide

Biosynthesis of thyroid hormone

- Two raw materials (substrates) required by thyroid gland to synthesize the thyroid hormones
  - Thyroglobulin
  - Iodine

Thyroglobulin

1. Glycoprotein
   a. Protein (90%)
   b. CHO (8 -10%)
      - The carbohydrates are:
        – N-acetyl glucosamine, mannose, glucose, galactose, fucose and sialic acid.
2. Iodide is 0.2 – 1%

Thyroglobulin

1. Glycoprotein
   a. Protein (90%)
   - It consists of two monomeric chains
   - Each chain has:
     – 2750 amino acids (2750×2 =5500)
     – 50 – 60 tyrosine residues
   - About 20% of the tyrosine residues are subject to iodination (spatially oriented)
     – 20% of 50 = 10
   b. CHO (8 -10%)
2. Iodide is 0.2 – 1%

MCQ

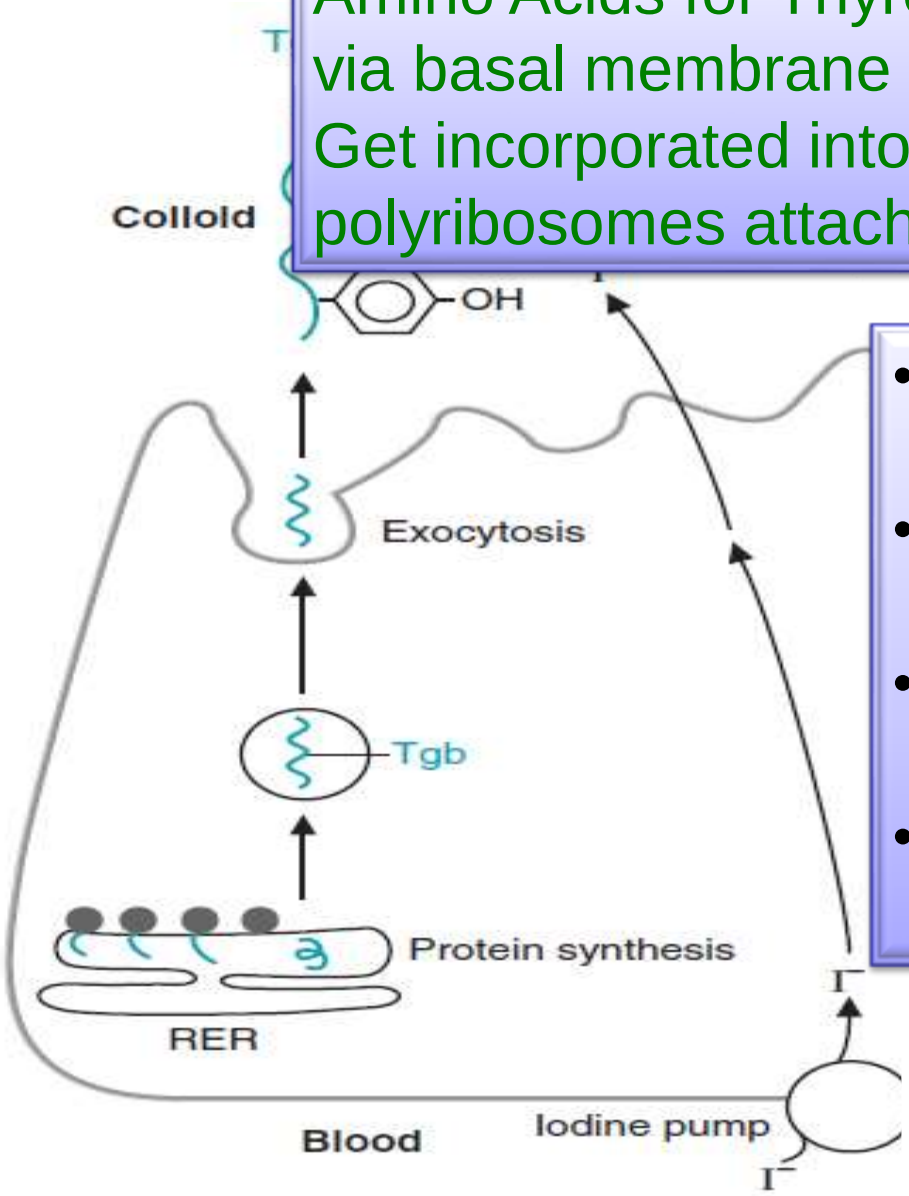
- How many T3 or T4 molecules will be synthesized from one thyrogloglobulin molecule.

  a. 05
  b. 10
  c. 15
  d. 20
  e. 25

Synthesis of Thyroglobulin

Amino Acids for Thyroglobulin synthesis enter the cell via basal membrane

Get incorporated into nascent thyroglobulin by polyribosomes attached to RER.



- Glycosylation starts in RER & completed in Golgi apparatus.
- Several weeks supply exists in normal thyroid gland.
- Thyroglobulin enters the lumen of follicle by exocytosis
- Where iodination of its tyrosine residues occur

Iodine

- Sources:
  - Vegetables and fruits grown in sea-shore
  - Sea fishes are rich in iodine.
- A small amount enters the atmosphere and, through rain, enters ground water and soil near the sea.
- Vegetables and fruits grown in hilly regions lack iodine (for people residing in hilly regions, table salt should be iodinated)
- Fortifying table salt with iodide (typically 70 mcg/g) helps ensure adequate intake (150 mcg/day).

Iodine

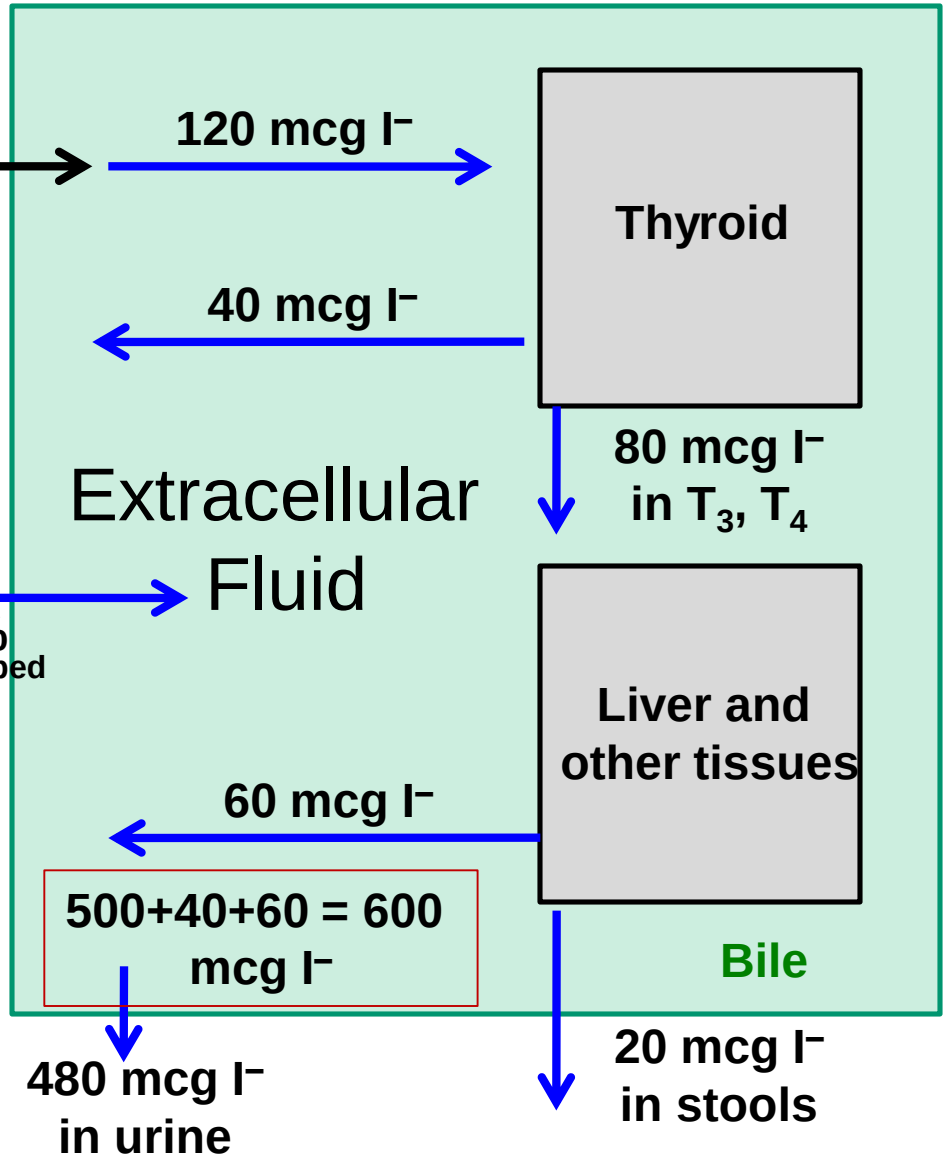
- Ingested dietary iodine is converted to iodide and absorbed from the gut.
- About 2/3 (40-80%) of the ingested iodide is excreted by the kidneys, the remaining 1/3 is taken up by the thyroid glands for synthesis of thyroid hormones.
- In the kidneys, 97 per cent of the filtered iodide is reabsorbed

Iodine and thyroid hormones

- Dietary intake of about 500 µg per day is typical, mainly in the form of iodide (I–) or iodine (I).
- To maintain normal thyroid hormone secretion, 150 µg is the minimal intake necessary.

- The total amount of I– entering the ECF is thus 500 + 40 + 60,or 600µg/d.

- 20% of this I–enters the thyroid,
- 80% is excreted in the urine.



Chronic toxicity of Iodine

- The relation of thyroid function to iodide is unique.
- iodide is essential for normal thyroid function, but iodide deficiency and iodide excess both inhibit thyroid function.

Chronic toxicity of Iodine

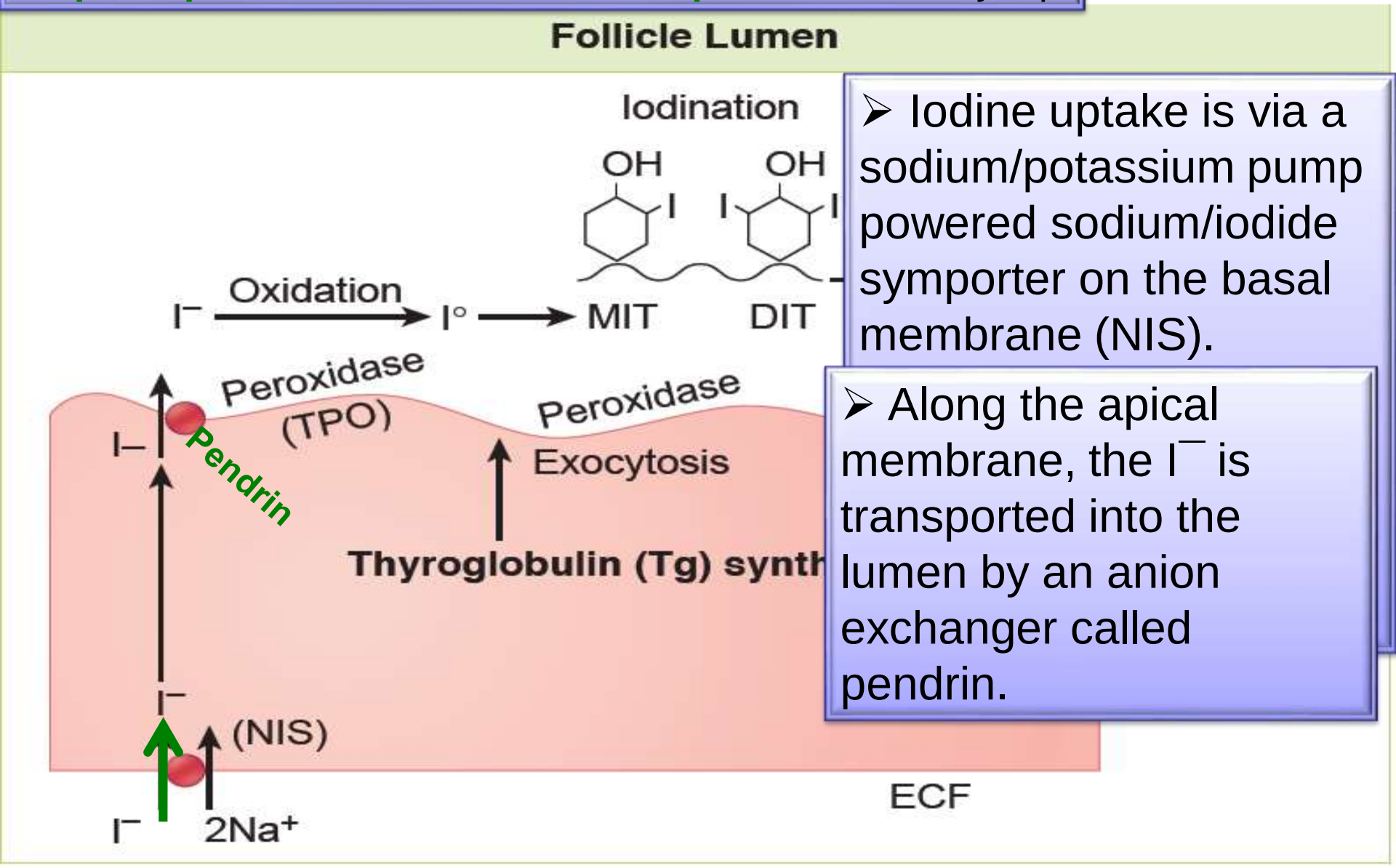
- May develop when intake is > 1.1 mg/day.
  - Most people who ingest excess amounts of iodine remain euthyroid.
- Some people who ingest excess amounts of iodine, particularly those who were previously deficient, develop hyperthyroidism (Jod-Basedow phenomenon).
- Paradoxically, excess uptake of iodine by the thyroid may inhibit thyroid hormone synthesis (called Wolff-Chaikoff effect).
  - Thus, iodine toxicity can eventually cause iodide goiter, hypothyroidism, or myxedema.

Biosynthesis of thyroid hormone; Steps

1. Uptake of iodide
2. Oxidation of iodide
3. Iodination of tyrosine
4. Coupling
5. Storage

Biosynthesis of thyroid hormone; Steps

Step-1: Uptake of iodide or Iodide trap; one way trip

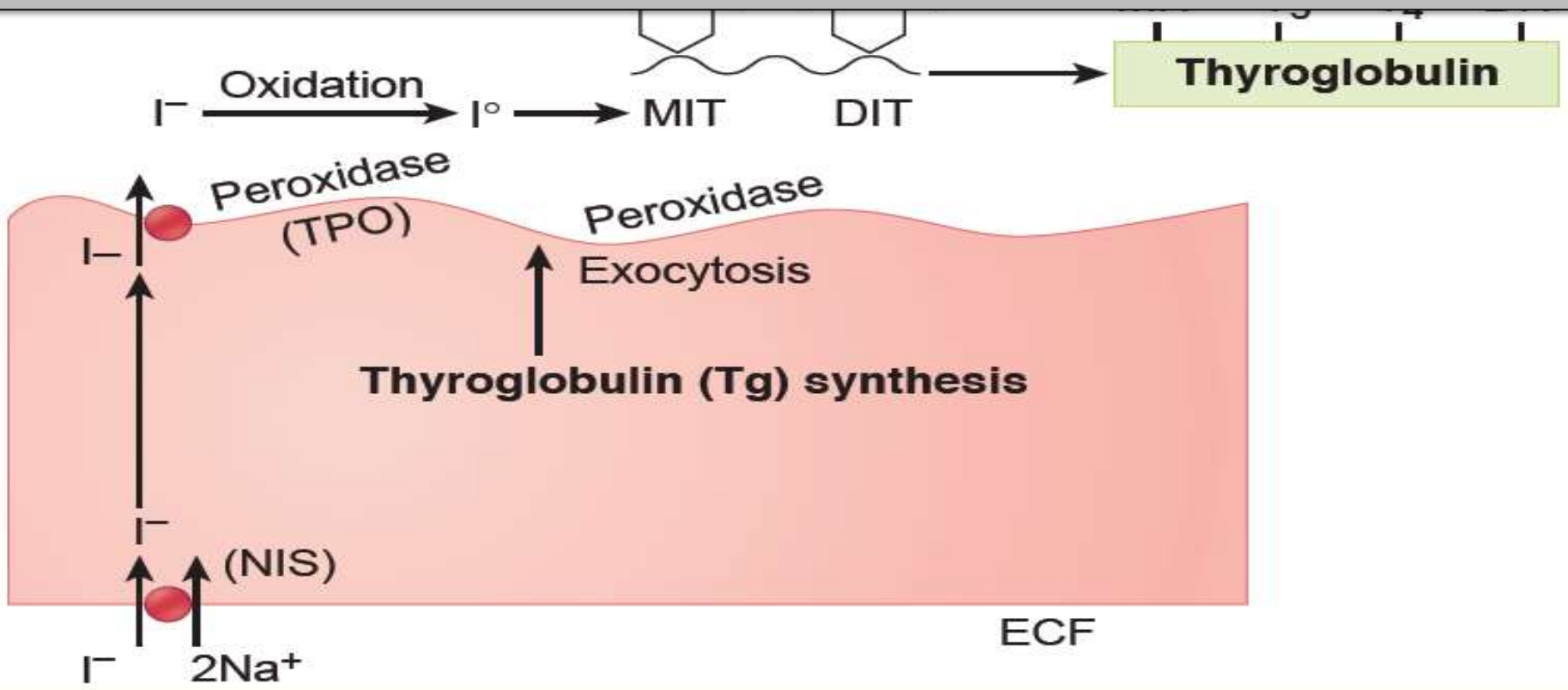


- Iodine uptake is via a sodium/potassium pump powered sodium/iodide symporter on the basal membrane (NIS).
- Along the apical membrane, the I^- is transported into the lumen by an anion exchanger called pendrin.

Step-2: Oxidation of iodide; Needs H_2O_2

Iodide in the follicular lumen is oxidized at the apical membrane by thyroperoxidase (TPO) using H_2O_2 as the other substrate.

H_2O_2 is generated at the apical surface of the thyrocytes by the dual oxidases DUOX1 and DUOX2.



Dual Oxidases: DUOX1 and DUOX2

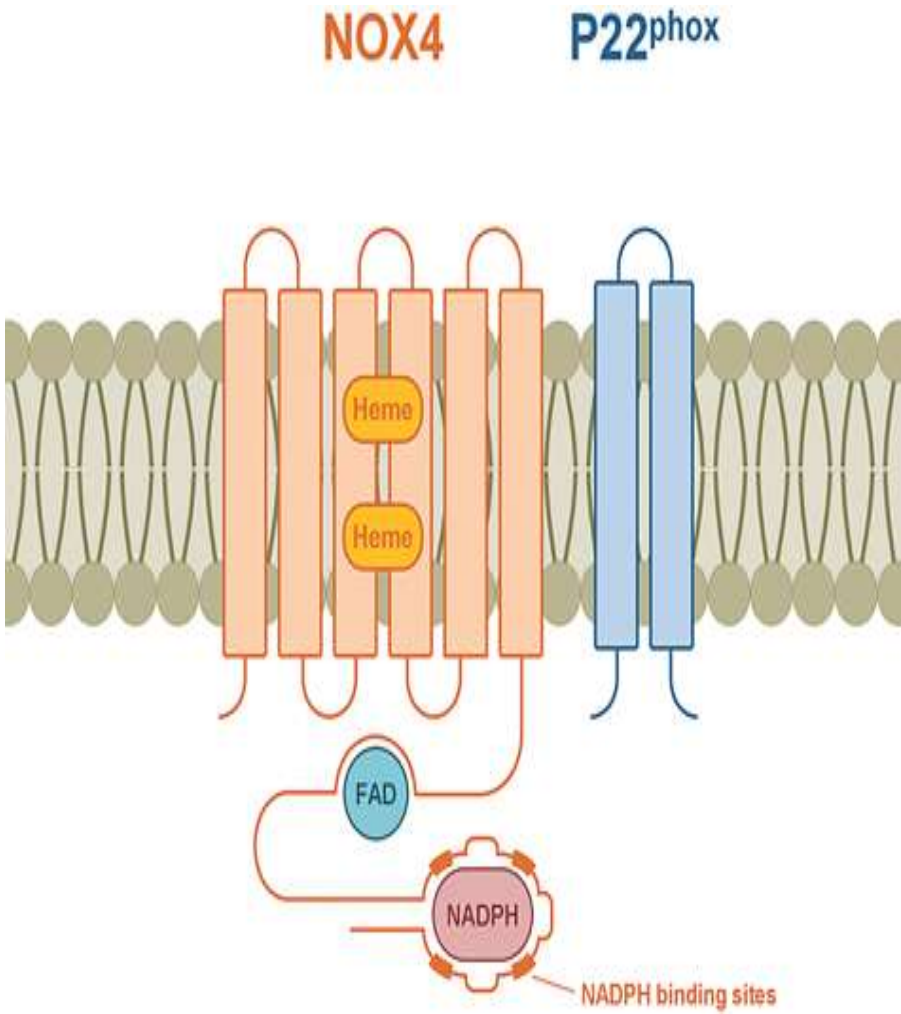
- These enzymes are members of the NADPH oxidase (NOX) family of oxidoreductase enzymes

Dual Oxidases

- The NOX family is composed of seven members:
- five NOXes
  - (NOX1, NOX2, NOX3, NOX4, and NOX5)
- and two DUOXes
  - (DUOX1 and DUOX2).

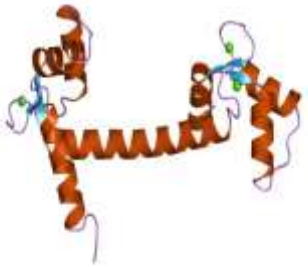
NOXes

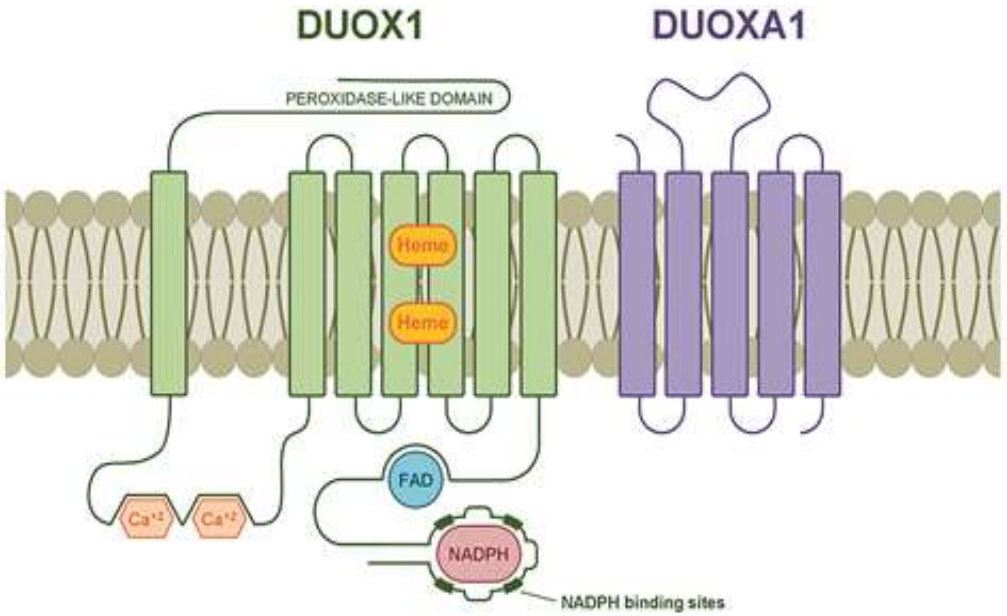
- All NOX family members have six transmembrane domains containing:
  - the two heme-binding regions,
  - and a long cytoplasmic C-terminus that contains the FAD and the NADPH-binding regions

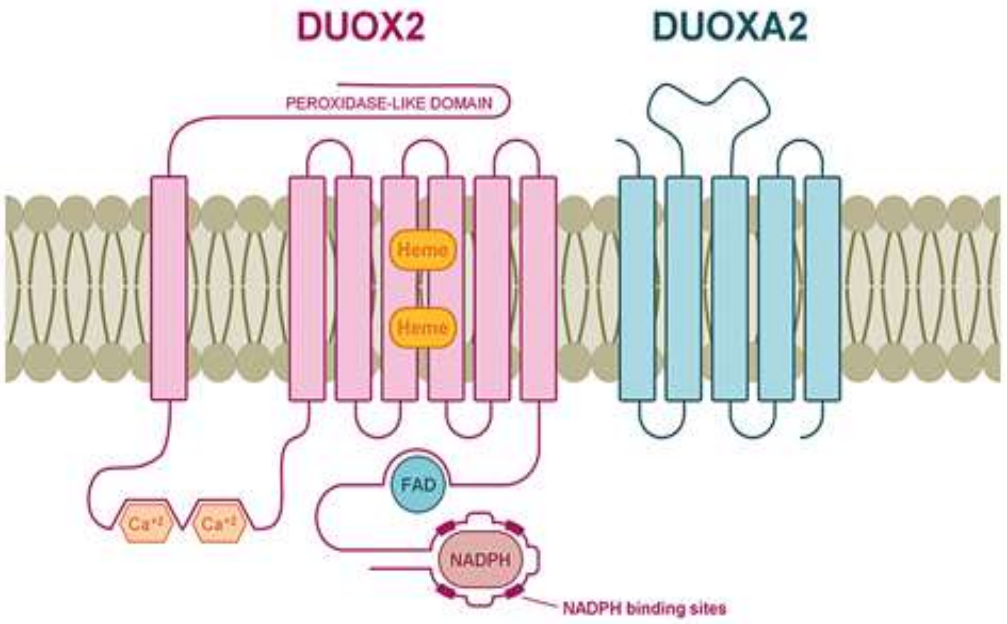


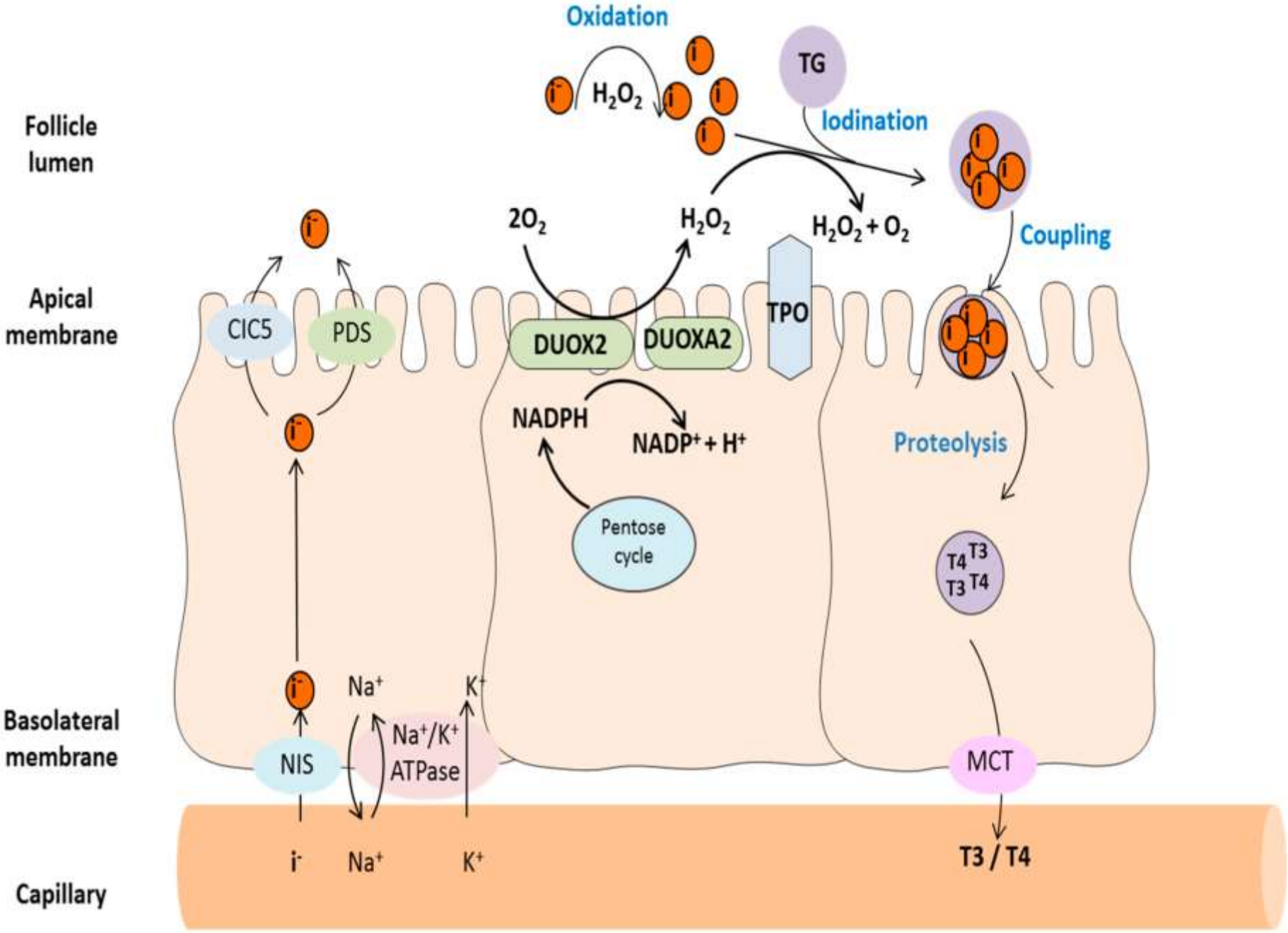
DUOXes

- The extracellular peroxidase-like domain
- intracellular calcium-binding EF-hand motifs

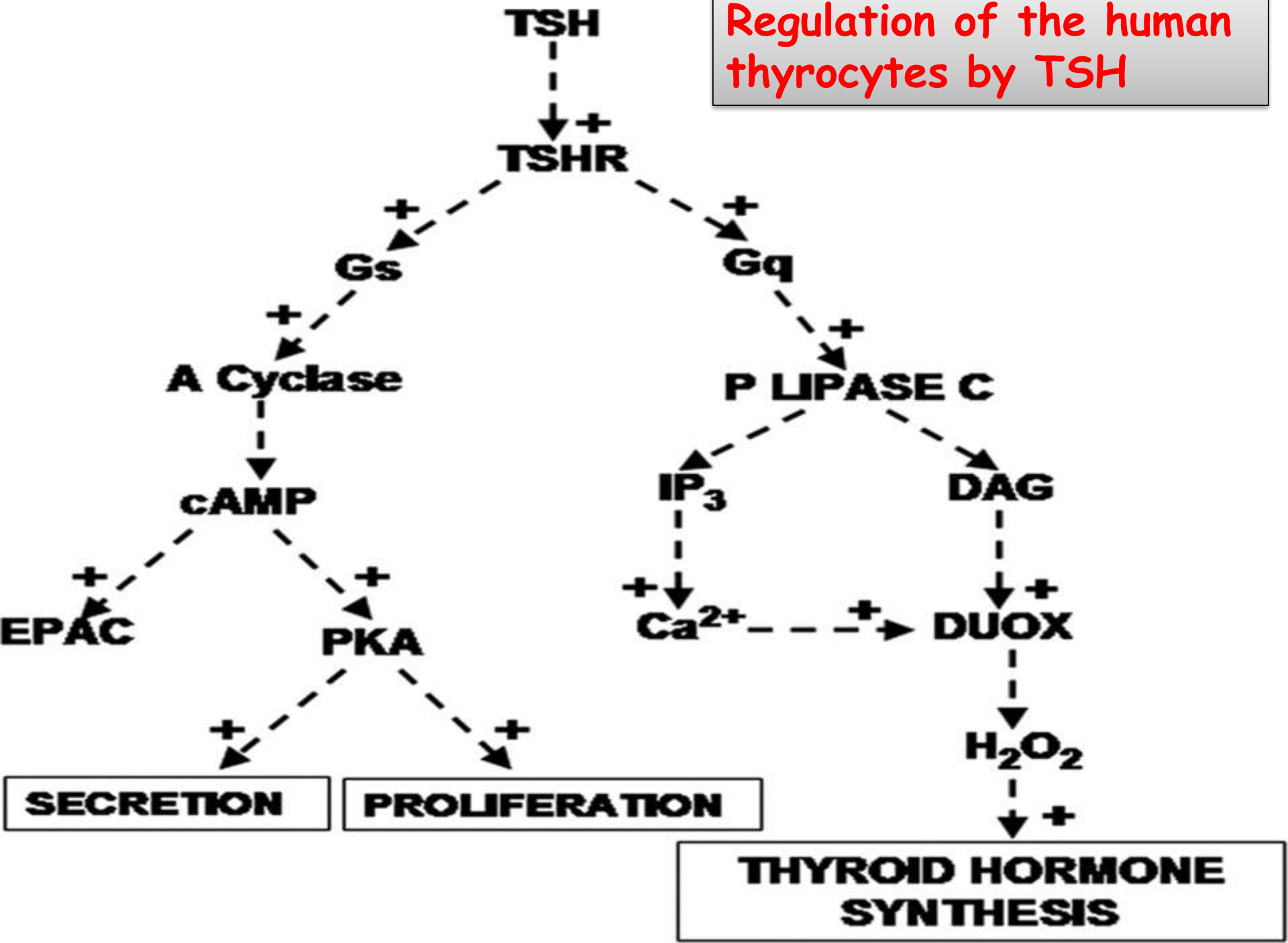




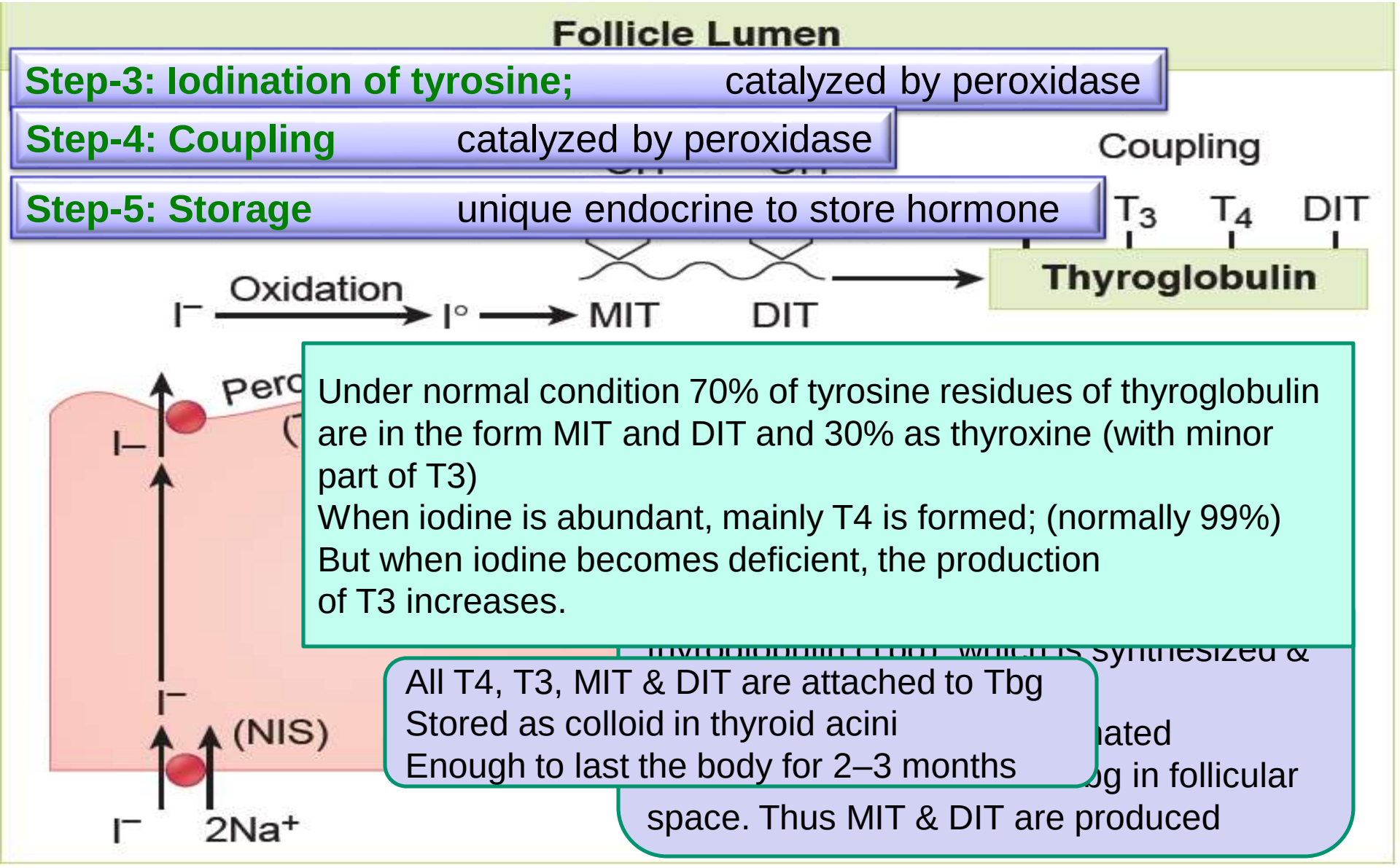



Oxidation
TG
Iodination
Follicle lumen
H_2O_2
$2O_2$
H_2O_2
$H_2O_2 + O_2$
Coupling
Apical membrane
CIC5
PDS
DUOX2
DUOXA2
TPO
NADPH
$NADP^+ + H^+$
Proteolysis
Pentose cycle
$T_4^{T_3}$
$T_3^{T_4}$
Basolateral membrane
Na^+
K^+
Na^+/K^+ ATPase
NIS
MCT
i^-
Na^+
K^+
T3 / T4
Capillary

Regulation of the human thyrocytes by TSH



Biosynthesis of thyroid hormone; Steps

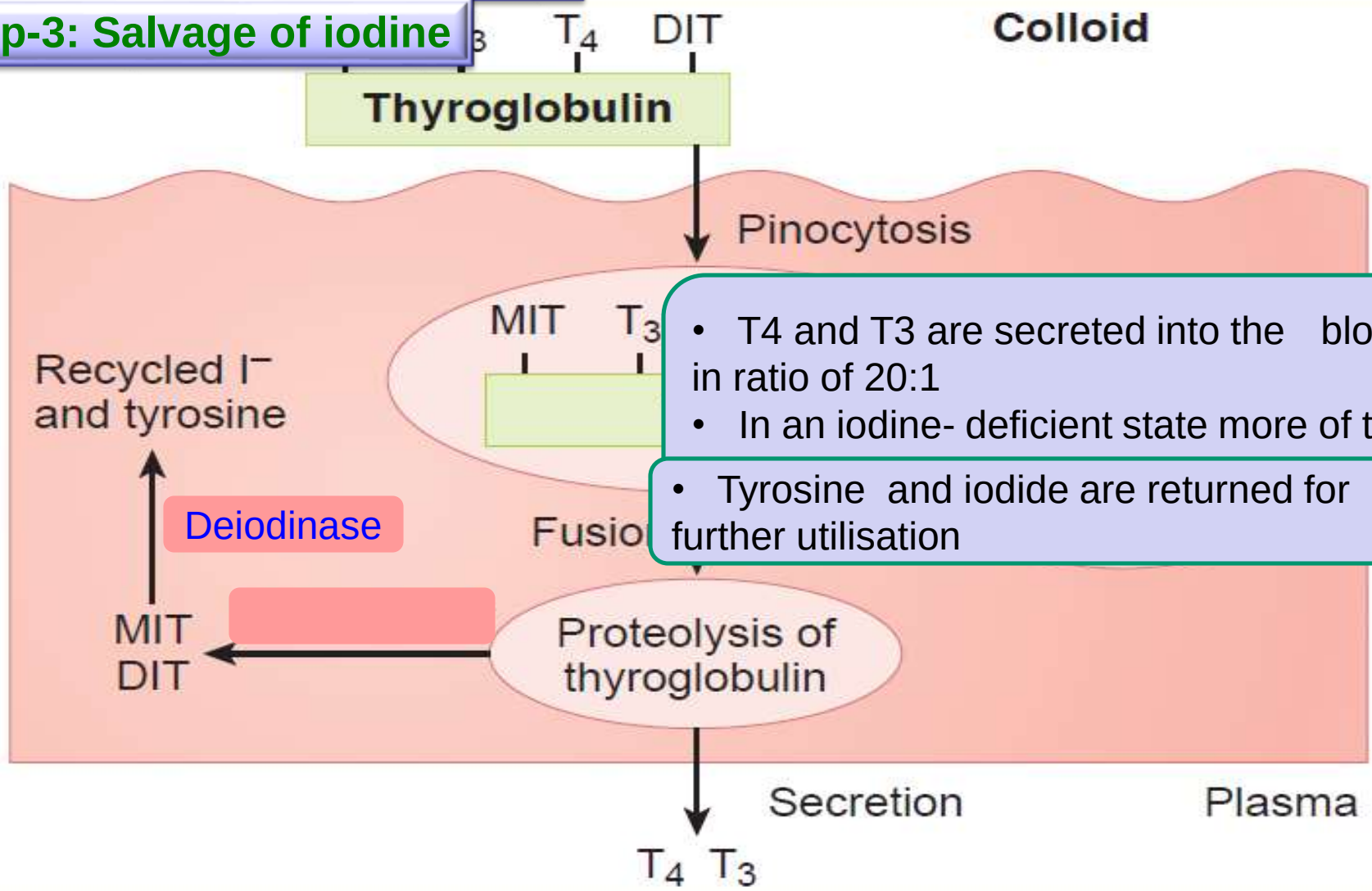


Secretion of Thyroid Hormone; Steps

Step-1: Utilization On need, From colloid to cell, By pinocytosis

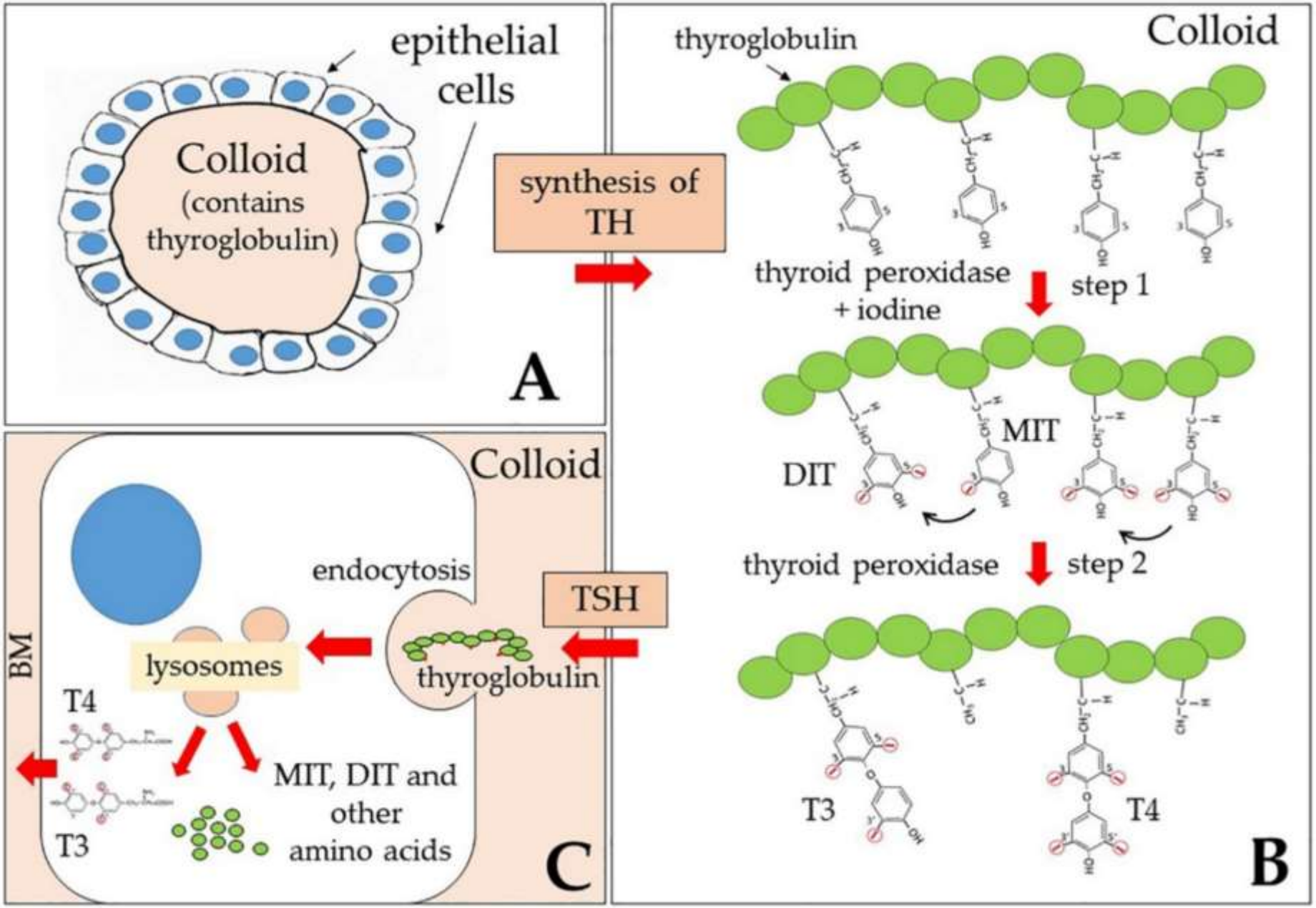
Step-2: Release of T4 & T3

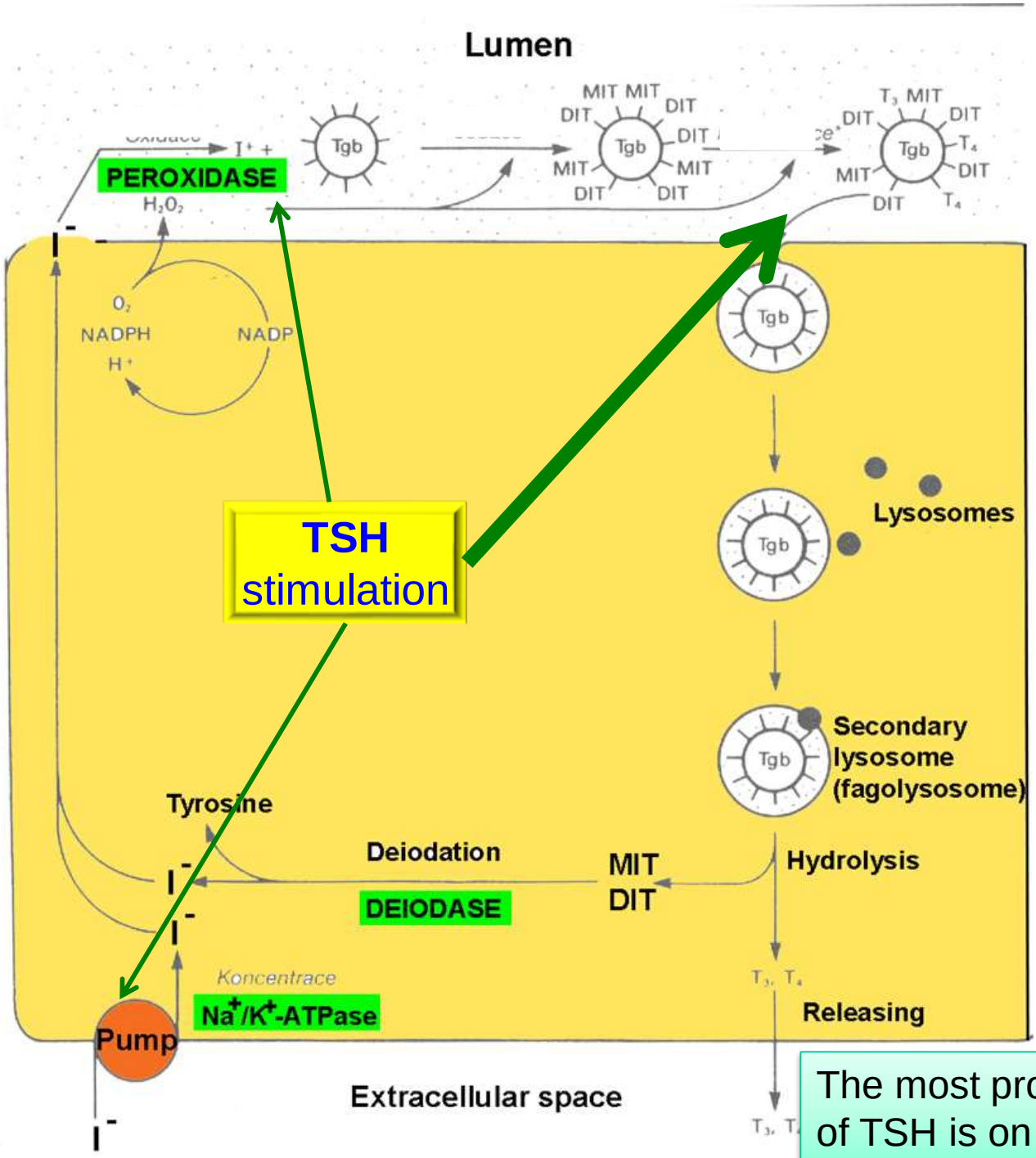
Step-3: Salvage of iodine



- T4 and T3 are secreted into the blood in ratio of 20:1
- In an iodine- deficient state more of the
- Tyrosine and iodide are returned for further utilisation

Release of T4 & T3





The most prominent function of TSH is on pinocytosis

Clinical significance

- While most thyroglobulin stays in the thyroid, a small amount leaks out into the bloodstream. Levels in the blood are directly proportional to the size of the thyroid. For example, thyroid cancer cells enlarge the gland and make thyroglobulin in high amounts.
- Normal levels of Tg
- 1.40 – 29.2 ng/mL (µg/L) for men
- 1.50 – 38.5 ng/mL for women

Tgb as Tumour marker

- Following thyroidectomy, it may take many weeks before thyroglobulin levels become undetectable. Thyroglobulin levels may be tested regularly for a few weeks or months following the removal of the thyroid.[9] After thyroglobulin levels become undetectable (following thyroidectomy), levels can be serially monitored in follow-up of patients with papillary or follicular thyroid carcinoma.

Tgb as Tumour marker

- A subsequent elevation of the thyroglobulin level is an indication of recurrence of papillary or follicular thyroid carcinoma. In other words, a rise in thyroglobulin levels in the blood may be a sign that thyroid cancer cells are growing and/or the cancer is spreading.[9] Hence, thyroglobulin levels in the blood are mainly used as a tumor marker[10][9] for certain kinds of thyroid cancer (particularly papillary or follicular thyroid cancer).