Thyroid

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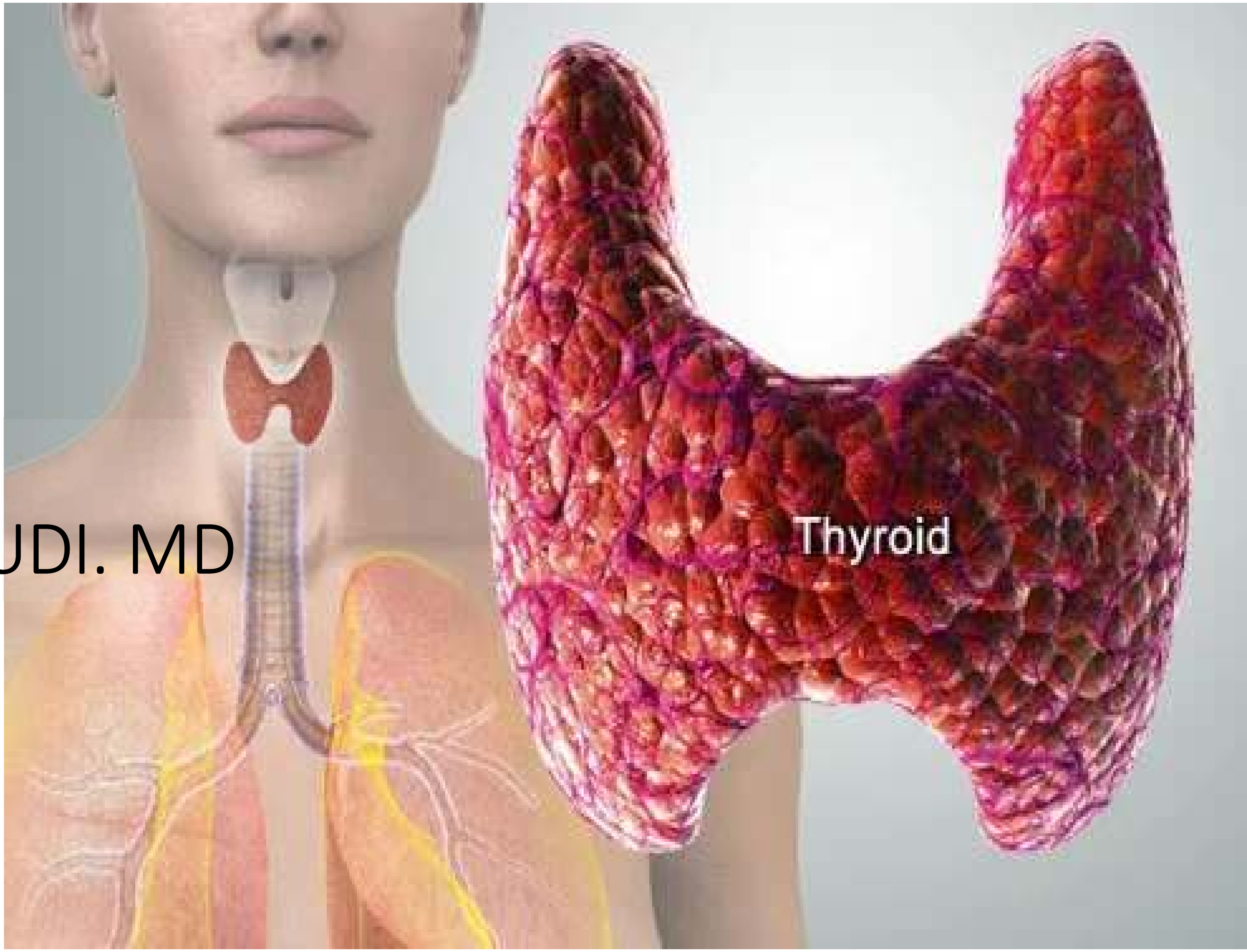


What Does Thyroid Hormone Do?

- **Quick answer: increase growth and metabolism.**
- **More detailed answer:**
  - stimulate mitochondrial protein synthesis
  - increase absorption of carbohydrates
  - regulate fat metabolism
  - promote cell growth.
- **Bottom line: it increases basal metabolic rate and revs up most bodily functions** (increases heart rate, raises body temperature, increases nervous reactivity, increases GI motility…the list goes on).

Iodine Metabolism

i. Daily requirement of iodine is 150–200 mg/day.

- **Its** sources are drinking water, fish, cereals, vegetables and iodinated salt.

ii. Total body contains 25–30 mg of iodine.

- **All cells do contain iodine**
- **but 80% of the total is stored in the thyroid gland.**
- **Iodine level in blood is 5–10 µg/dL.**

iii. In most parts of the world, iodine is a scarce component of the soil.

- Upper regions of mountains generally contain less iodine.
- Such areas are called **goitrous belts, e.g. Himalayan region.**

i v. Commercial source of iodine is seaweeds.

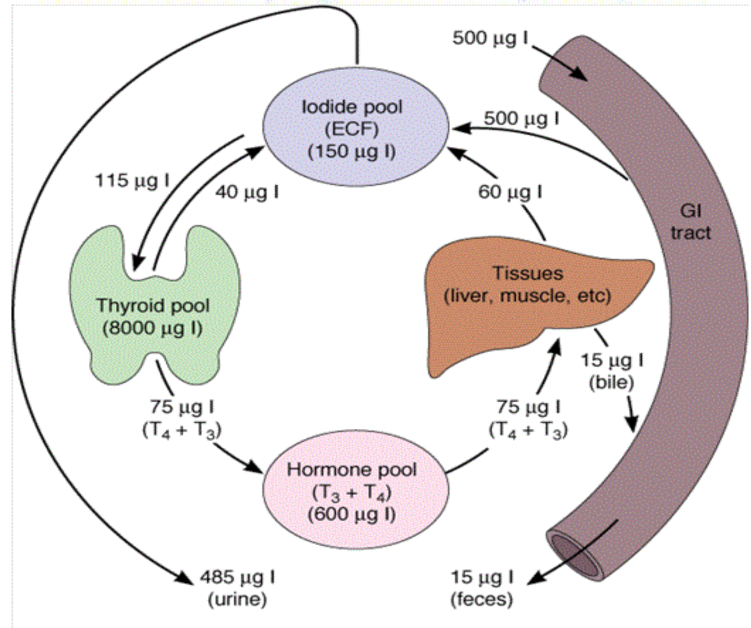
The program of iodination of common salt has resulted in increased availability of iodine.

v. Ingredients in foodstuffs, which prevent utilization of iodine are called **goitrogens.**

- **Goitrogens are seen in cassava, maize, millet, bamboo shoots, sweet potatoes and beans.**
- **Cabbage and tapioca contain thiocyanate**, **which inhibits iodine uptake by thyroid**.
- Mustard seed contains **thiourea, which inhibits iodination of** thyroglobulin.

vi. The only biological role of iodine is in formation of thyroid hormones, thyroxine (T4) and tri-iodo thyronine (T3).

- **Iodine is absorbed from upper small intestine.**
- **Iodine is transported in plasma by loosely binding to plasma proteins.**
- **Iodine absorption also occurs through skin & lungs.**
- **80% of body's iodine is stored in the organic form as iodothyroglobulin in thyroid gland.**



Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

Thyroid Hormones

- **Thyroxine (T4) and Triiodothyronine (T3)-**
  - increases rate of energy release from carbohydrates
  - increases rate of protein synthesis
  - accelerates growth
  - stimulates activity in the nervous system
  - **controlled by TSH**
- **Calcitonin-**
  - **lowers blood calcium and phosphate ion concentrations by inhibiting release of calcium and phosphate from bones**
  - increases rate at which calcium and phosphate are deposited in bones

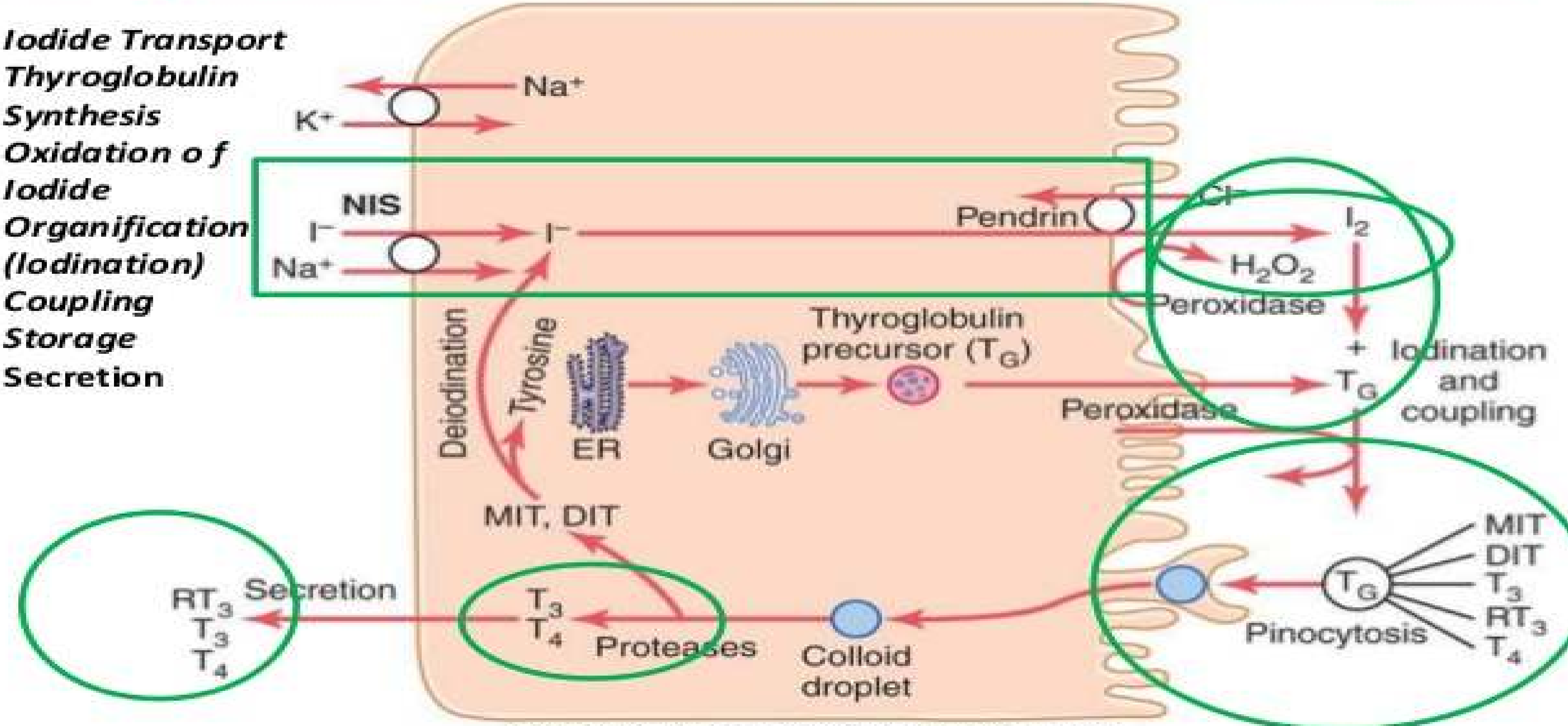
Thyroid Gland

- Follicular cells synthesize **thyroglobulin** (a protein backbone) and secrete it into the colloid.
- Follicular cells take up iodide from the blood and attach it to tyrosine residues on thyroglobulin, forming T3 and T4 (thyroid hormones), which stay attached to thyroglobulin until needed.
- When stimulated by TSH, follicular cells eat a bit of colloid, digest it in a vesicle, cleave off the T3 and T4 and release it into the blood.

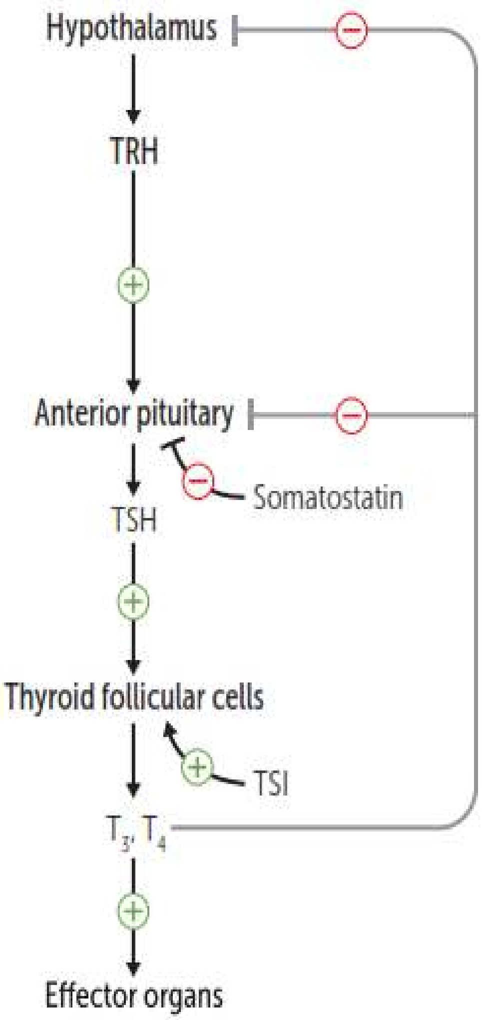
There are two groups of hormones derived from the amino acid tyrosine: Thyroid hormones are basically a "double" tyrosine with the critical incorporation of 3 or 4 iodine atoms. Catecholamines include epinephrine and norepinephrine, which are used as both hormones and neurotransmitters.

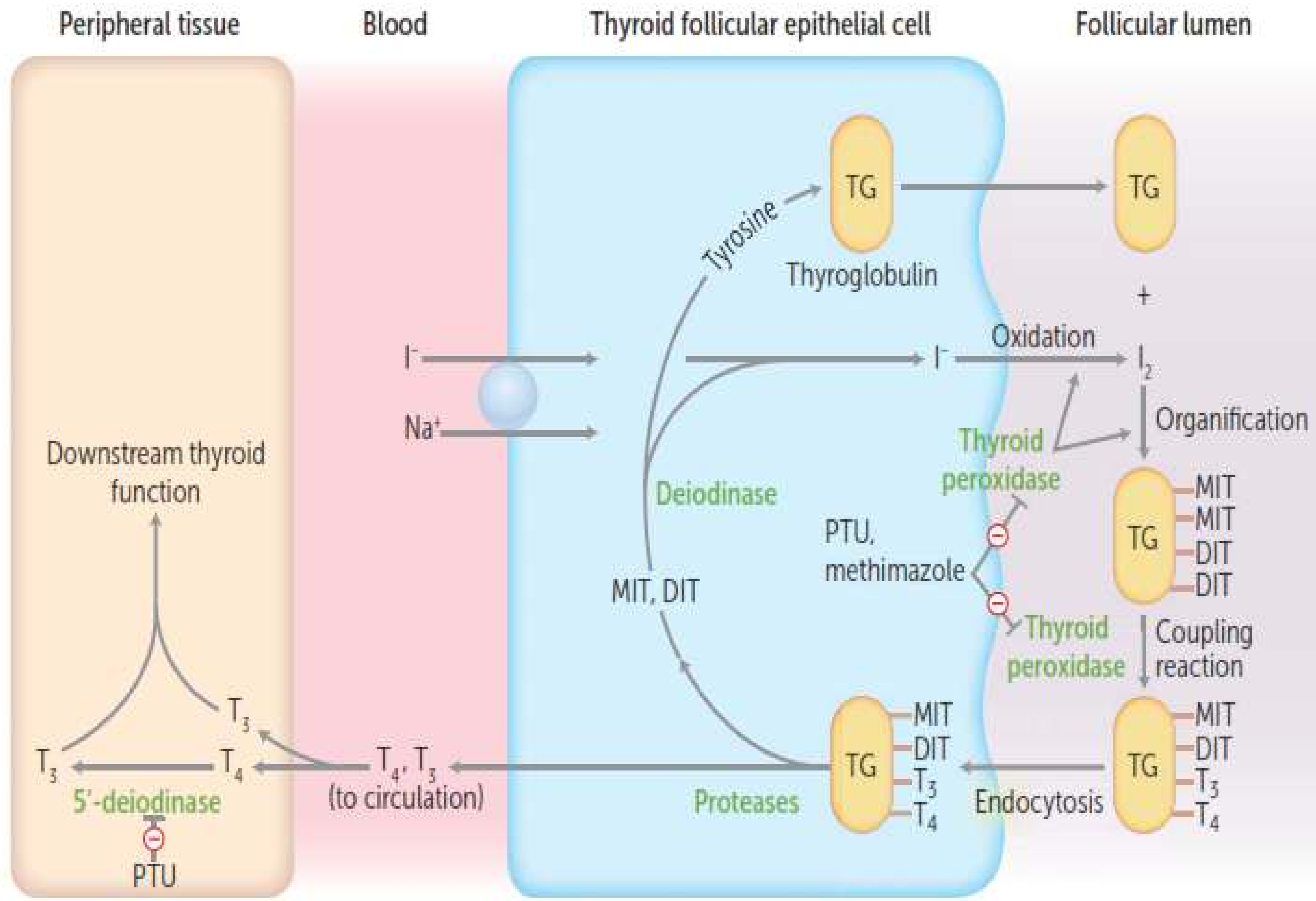
Bio-synthesis and Secretion of Thyroid Hormone

1. *Iodide Transport*
2. *Thyroglobulin Synthesis*
3. *Oxidation o f Iodide*
4. *Organification (Iodination)*
5. *Coupling*
6. *Storage*
7. *Secretion*



monoiodotyrosine (MIT) and diiodotyrosine (DIT)





monoiodotyrosine (MIT) and diiodotyrosine (DIT)

<u>**Synthesis of T4 and T3 by the thyroid gland involves six major steps:**</u>

(1) active transport of iodide across the basement membrane into the thyroid cell (trapping)

(2) oxidation of iodide and iodination of tyrosyl residues in thyroglobulin (organification)

(3) linking pairs of iodotyrosine molecules within thyroglobulin to form the iodothyronines T3 and T4 (coupling)

(4) pinocytosis and then proteolysis of thyroglobulin with release of free iodothyronines and iodotyrosines into the circulation

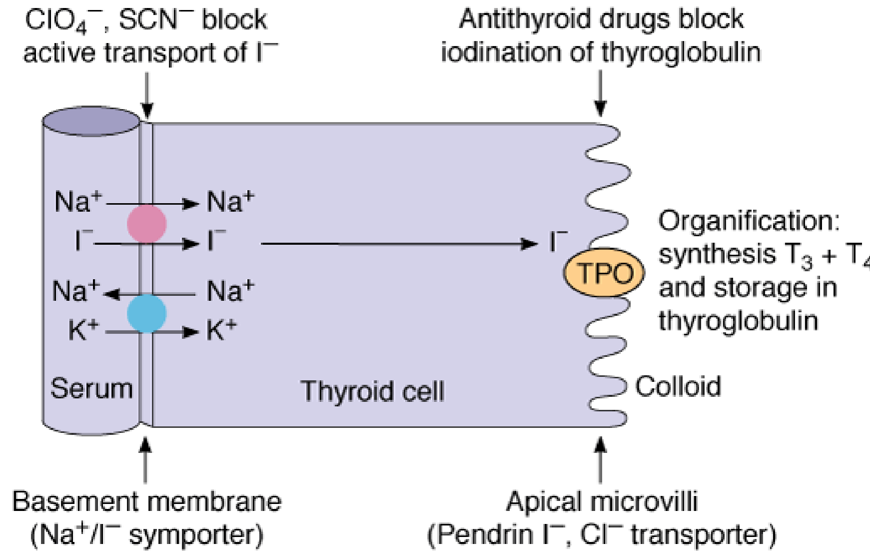
(5) deiodination of iodotyrosines within the thyroid cell, with conservation and reuse of the liberated iodide

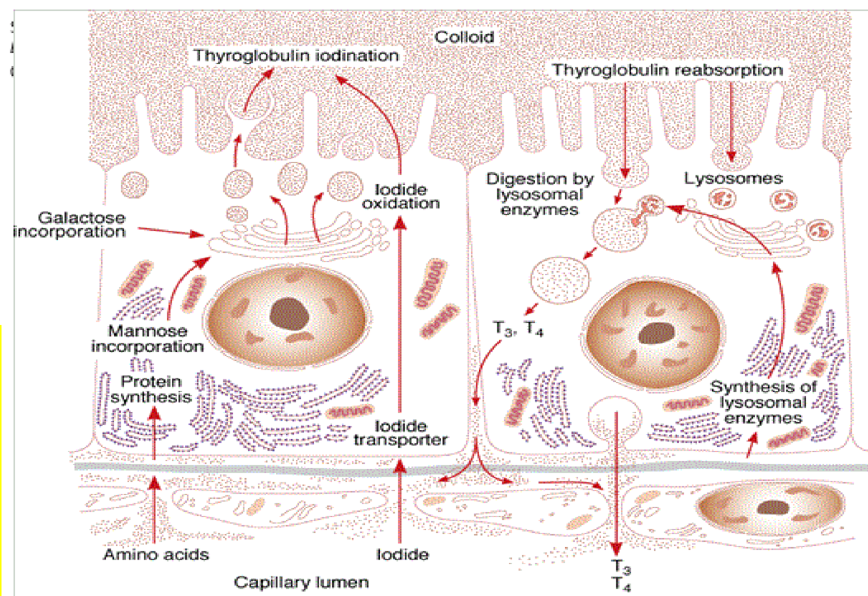
(6) intrathyroidal 5′-deiodination of T4 to T3.

Thyroid hormone synthesis requires that NIS, thyroglobulin, and the enzyme thyroid peroxidase (TPO) all be present, functional, and uninhibited

The thiocarbamide drugs, including

- **methimazole,**
- **carbimazole,**
- **propylthiouracil (PTU)**
- are competitive inhibitors of TPO. Their resulting ability to block thyroid hormone synthesis





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- **Synthesis**
  - created in the thyroid gland
  - stored in thyroid follicles
  - **thyroid peroxidase responsible for oxidation, organification, and coupling**
    - **forms I_2 via oxidation of I-**
    - **forms thyroglobulin via organification of I_2**
  - **T_4 converted to T_3 in peripheral tissues by outer ring deiodinase**
  - **T_4 converted to rT_3 by inner ring deiodinase**

- **Regulation**
  - **TRH released from the hypothalamus to stimulates TSH release from the pituitary**
    - **TSH stimulates follicular cells to produce T_3 and T_4**

Abnormally low levels of T4 may indicate: dietary issues, such as fasting, malnutrition, or an iodine deficiency. medications that affect protein levels. hypothyroidism.

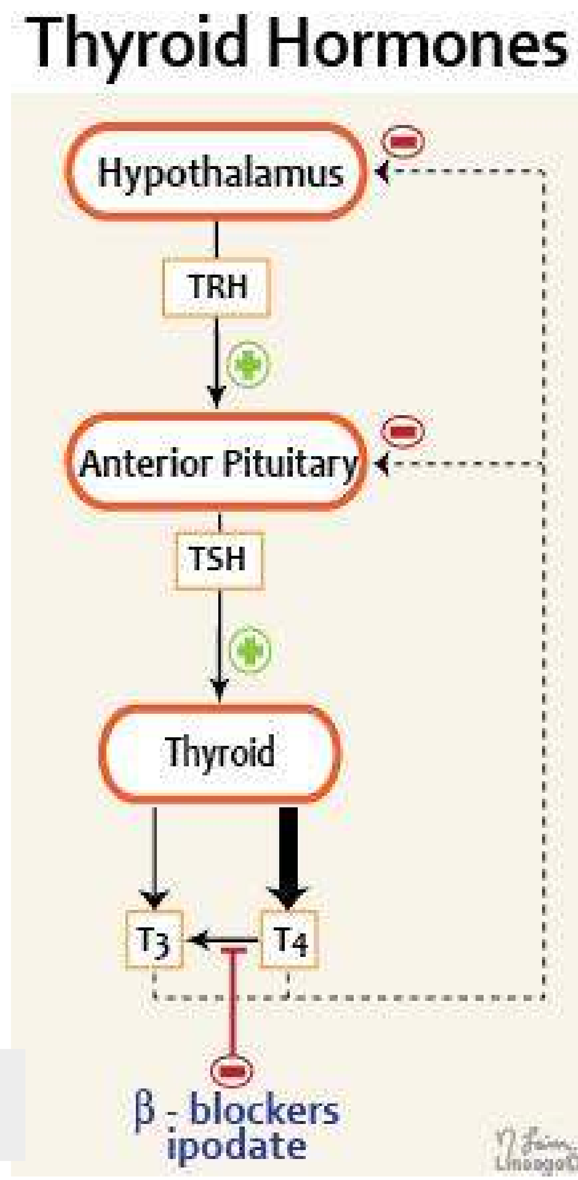
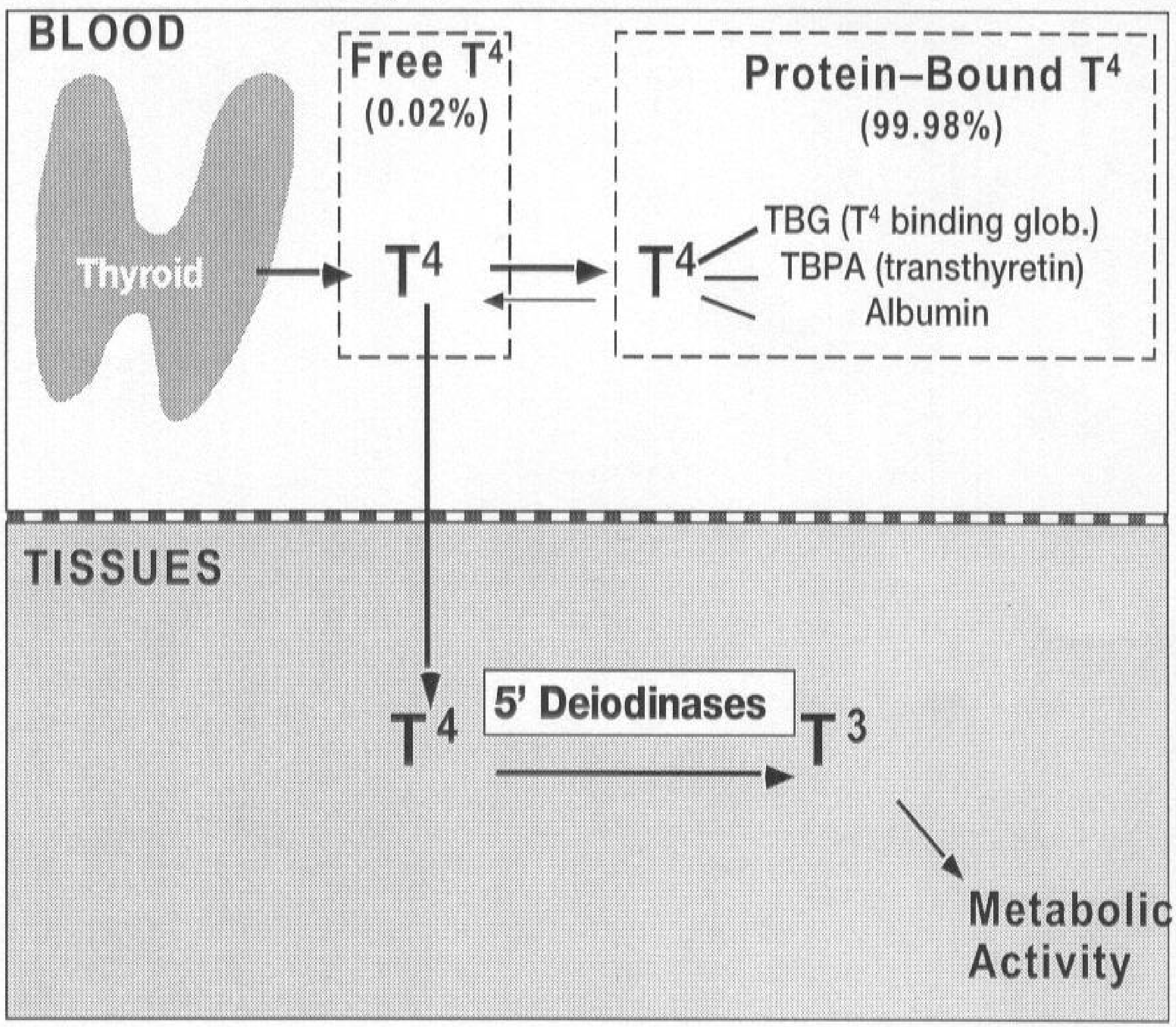


FIG 2. Thyroxine (T^4) Distribution in the Circulation



Function

- bone growth
- CNS maturation
    - **recall cretinism involves short stature and mental retardation**
- increase the basal metabolic rate
    - **via ↑ Na^+/K^+-ATPase activity**
    - **results in ↑ O2 consumption, RR, and body temperature**
- ↑ β_1 receptors in heart
    - **results in ↑ CO, HR, SV, and contractility**
        - **recall the importance of treating hyperthyroidism with β-blockers**
- **↑ glycogenolysis, gluconeogenesis, and lipolysis**

Thyroid hormones (T_3/T_4)

Iodine-containing hormones that control the body's metabolic rate.

SOURCE

Follicles of thyroid. Most T_3 formed in target tissues.

FUNCTION

Bone growth (synergism with GH)
CNS maturation
↑ β_1 receptors in heart = ↑ CO, HR, SV, contractility
↑ basal metabolic rate via ↑ Na^+/K^+-ATPase activity → ↑ O_2 consumption, RR, body temperature
↑ glycogenolysis, gluconeogenesis, lipolysis

REGULATION

TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells.
May also be stimulated by thyroid-stimulating immunoglobulin (TSI) in Graves disease.
Negative feedback primarily by free T_3/T_4 to anterior pituitary (↓ sensitivity to TRH) and hypothalamus (↓ TRH secretion).
Wolff-Chaikoff effect—excess iodine temporarily inhibits thyroid peroxidase → ↓ iodine organification → ↓ T_3/T_4 production.

T_3 functions—**4 B's**:
- **B**rain maturation
- **B**one growth
- **β**-adrenergic effects
- **B**asal metabolic rate ↑

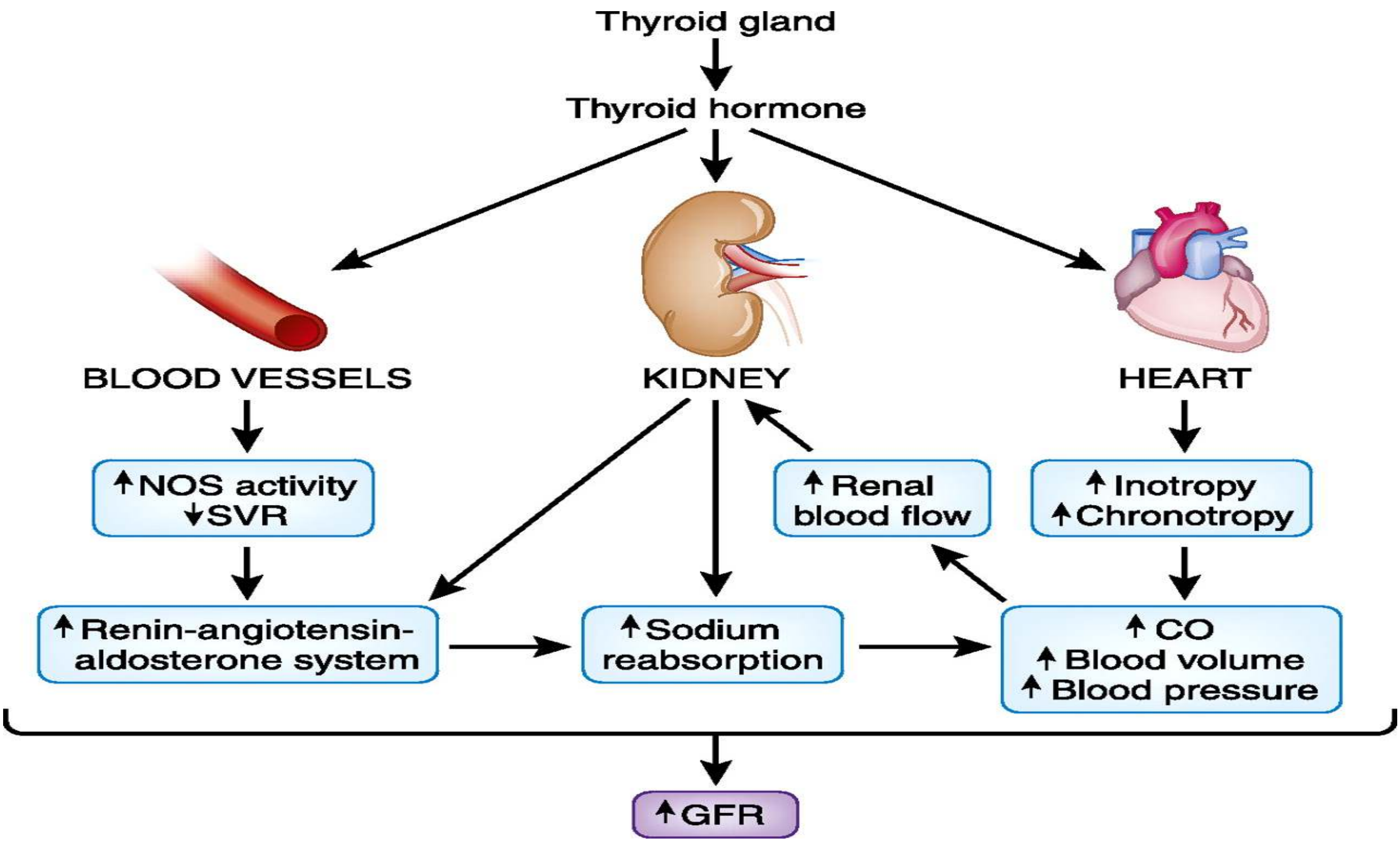
Thyroxine-binding globulin (TBG) binds most T_3/T_4 in blood; only free hormone is active.
↓ TBG in hepatic failure, steroids; ↑ TBG in pregnancy or OCP use (estrogen ↑ TBG).

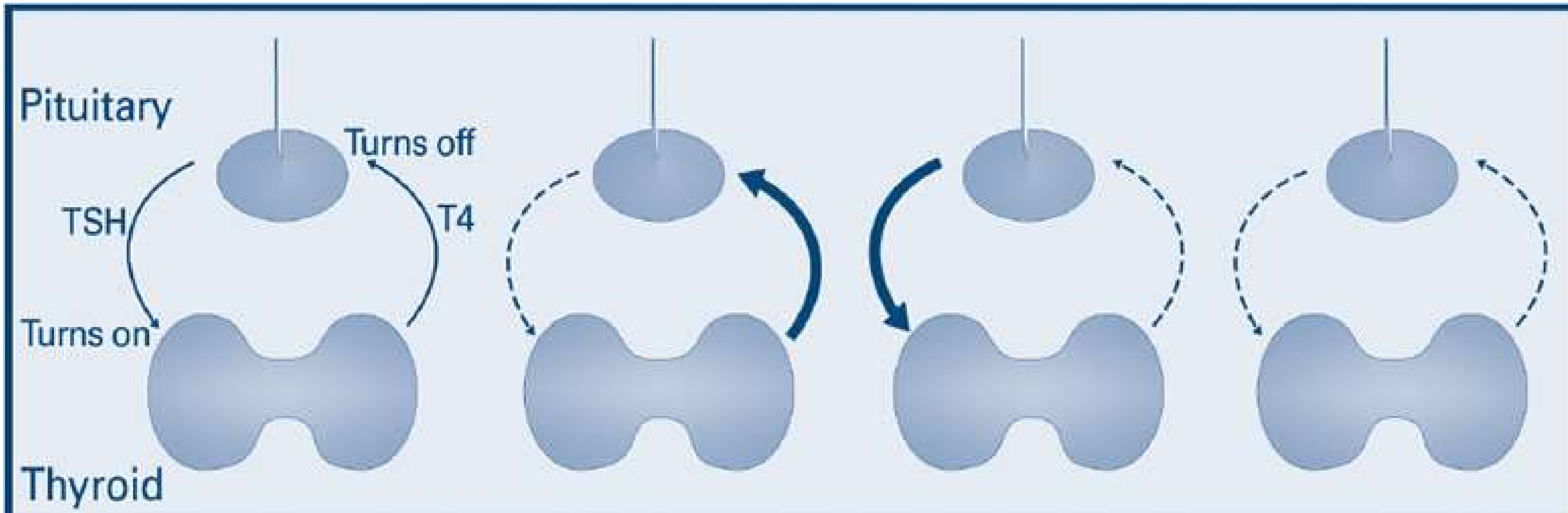
T_4 is major thyroid product; converted to T_3 in peripheral tissue by 5′-deiodinase.

T_3 binds nuclear receptor with greater affinity than T_4.

Thyroid peroxidase is the enzyme responsible for oxidation and organification of iodide as well as coupling of monoiodotyrosine (MIT) and di-iodotyrosine (DIT). DIT + DIT = T_4. DIT + MIT = T_3.

Propylthiouracil (PTU) inhibits both thyroid peroxidase and 5′-deiodinase.
Methimazole inhibits thyroid peroxidase only.
Glucocorticoids inhibit peripheral conversion of T_4 to T_3.


Thyroid gland
Thyroid hormone
BLOOD VESSELS
KIDNEY
HEART
↑NOS activity
↓SVR
↑Renal blood flow
↑Inotropy
↑Chronotropy
↑Renin-angiotensin-aldosterone system
↑Sodium reabsorption
↑CO
↑Blood volume
↑Blood pressure
↑GFR



CONDITION:	Normal	Hyperthyroidism	Hypothyroidism Primary	Hypothyroidism Secondary
TSH	Normal	Low	High	Low
T4	Normal	High	Low	Low

Parafollicular Cells (C Cells)

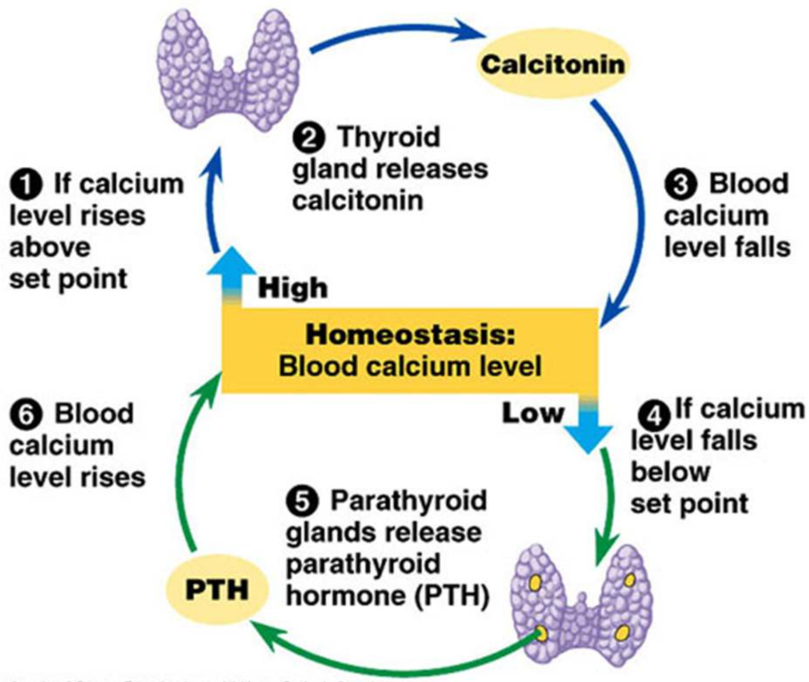
- Derived from neural crest ectoderm.
- Located between follicular cells and between follicles.
- Parafollicular cells are larger cells with clear cytoplasm and small secretory granules containing calcitonin.
- Calcitonin is made in response to high blood calcium (it’s not affected by a pituitary hormone!).
- Calcitonin lowers blood calcium levels by inhibiting osteoclastic resorption.

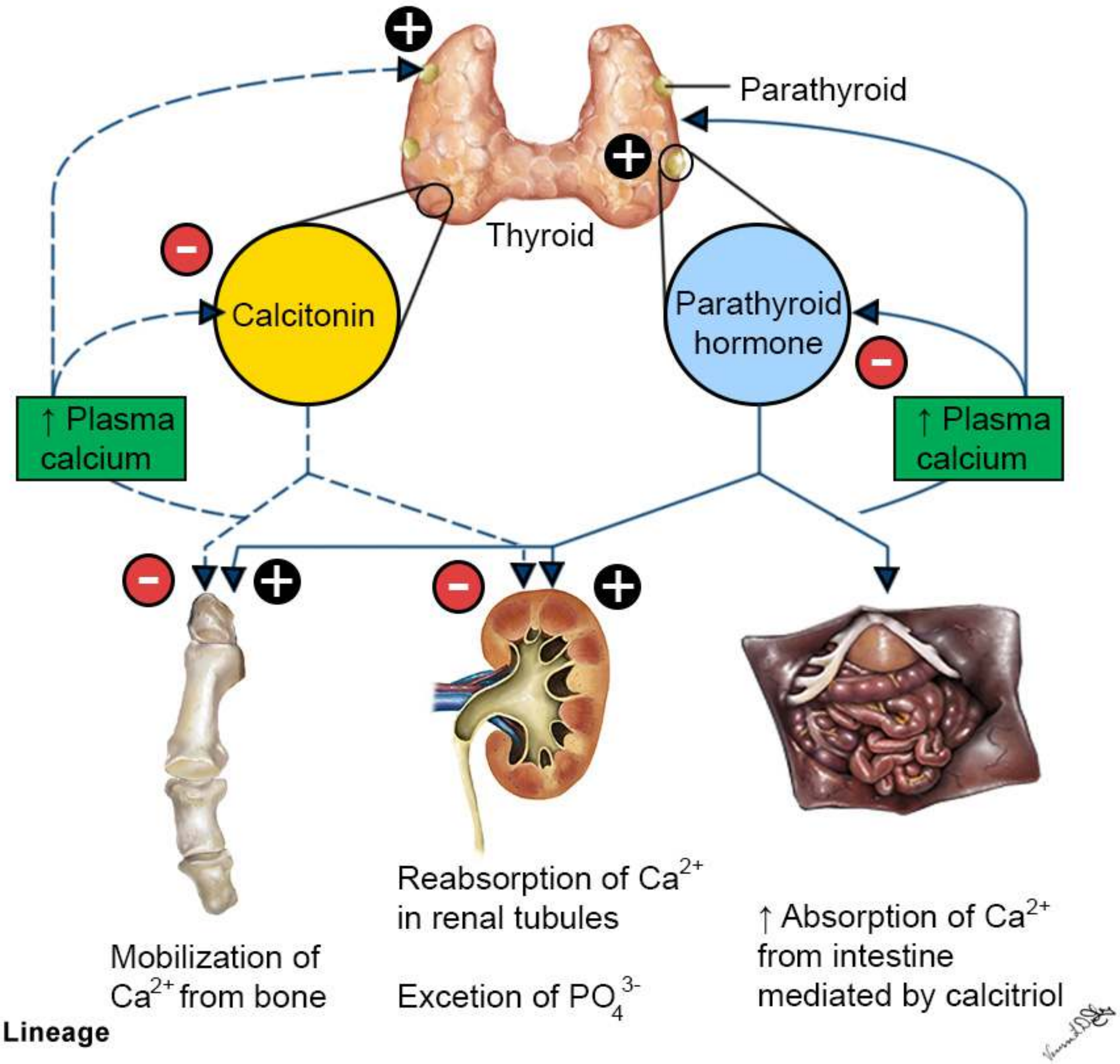
Calcitonin

SOURCE	Parafollicular cells (C cells) of thyroid.
FUNCTION	↓ bone resorption of Ca^{2+}.
REGULATION	↑ serum Ca^{2+} → calcitonin secretion.

Calcitonin opposes actions of PTH. Not important in normal Ca^{2+} homeostasis.

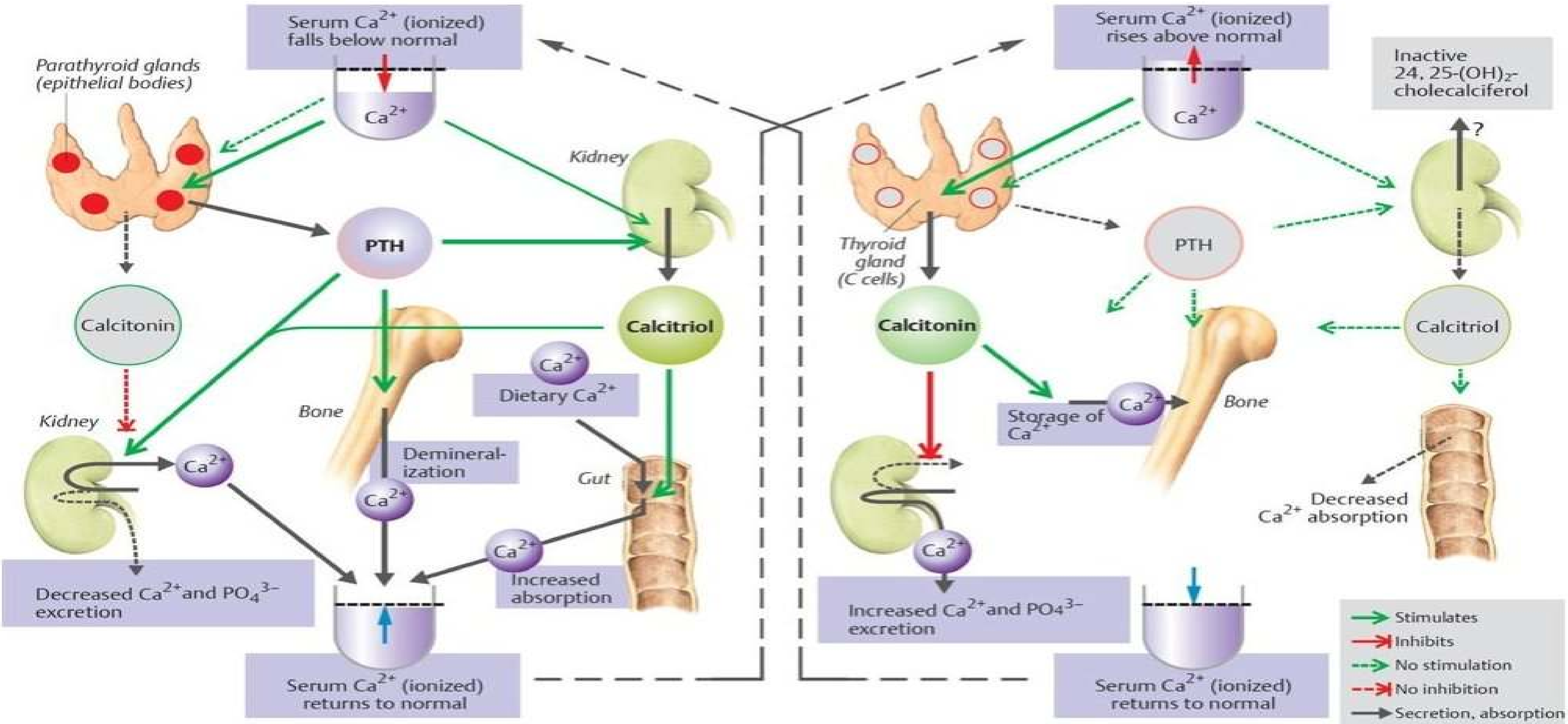
Calcitonin tones down serum Ca^{2+} levels and keeps it in bones.




Parathyroid
Thyroid
Calcitonin
Parathyroid hormone
↑ Plasma calcium
↑ Plasma calcium
Reabsorption of Ca2+ in renal tubules
Exception of PO4 3-
↑ Absorption of Ca2+ from intestine mediated by calcitriol
Mobilization of Ca2+ from bone

Hormonal regulation of the blood Ca^{2+} concentration.

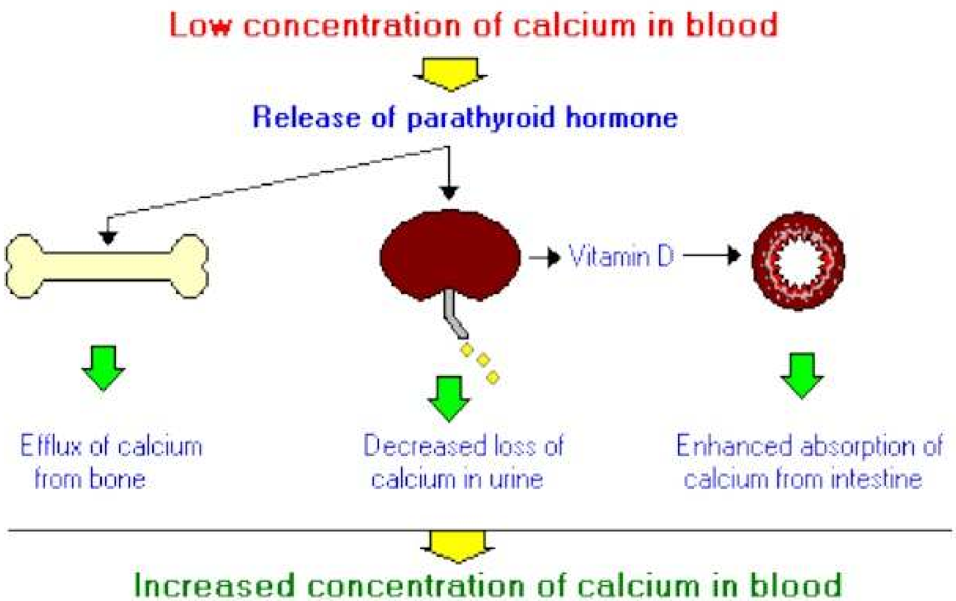
Ca^{2+} homeostasis is achieved by three main hormones: parathyroid hormone (PTH, from parathyroid gland), calcitonin (from parafollicular cells of the thyroid gland), and calcitriol (mainly produced in the kidney). In low serum Ca^{2+} states, the actions of parathyroid hormone and calcitriol predominate, causing increased Ca^{2+} uptake from the gut and bone and decreased renal excretion. In high serum Ca^{2+} states, the action of calcitonin predominates, causing decreased Ca^{2+} uptake from the gut, increased renal excretion, and storage of excess Ca^{2+} in bone.



Source : Pharmacology - An Illustrated Review (Thieme Illustrated Review Series) - Simmons, Mark

	PTH	Vitamin D	Calcitonin
Bone:	↑ resorption.	↑ resorption & formation.	↓ resorption.
Kidney:	↑ tubular Ca^{++} reabsorption. ↑ tubular PO_4^{-} excretion.	↑ tubular Ca^{++}& PO_4^{-} reabsorptn	↓ tubular Ca^{++} & PO_4^{-} reabsorptn.
G.I.T.	Indirect through calcitriol (↑ Ca^{++}&PO_4^{-} reabsorption).	↑ Ca^{++} &PO_4^{-} reabsorption.	
Serum Ca^{++}	↑	↑	↓
PO_4^{-}	↓	↑	↓

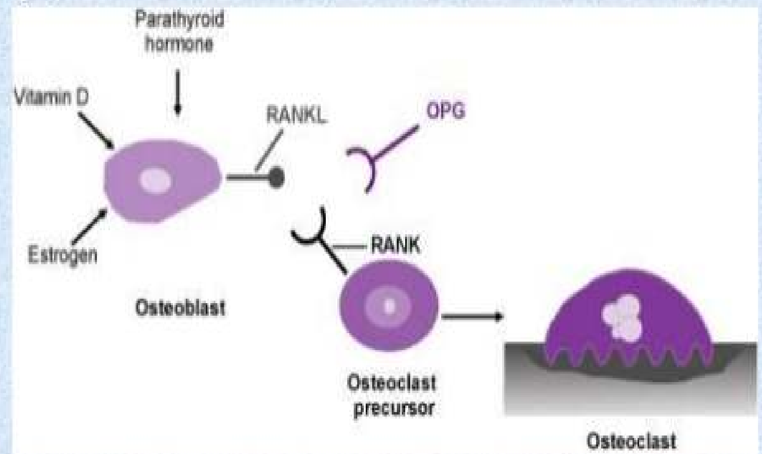
Parathyroid



PTH binds to **osteoblasts**.

Osteoblasts **increase expression of RANK-L** and inhibits their expression of Osteoprotegerin (OPG). *(OPG blocks RANK-L)*

RANK-L **binds RANK** on **osteoclast precursors**, and they form new osteoclasts. And osteoclasts **enhance bone resorption** thus increasing Blood Calcium and Decreasing Bone Calcium

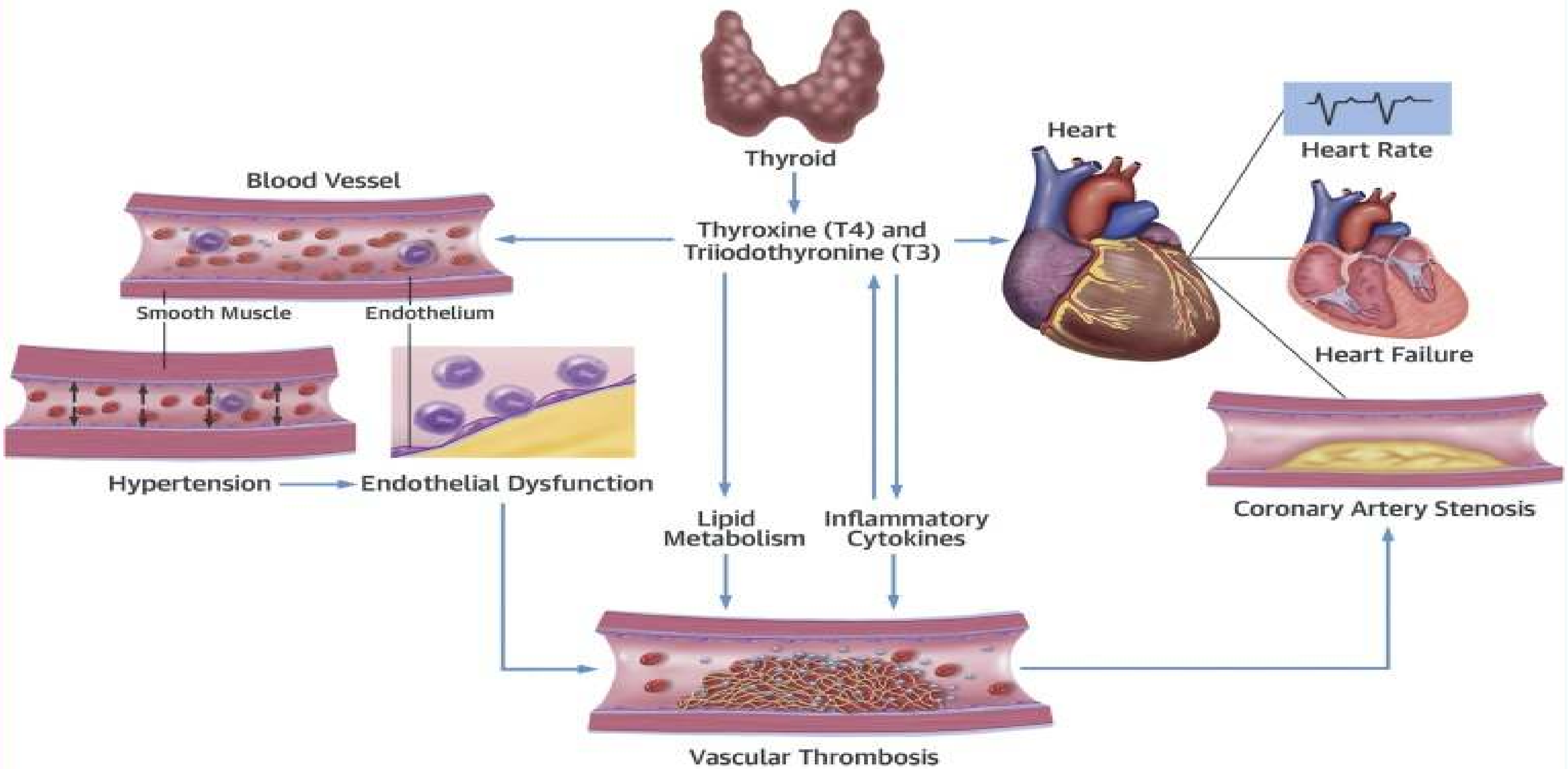


Heart

- The natriuretic peptide family consists of three biologically active peptides: (will be discussing this in cardiovascular)
  - **atrial natriuretic peptide (ANP),**
  - **brain (or B-type) natriuretic peptide (BNP),**
  - **and C-type natriuretic peptide (CNP).**

  - Among these, ANP and BNP are secreted by the heart and act as cardiac hormones.

CENTRAL ILLUSTRATION: The Interactions Between Thyroid Hormones and the Cardiovascular System



Razvi, S. et al. J Am Coll Cardiol. 2018;71(16):1781–96.