Calcium Homeostasis

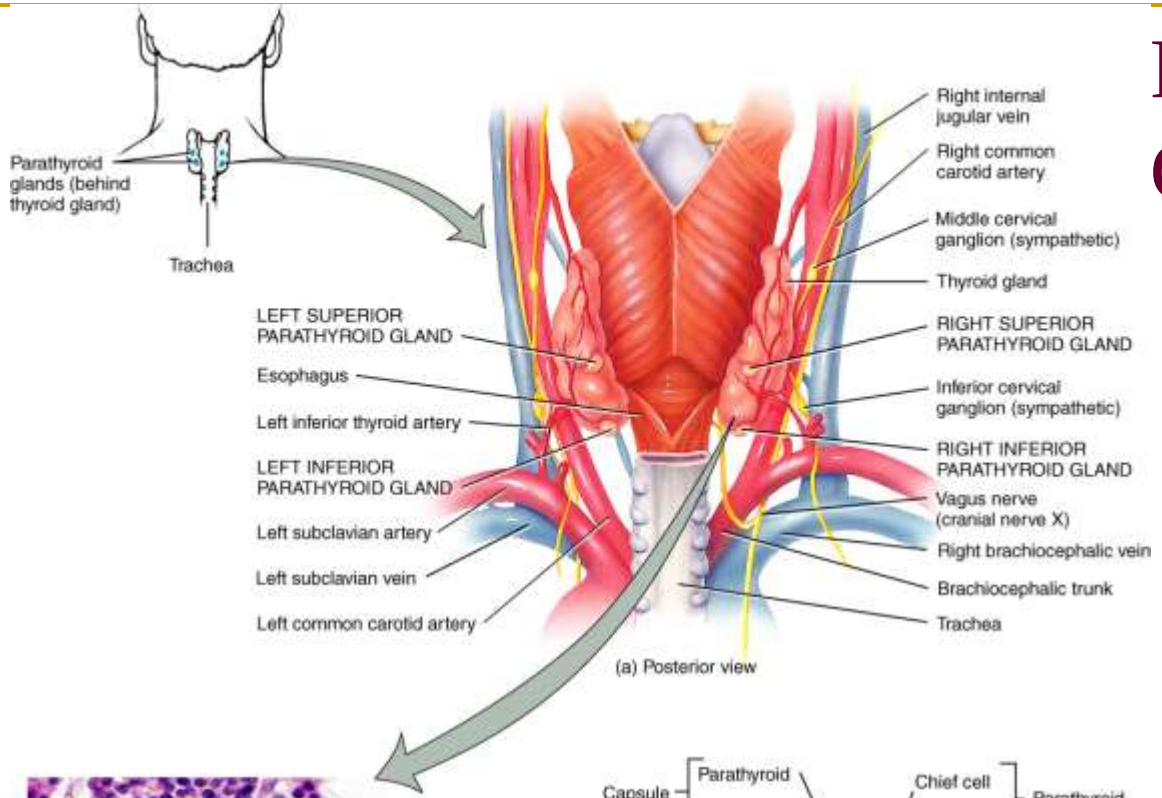
Objectives

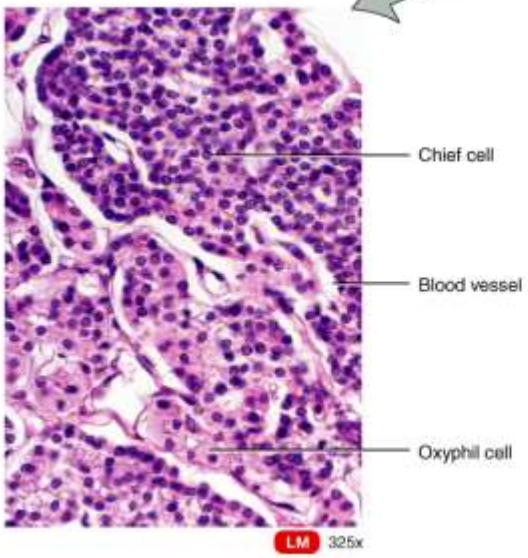
- List the hormones involved in calcium homeostasis
- Determine the structures of PTH, Calcitonin and vitamin D
- Explain the mechanism of action of PTH, Calcitonin and Vitamin D
- Give an account for the interaction between PTH, Calcitonin and Vitamin D actions
- Describe calcium homeostatic abnormalities

Parathyroid Glands

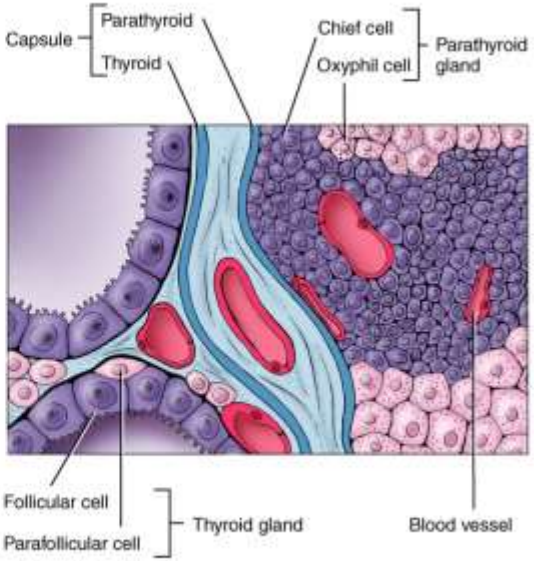
- Embedded in lobes of thyroid gland, usually 4.
- Parathyroid hormone (PTH) or parathormone
  - Major regulator of calcium, magnesium, and phosphate ions in the blood
  - Increases number and activity of osteoclasts
  - Elevates bone resorption
  - Stimulates the conversion of 25-hydroxycholecalciferol (inactive vitamin D) into 1,25-dihydroxycholecalciferol (Active vitamin D-calcitriol) which will increase intestinal Ca^{++} reabsorption.
- Blood calcium level directly controls secretion of both calcitonin and PTH via negative feedback

Parathyroid Glands





(b) Parathyroid gland



(c) Portion of the thyroid gland (left) and parathyroid gland (right)

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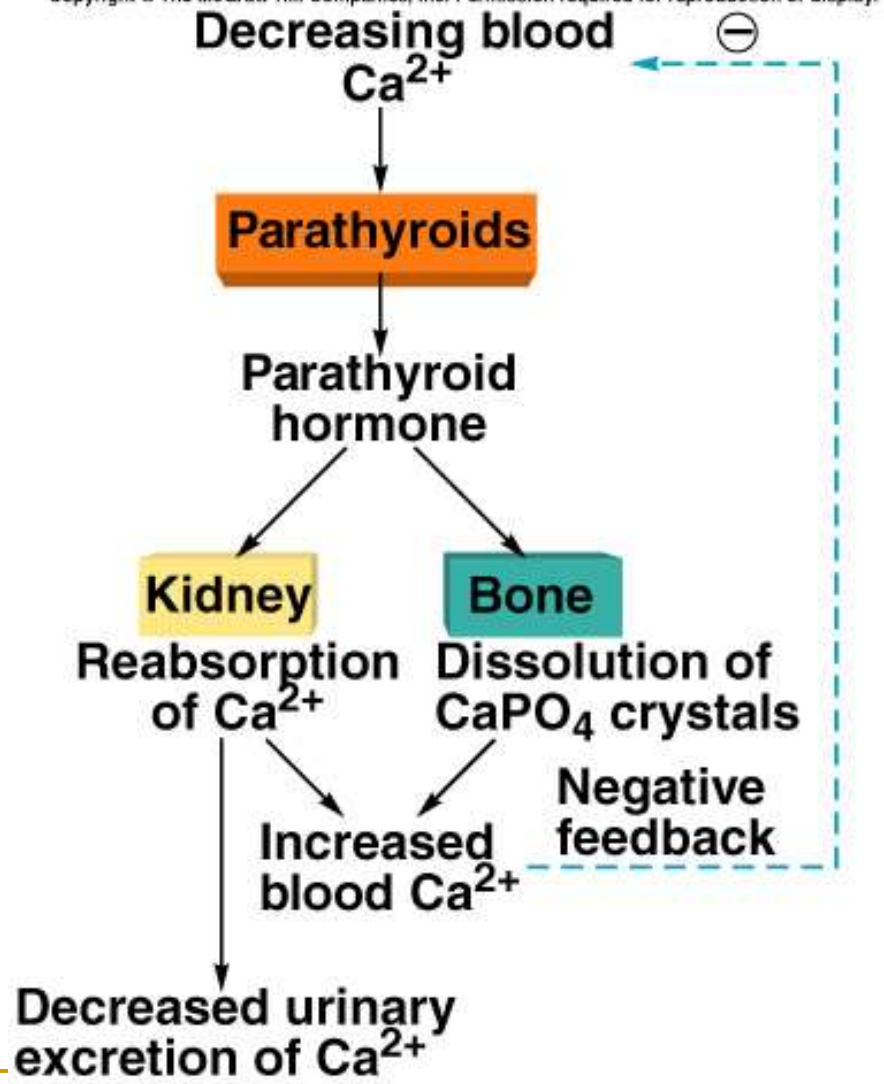
Parathyroid Glands

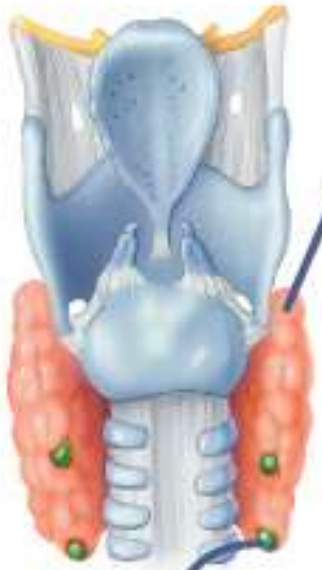
- Embedded in the lateral lobes of the thyroid gland.
- Parathyroid hormone (PTH):
  - Only hormone secreted by the parathyroid glands.
- Single most important hormone in the control of blood [Ca^{2+}].
- Stimulated by decreased blood [Ca^{2+}].
- Promotes rise in blood [Ca^{2+}] by acting on bones, kidney and intestines.



Roles of Calcitonin, Parathyroid hormone, Calcitrol in Calcium Homeostasis

1 High level of Ca^{2+} in blood stimulates thyroid gland parafollicular cells to release more CT.

3 Low level of Ca^{2+} in blood stimulates parathyroid gland chief cells to release more PTH.



6 CALCITRIOL stimulates increased absorption of Ca^{2+} from foods, which increases blood Ca^{2+} level.

5 PTH also stimulates the kidneys to release CALCITRIOL.

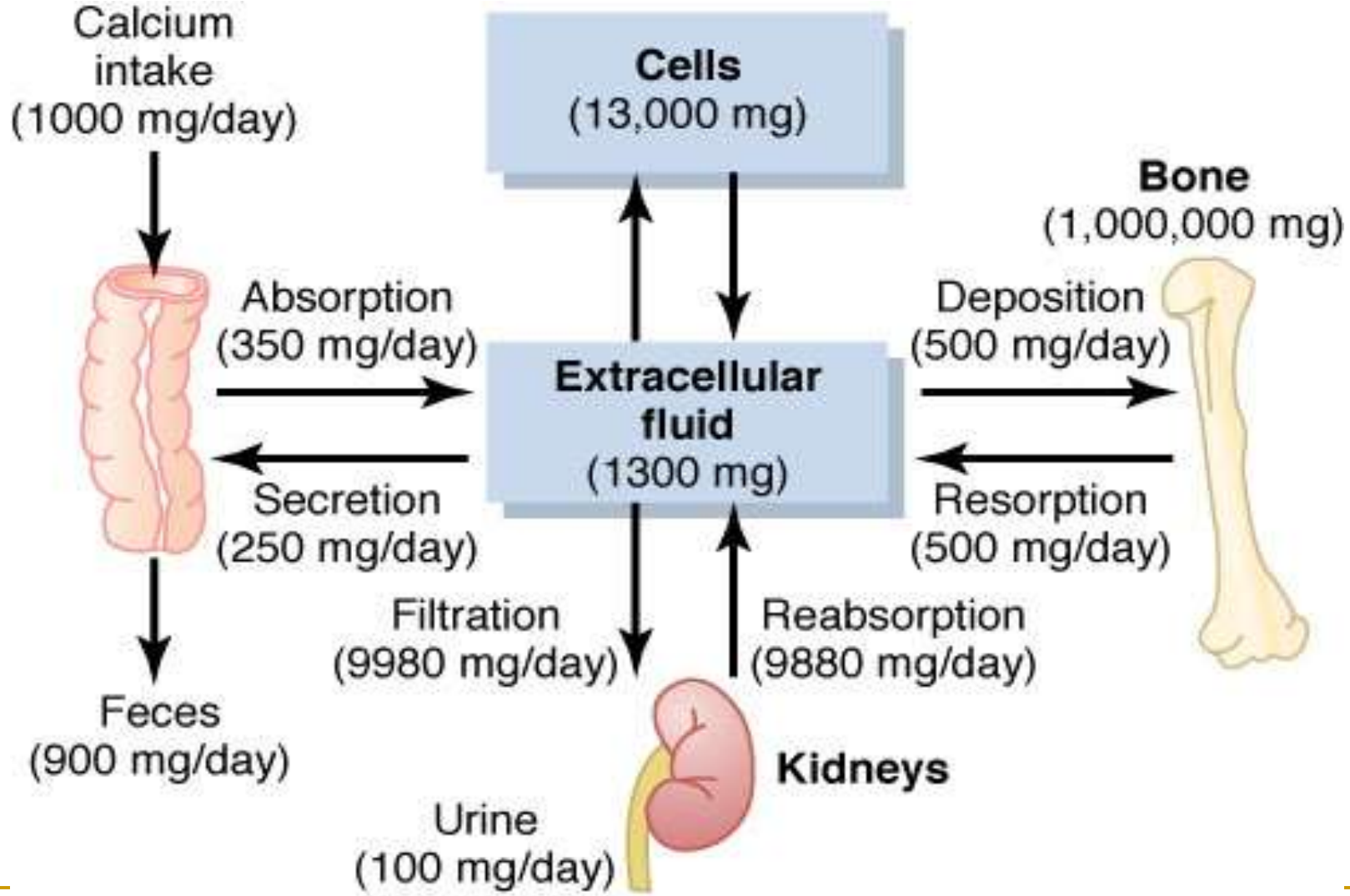
4 PARATHYROID HORMONE (PTH) promotes release of Ca^{2+} from bone extracellular matrix into blood and slows loss of Ca^{2+} in urine, thus increasing blood Ca^{2+} level.

2 CALCITONIN inhibits osteoclasts, thus decreasing blood Ca^{2+} level.

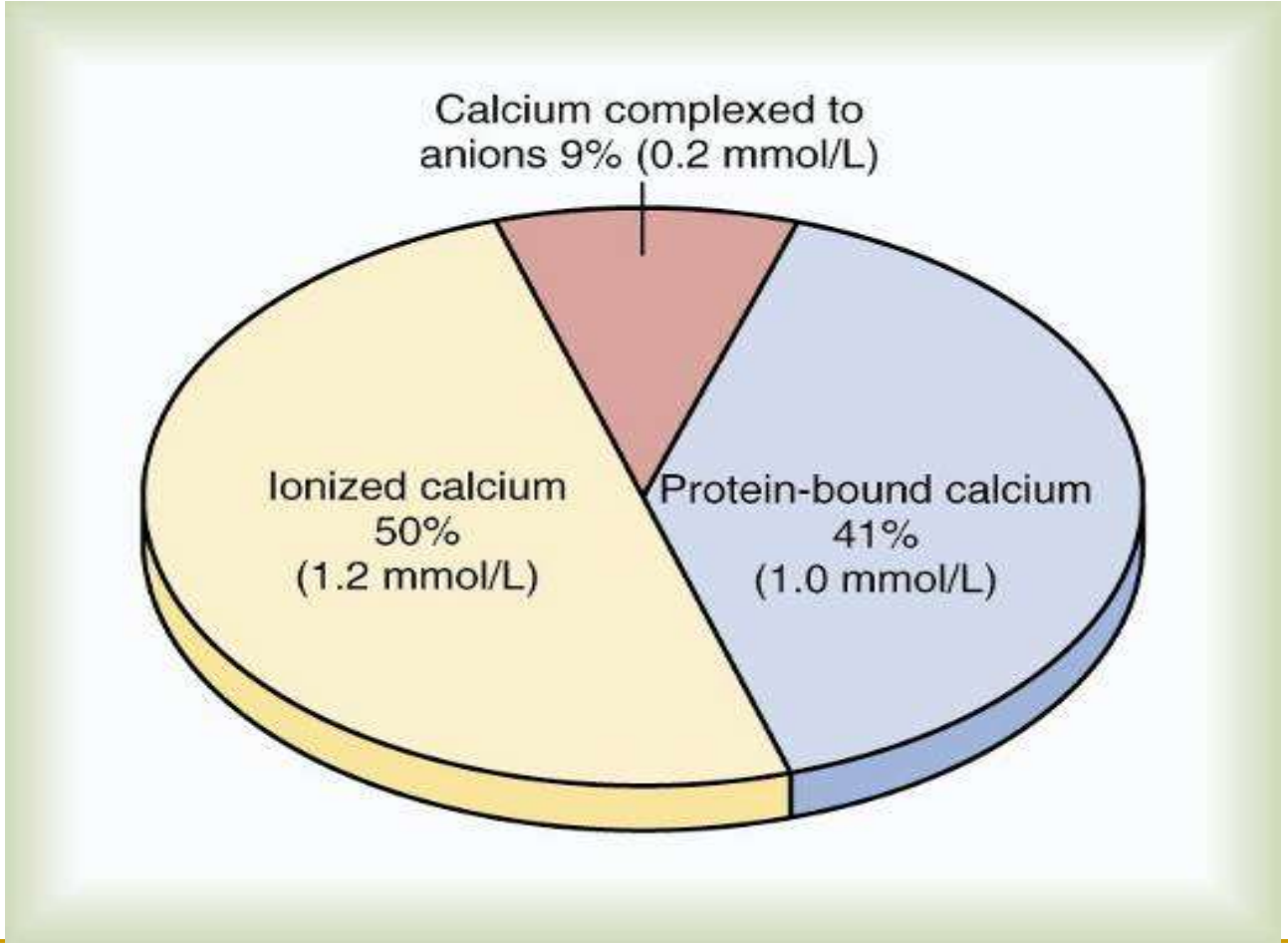
Hormonal Control of Calcium Metabolism

- PTH
- Vitamin D
- Calcitonin

Calcium Metabolism

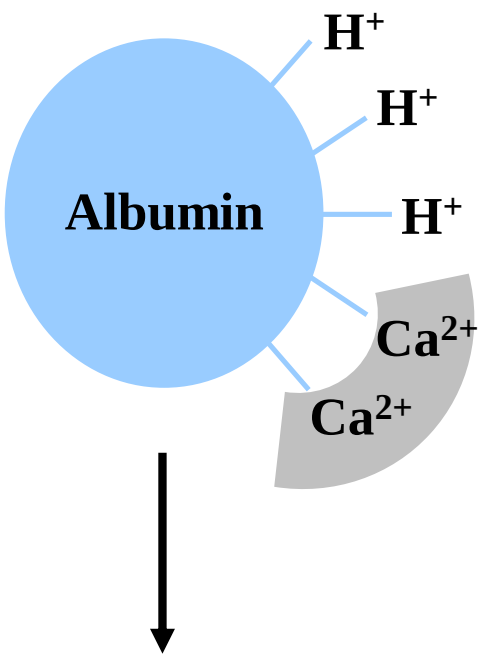


Distribution of Ionized Calcium in the Blood



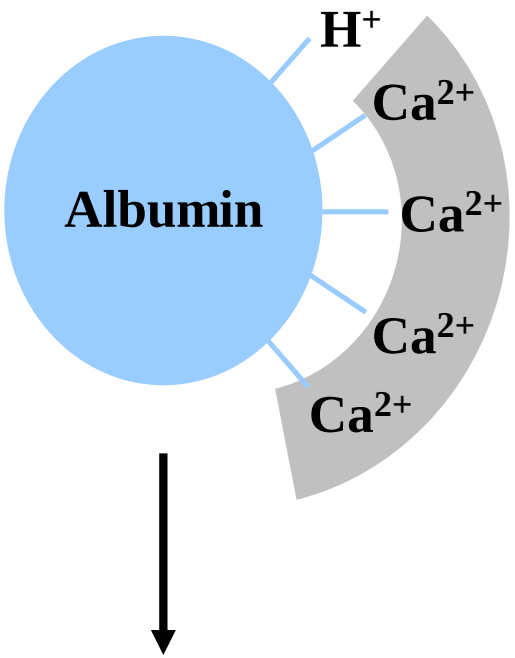
Effects of Acid-Base Disturbances on Ionized Calcium

Acidemia



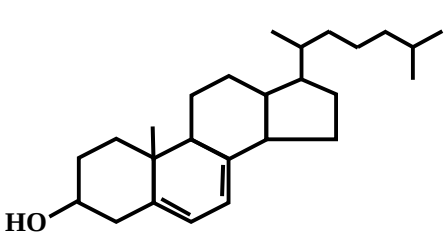
↑ Ionized [Ca^{2+}]

Alkalemia



↓ Ionized [Ca^{2+}]

Formation and Hydroxylation of Vitamin D_3

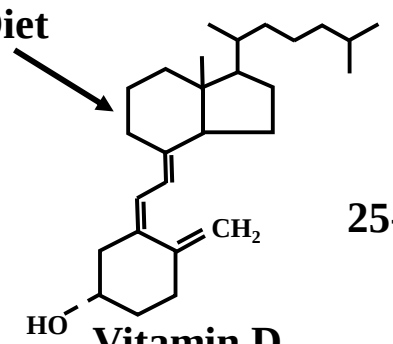


7-Dehydrocholesterol
(provitamin)

skin

UV light

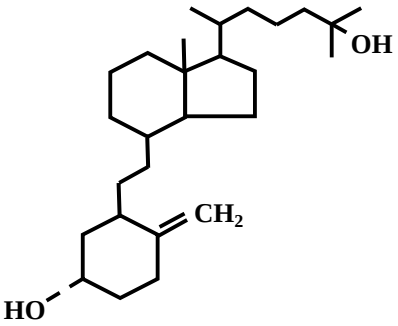
Diet



Vitamin D_3
(cholecalciferol)

liver

25-Hydroxylase



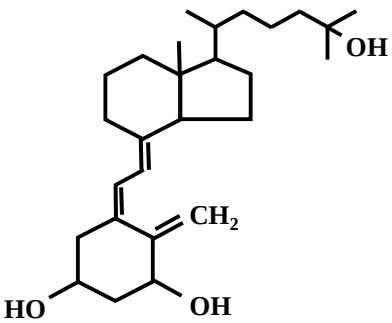
25-(OH)-cholecalciferol

PTH ⊕

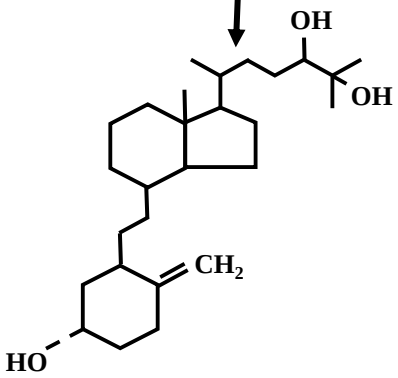
1α-Hydroxylase

kidney

24-Hydroxylase



1,25-$(OH)_2$-cholecalciferol
(calcitriol)

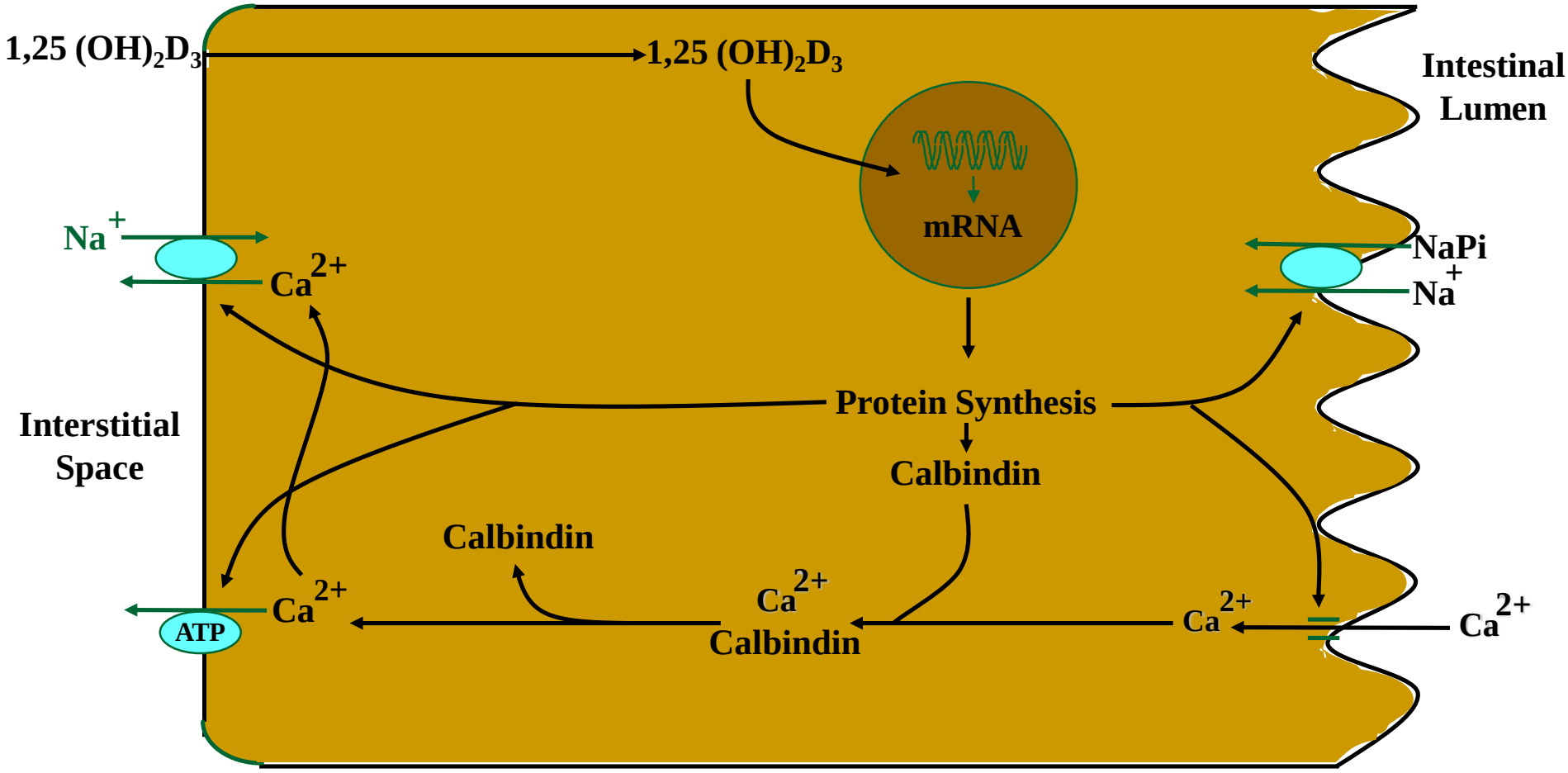


24,25-$(OH)_2$-cholecalciferol

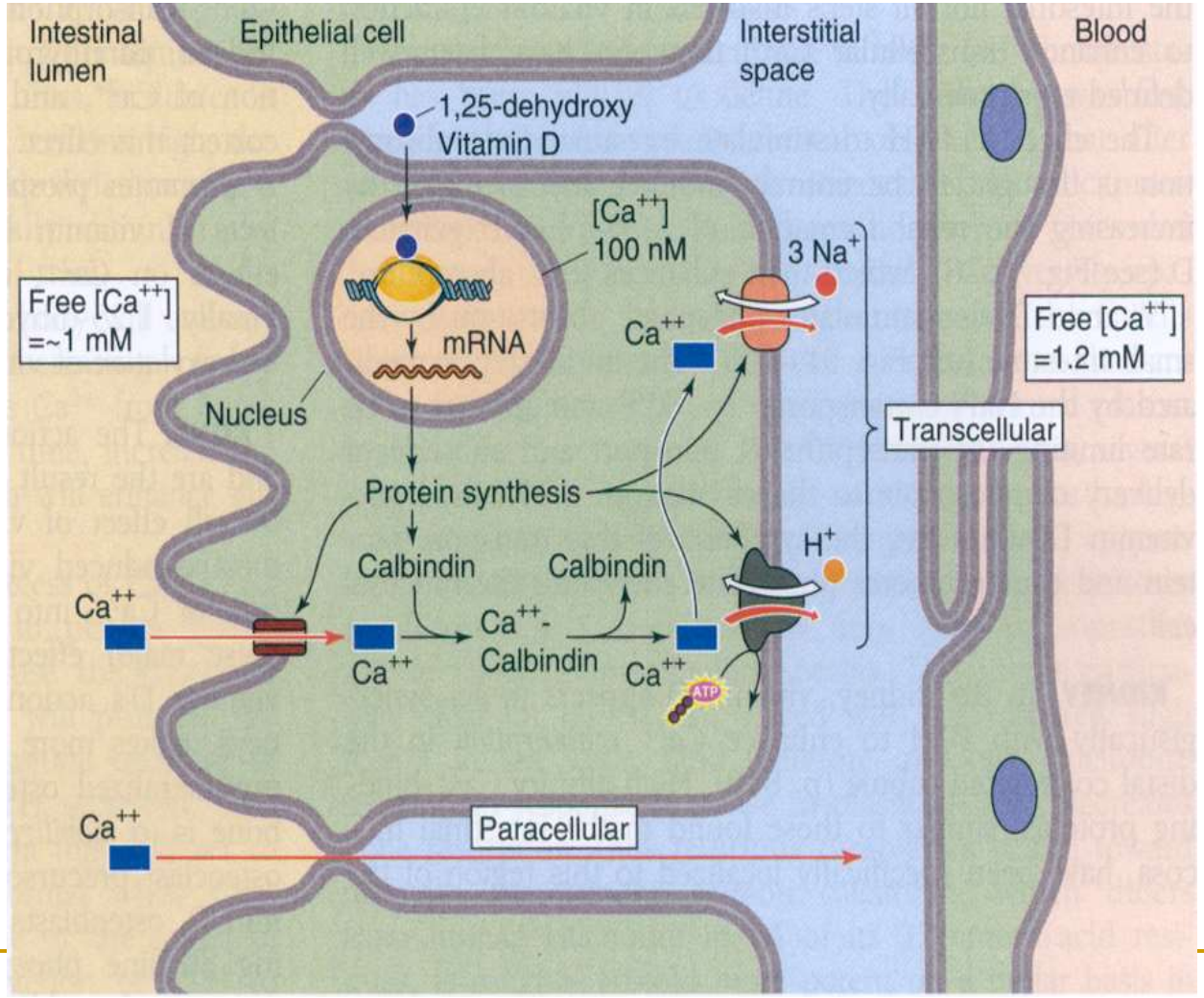
Vitamin D Actions

- **Intestine**
  - ↑ Ca^{2+} absorption
  - ↑ phosphate absorption
- **Bone**
  - ↑ mineralization (indirect effect)
  - ↑ bone resorption (direct effect)
- **Kidney**
  - ↑ Ca^{2+} reabsorption (weak effect)
  - ↑ phosphate reabsorption (weak effect)

Vitamin D and Intestinal Absorption of Ca^{2+} and Phosphate



Intestinal Absorption of Calcium



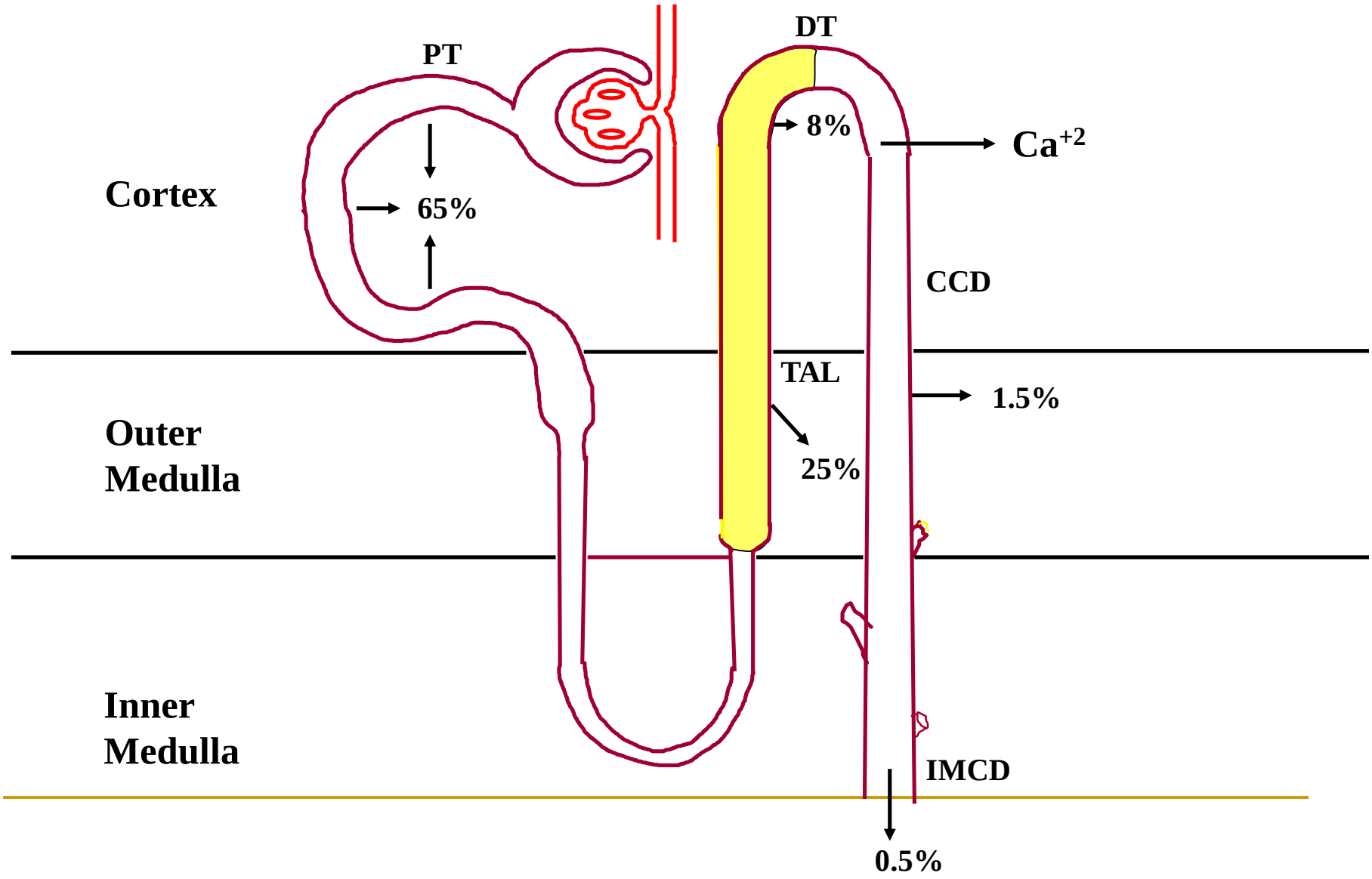
PTH Actions

- **Bone**
  - receptors on osteoblasts & osteocytes
  - ↑ osteocytic osteolysis
  - ↑ resorption (↑ osteoclasts)

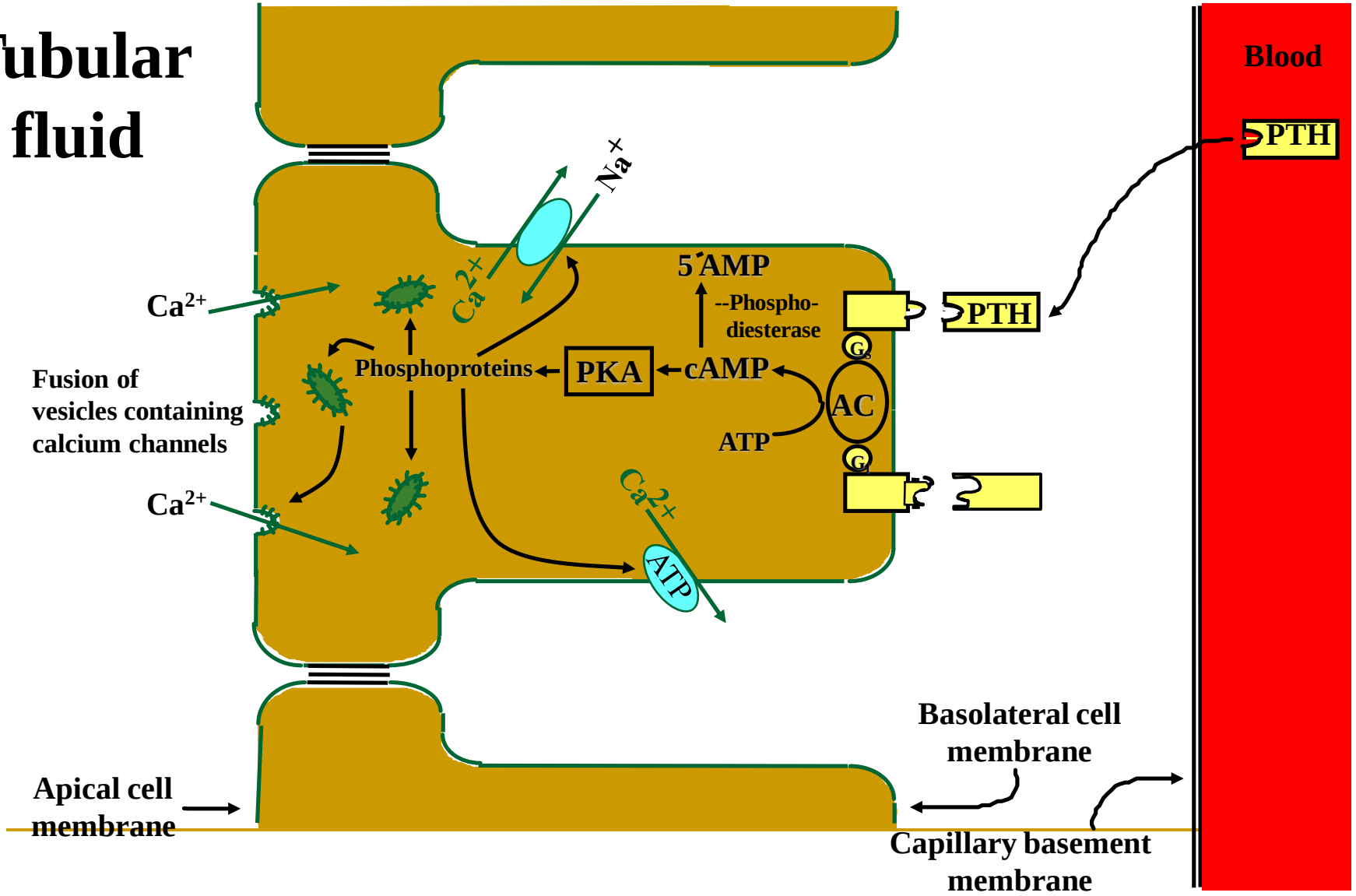
- **Kidney**
  - ↑ Ca^{2+} reabsorption
  - ↓ phosphate reabsorption
  - ↓ Na^{+} reabsorption (weak effect)
  - ↑ 1,25-$(OH)_2$-D_3

- ***Intestine***
  - ↑ Ca^{2+} absorption
  - ↑ phosphate absorption

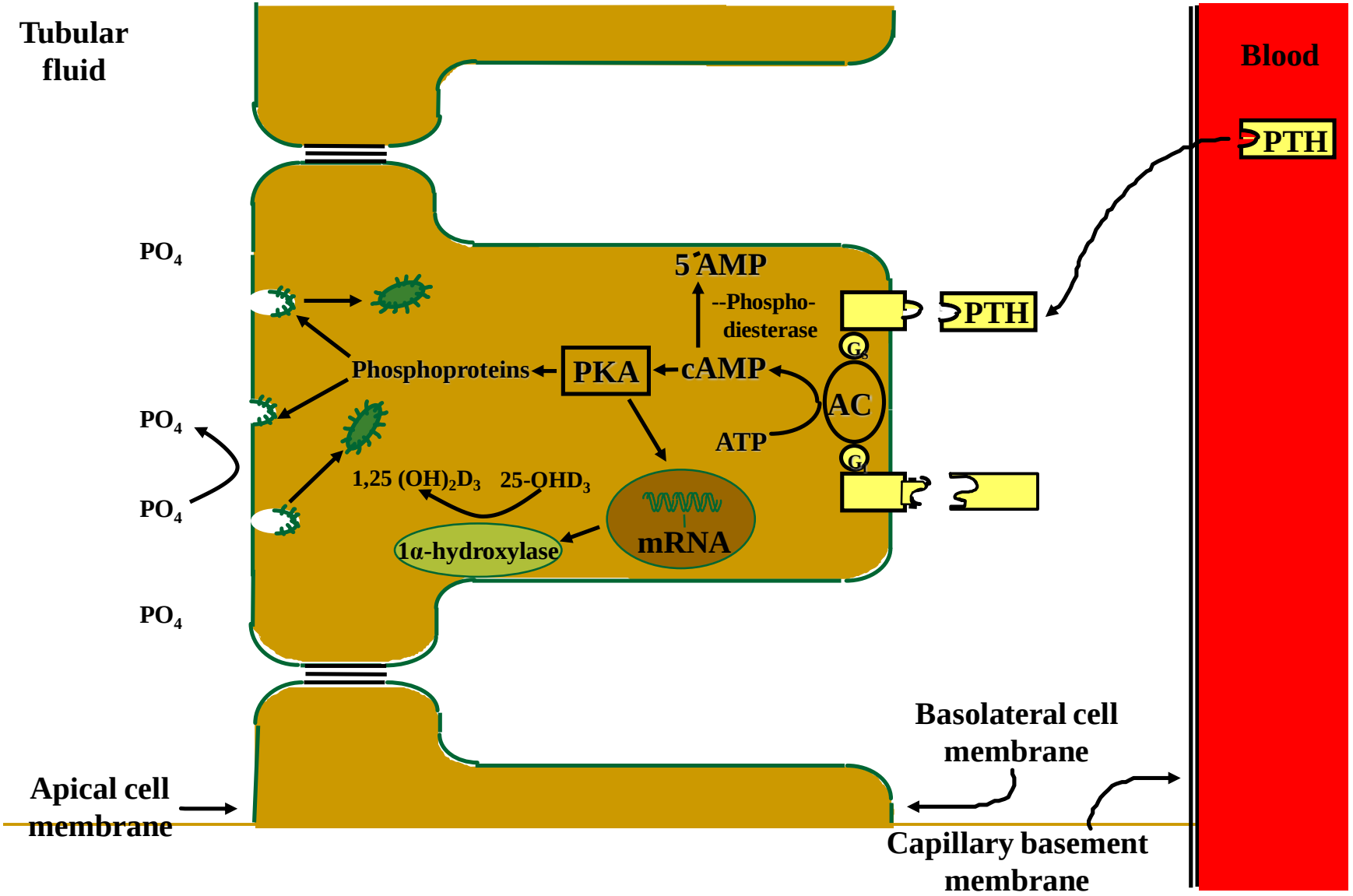
Tubular Effects of PTH



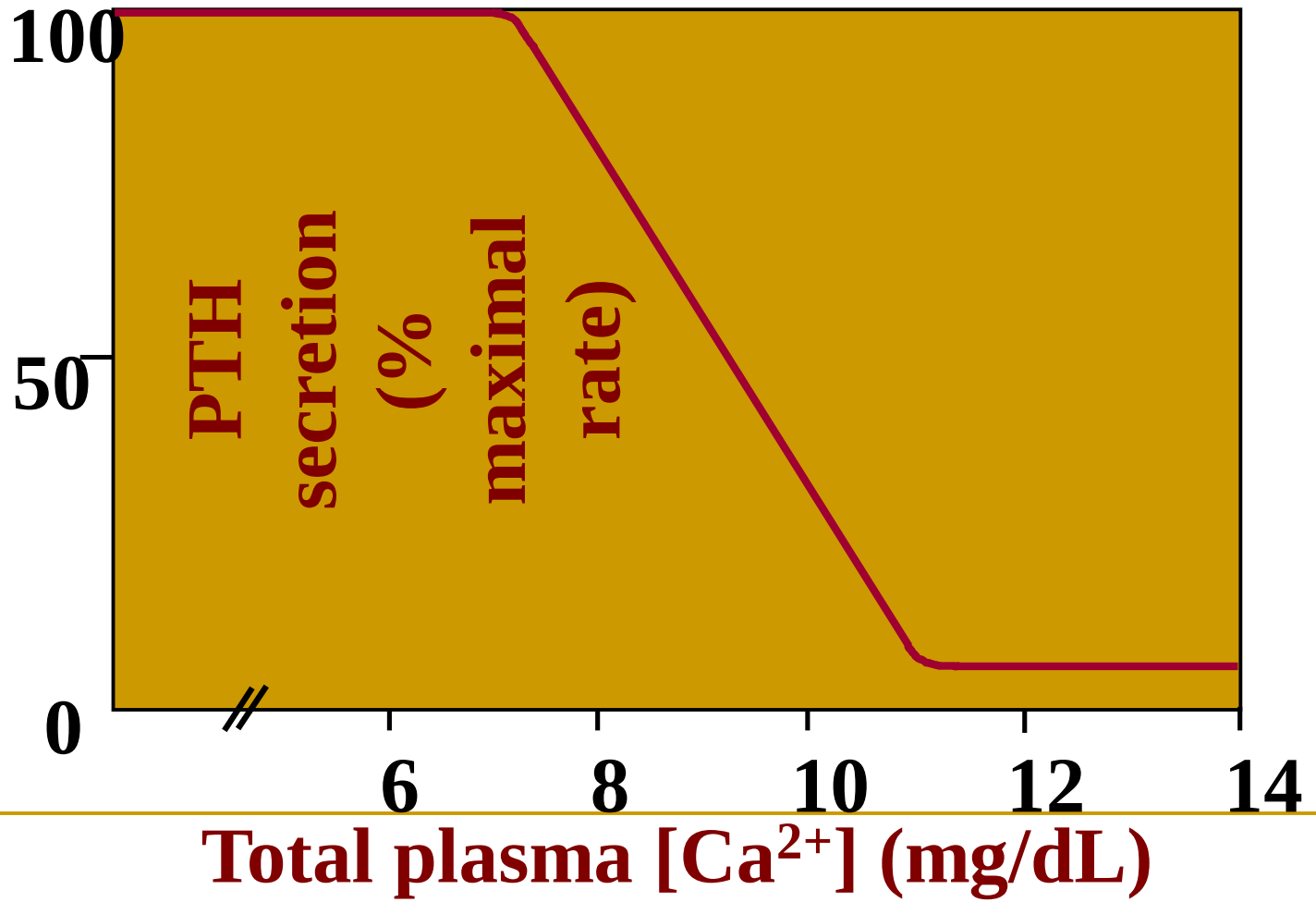
Cellular Actions of PTH in the TAL & Distal Tubule



Cellular Actions of PTH in the Proximal Tubule



Plasma [Calcium] & PTH Secretion



Calcitonin

- receptors on osteoclasts
- osteoclasts: ↓ activity; ↓ number
- minor role in acute regulation of plasma [Ca^{2+}]
- no role in chronic regulation of plasma [Ca^{2+}]
  - thyroidectomy
  - C-cell tumors

Rickets-Osteomalacia

- **Vitamin D deficiency**
  - Dietary
  - Deficient synthesis
- **GI disorders**
- **Hereditary**
  - Pseudovitamin D-deficient rickets or vitamin D-dependent rickets type I (↓ 1α–OHase)
  - Pseudovitamin D-deficient rickets or vitamin D-dependent rickets type II (↓ 1,25-$(OH)_2$-receptor)
- **Chronic renal failure**
- **Phosphate depletion**
  - Dietary
  - Renal

Treatment of Rickets-Osteomalacia

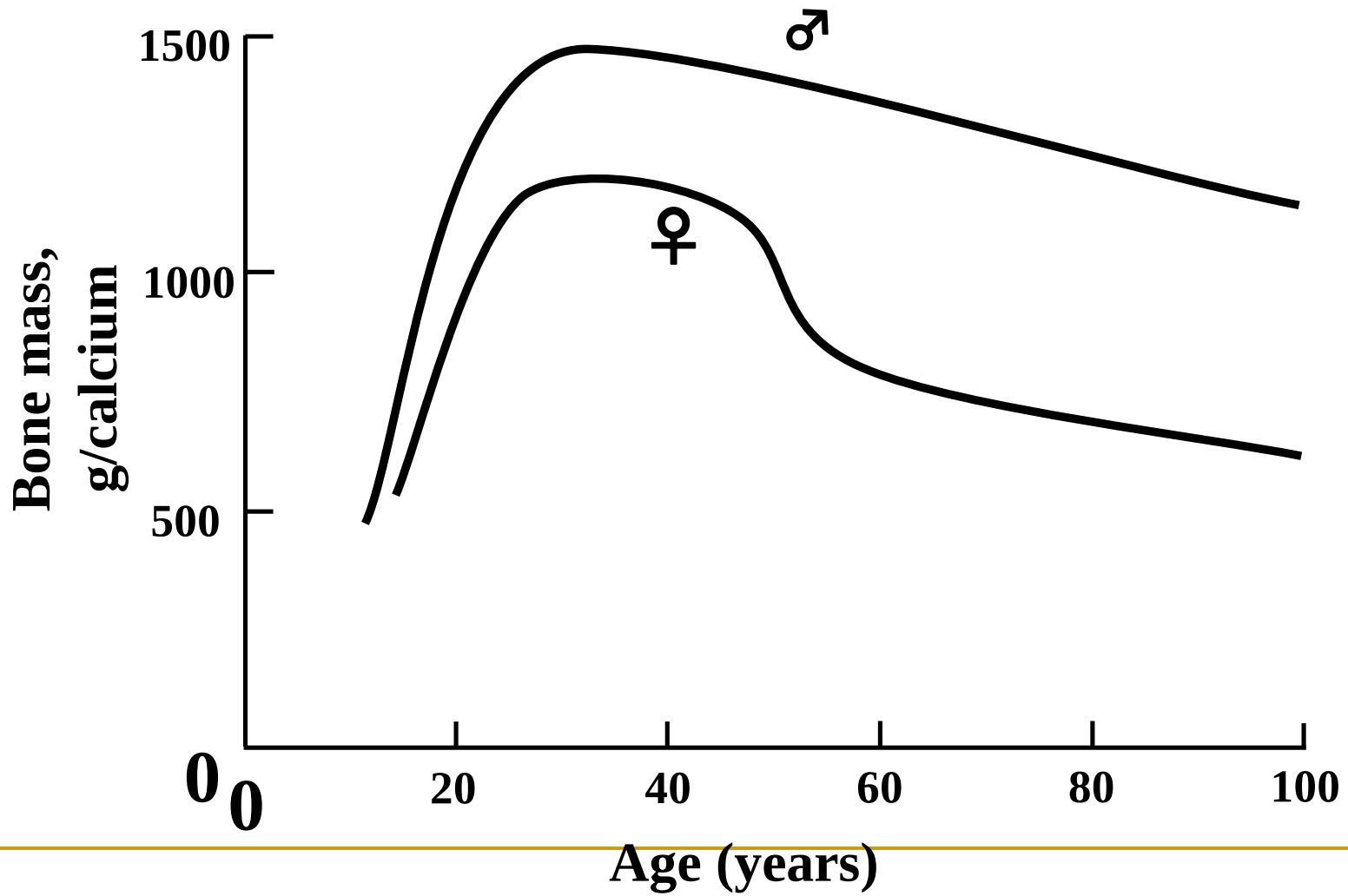
- Vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol)
- Calcium
- Sunlight
- 1,25-$(OH)_2$-D_3 (calcitriol)

Osteoporosis

- Aging
  - ↓ estrogen
  - ↓ testosterone
  - ↓ GH
- ↑ Glucocorticoids
- Immobilization
- (↓ Vitamin D + Ca^{2+})*

*secondary response

Time-Dependent Changes in Bone Mass



Hypocalcemia

Disorder	Plasma [PTH]	Plasma [1,25-$(OH)_2$-D_3]	Bone	Urine	Plasma [Ca^{2+}]	Plasma [Phosphate]
Surgical hypoparathyroidism	↓*	↓	↓ Resorption	↓ Phosphate ↓ cAMP	↓	↑
Vitamin D deficiency	↑ (2)	↓*	Osteomalacia ↑ Resorption	↑ Phosphate ↑ cAMP	↔↓	↓↓
Chronic renal failure	↑ (2)	↓*	Osteomalacia ↑ Resorption	↓ Phosphate (↓ GFR)*	↔↓	↑

* Primary events or disturbances

Prevalent Endocrine Disorders in the Adult

Disorder	Prevalence
• Type II DM	~8%
•Hypothyroidism	5-10%, ♀ 0.5-2%, ♂
•Graves' disease	1-3%, ♀ .1%, ♂
•Thyroid nodules	5%
•Osteoporosis	5%, ♀ 1%, ♂
•Hyperparathyroidism	0.1-0.5%, ♀>♂

Primary Hyperparathyroidism

Plasma [PTH]	Plasma [1,25-$(OH)_2$-D_3]	Bone	Urine	Plasma [Ca^{2+}]	Plasma [Phosphate]
↑*	↑	↑ Resorption	↑ Phosphate ↑ Ca^{2+} ↑ cAMP	↑	↓

* Primary disturbance

Endocrine Control of Calcium Metabolism

- Plasma Ca^{2+} must be closely regulated to prevent changes in neuromuscular excitability
  - Also plays vital role in a number of essential activities
    - Excitation-contraction coupling in cardiac and smooth muscle
    - Stimulus-secretion coupling
    - Maintenance of tight junctions between cells
    - Clotting of blood
  - Hypercalcemia
    - Reduces excitability
  - Hypocalcemia
    - Brings about overexcitability of nerves and muscles
    - Severe overexcitability can cause fatal spastic contractions of respiratory muscles

Endocrine Control of Calcium Metabolism

- Three hormones regulate plasma concentration of Ca^{2+} (and PO_4^{3-})
  - Parathyroid hormone (PTH)
  - Calcitonin
  - Vitamin D

Endocrine Control of Calcium Metabolism

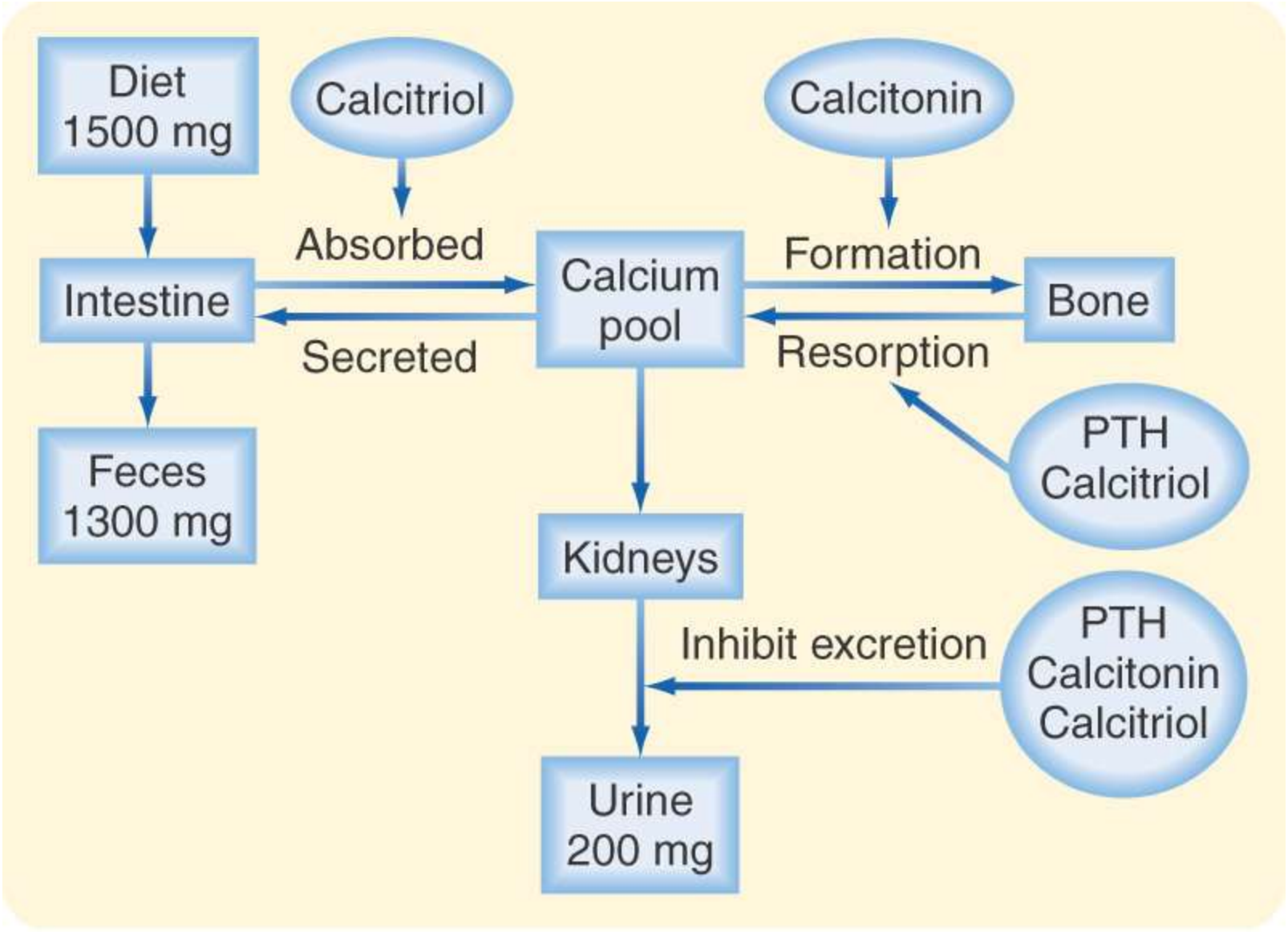
- Parathyroid hormone (PTH)
  - Secreted by parathyroid glands
  - Primary regulator of Ca^{2+}
    - Raises free plasma Ca^{2+} levels by its effects on bone kidneys, and intestines
  - Essential for life
    - Prevents fatal consequences of hypocalcemia
  - Facilitates activation of Vitamin D

Endocrine Control of Calcium Metabolism

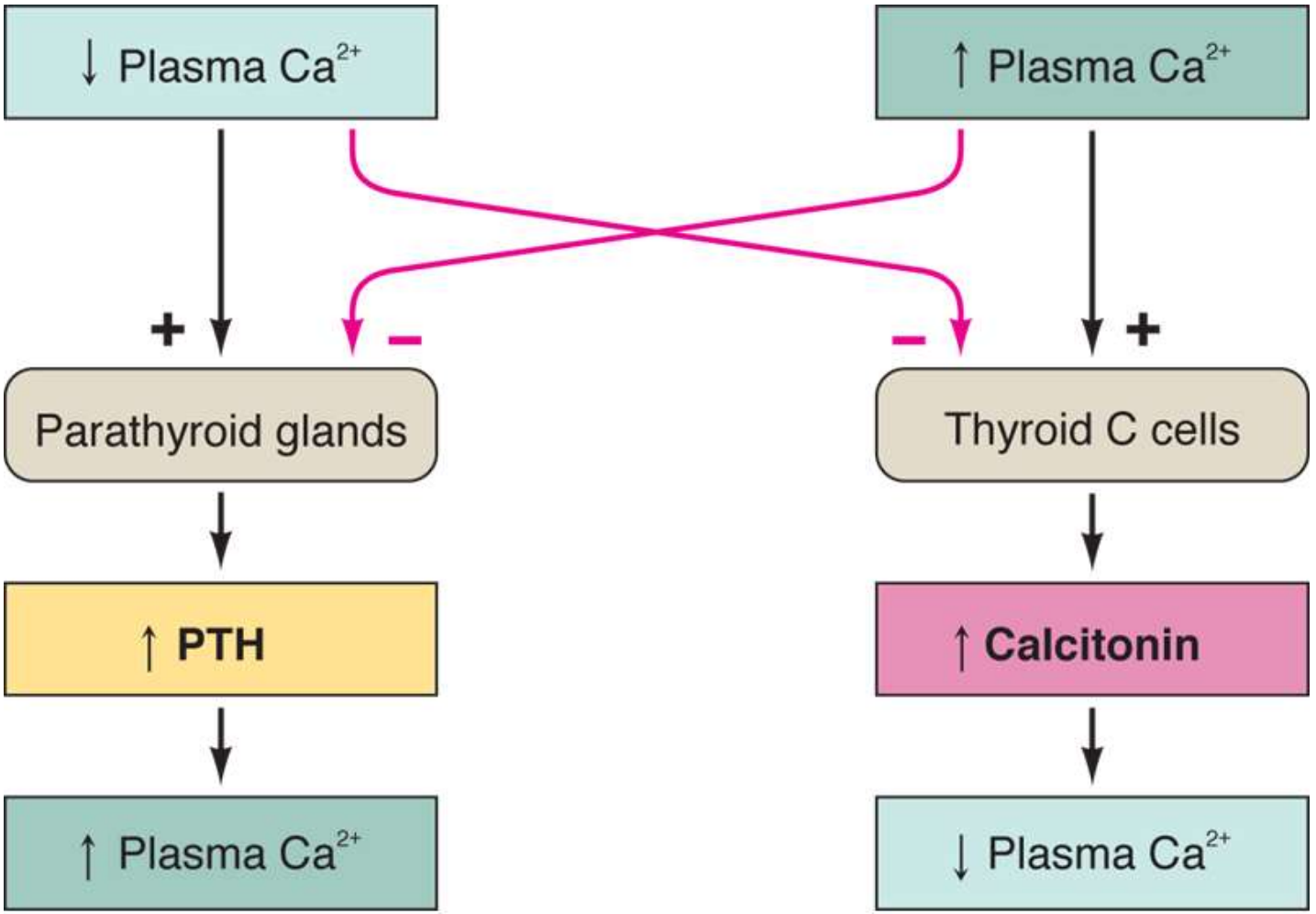
- Vitamin D
  - Stimulates Ca^{2+} and PO_4^{3-} absorption from intestine
  - Can be synthesized from cholesterol derivative when exposed to sunlight
    - Often inadequate source
  - Amount supplemented by dietary intake
  - Must be activated first by liver and then by kidneys before it can exert its effect on intestines

Endocrine Control of Calcium Metabolism

- Calcitonin
  - Hormone produced by C cells of thyroid gland
  - Negative-feedback fashion
    - Secreted in response to increase in plasma Ca^{2+} concentration
  - Acts to lower plasma Ca^{2+} levels by inhibiting activity of bone osteoclasts
  - Unimportant except during hypercalcemia

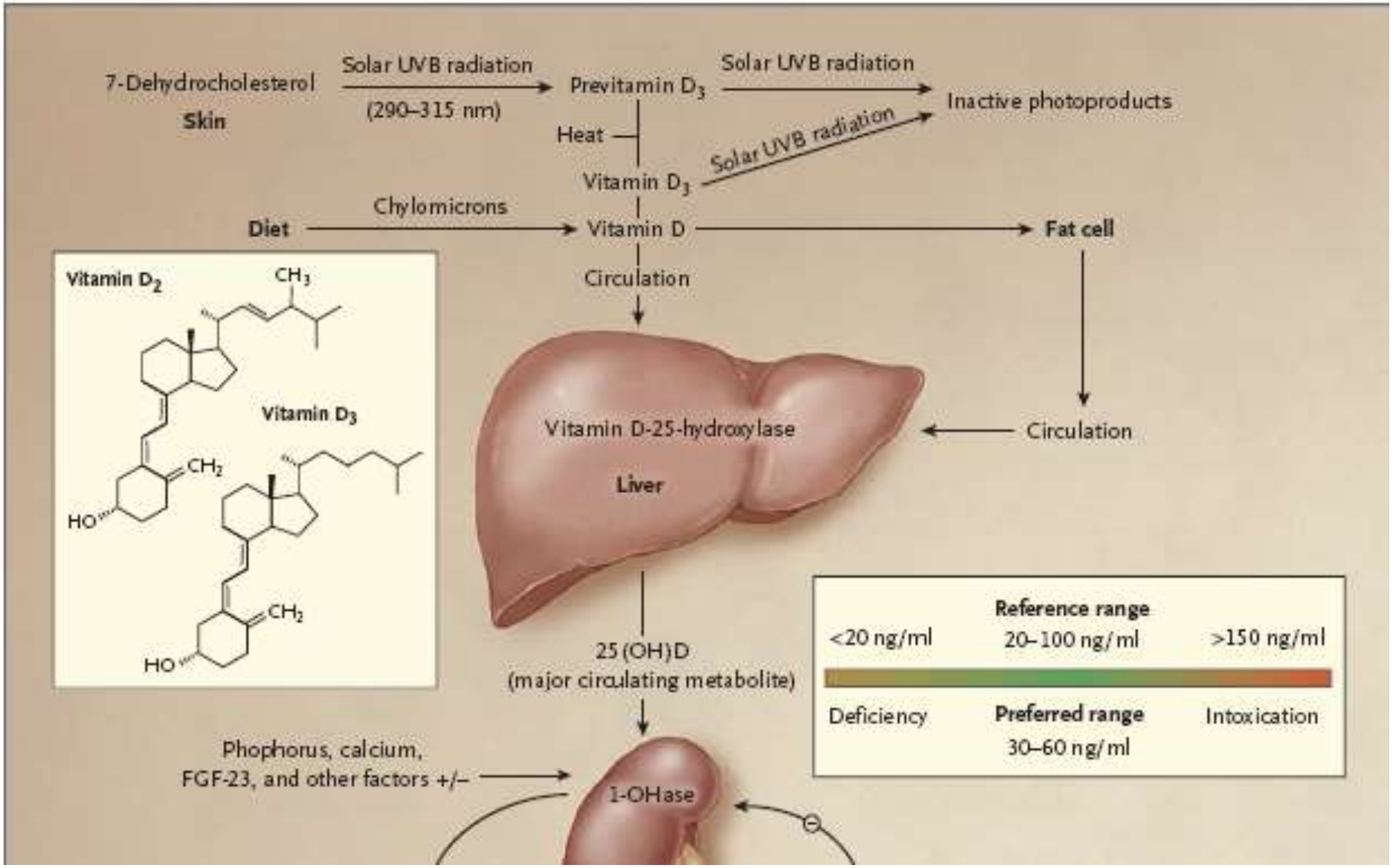


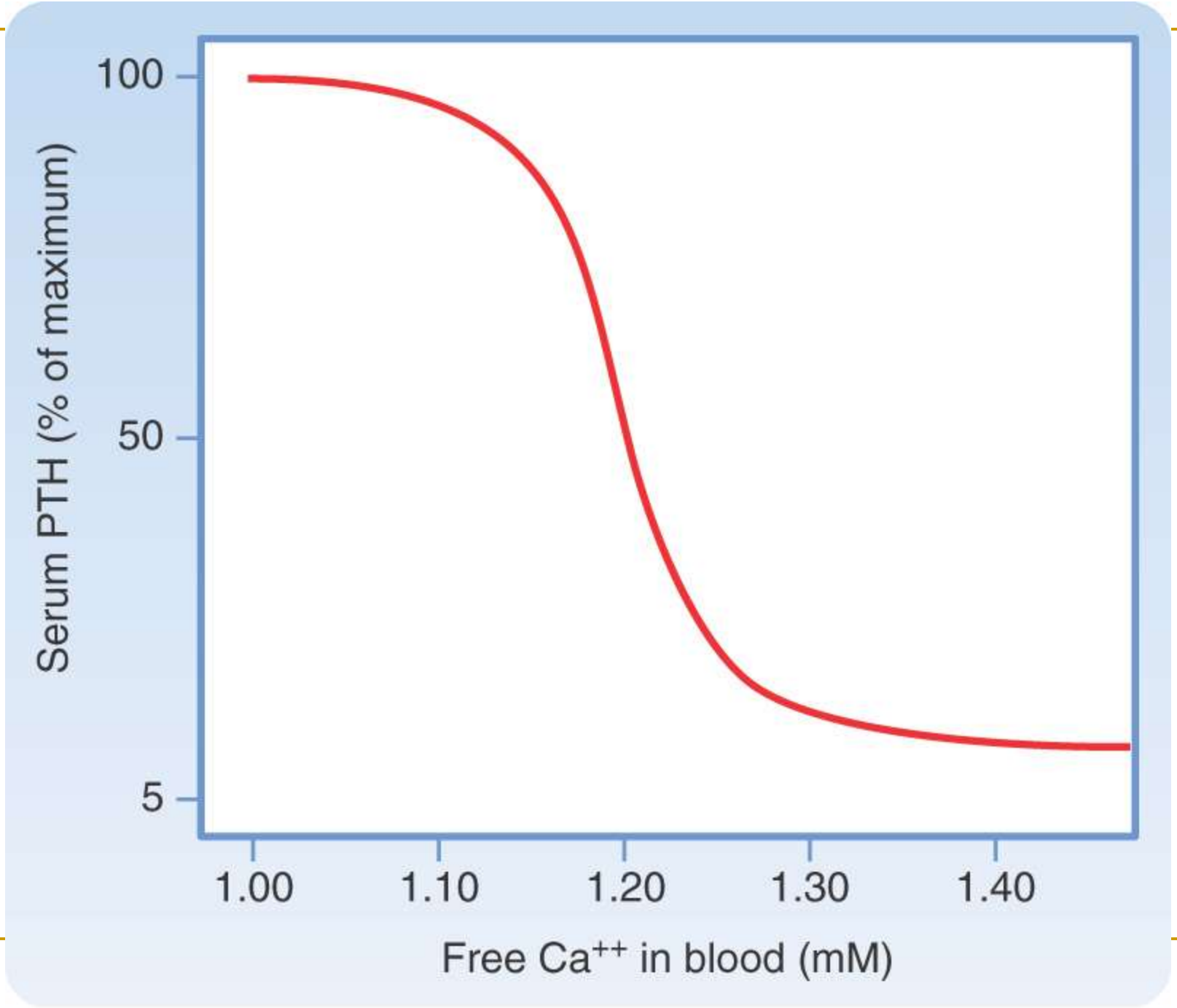
Negative-feedback Loops Controlling Parathyroid Hormone (PTH) and Calcitonin Secretion



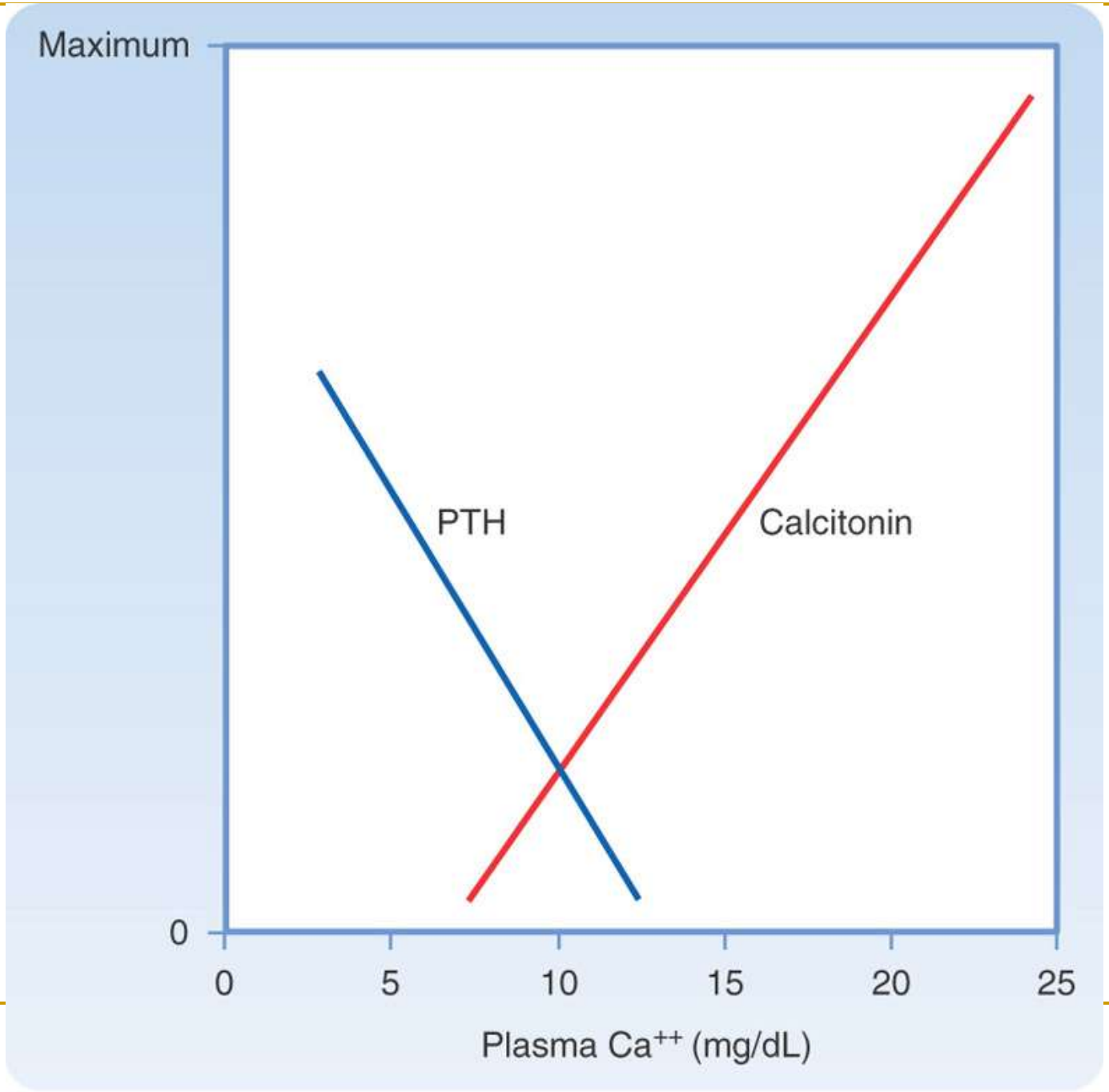
Calcium Disorders

- **PTH hypersecretion (hyperparathyroidism)**
  - Characterized by hypercalcemia and hypophosphatemia
- **PTH hyposecretion (hypoparathyroidism)**
  - Characterized by hypocalcemia and hyperphosphatemia
- **Vitamin D deficiency**
  - Children – rickets
  - Adults – osteomalacia


7-Dehydrocholesterol
Skin
Solar UVB radiation
(290–315 nm)
Previtamin D_3
Solar UVB radiation
Inactive photoproducts
Heat
Vitamin D_3
Solar UVB radiation
Diet
Chylomicrons
Vitamin D
Fat cell
Circulation
Vitamin D_2
CH_3
Vitamin D_3
CH_2
HO
CH_2
HO
Vitamin D-25-hydroxylase
Liver
Circulation
25 (OH)D
(major circulating metabolite)
Reference range
<20 ng/ml
20–100 ng/ml
>150 ng/ml
Deficiency
Preferred range
30–60 ng/ml
Intoxication
Phophorus, calcium,
FGF-23, and other factors +/–
1-OHase



(Modified from Porterfield SP, White BA: Endocrine Physiology, 3rd ed. Philadelphia, Mosby, 2007.)



(Modified from Azria M: The Calcitonins: Physiology and Pharmacology. Basel, Karger, 1989.)

Thank You