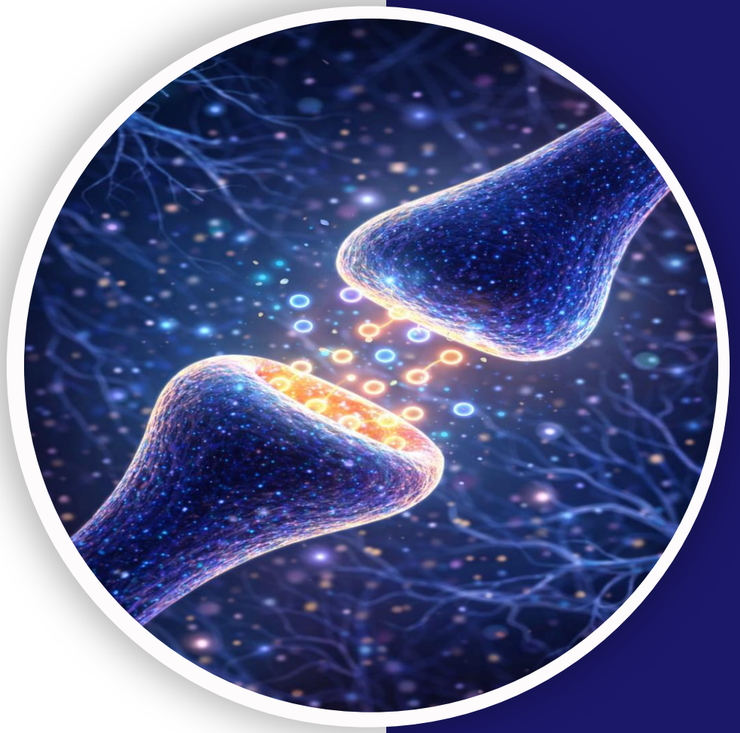
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Physiology | MID L7

Calcium homeostasis



Written by : Leen aljarrah

Leen Abukhalaf

Calcium Homeostasis

Calcium homeostasis maintains the concentration of calcium within a very narrow range because calcium is essential for many physiological processes. Cardiac contraction: Calcium is required for the normal contraction of the heart. For example, during heart transplantation, the heart is preserved in a solution containing calcium to maintain its viability. Without calcium, the heart would not function properly and could become nonviable.
Blood coagulation: Blood clotting involves 12 coagulation factors. Most of these factors are proteins, whereas Factor IV is calcium, which plays a crucial role in the coagulation process.
Cell secretion: Calcium is essential for the secretion of substances from cells, as it triggers the release of secretory vesicles.

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; 2 superior & 2 inferior. They are located posterior to the thyroid gland. Both glands have completely different functions and secrete different hormones.

☺ Parathyroid hormone (PTH) or parathormone, .

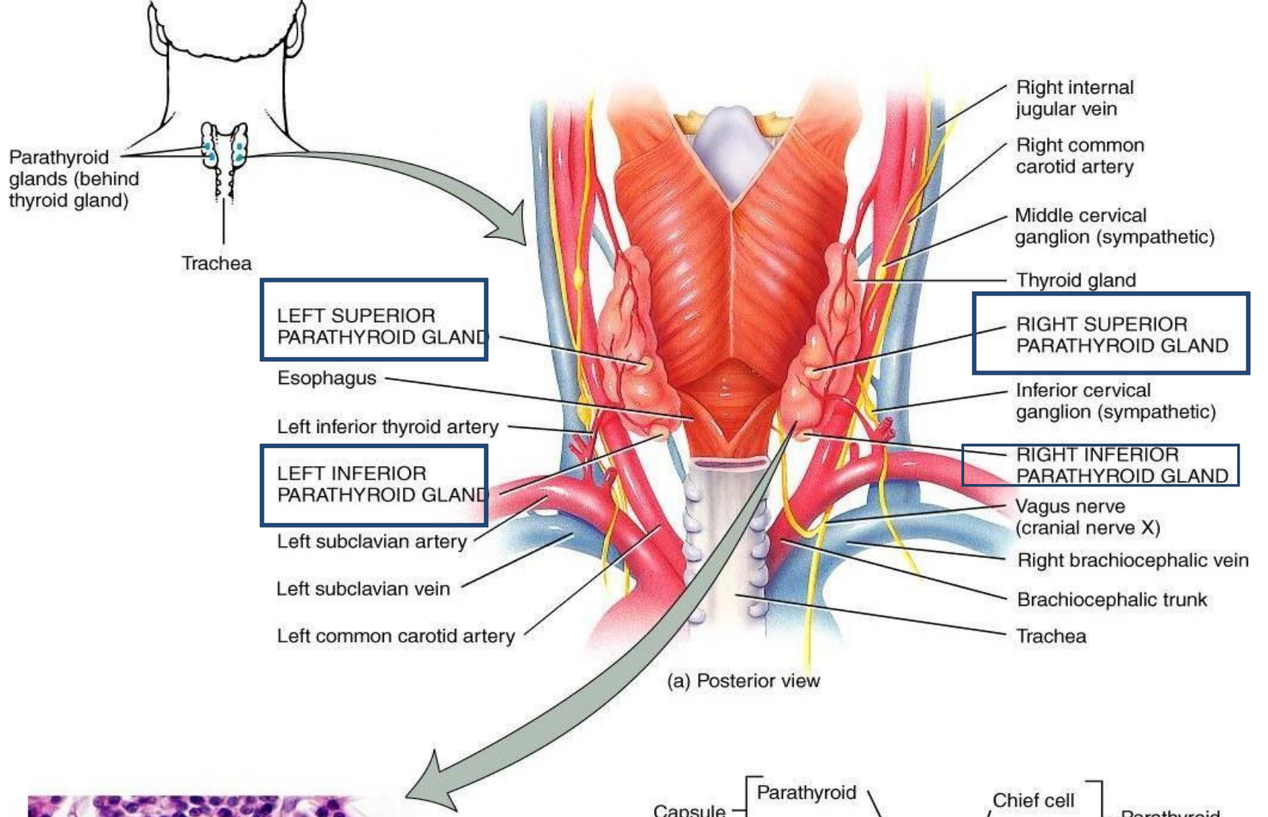
- ☺ Major regulator of calcium, magnesium, and phosphate ions in the blood
- ☺ Increases number and activity of osteoclasts (catabolic cells- bone resorption)
- ☺ Elevates bone resorption
- ☺ Functions in the kidney where it stimulates the conversion of 25-hydroxycholecalciferol (inactive vitamin D), a cholesterol derivative, into 1,25-dihydroxycholecalciferol (active vitamin D-calcitriol) which will increase intestinal Ca^{++} reabsorption.

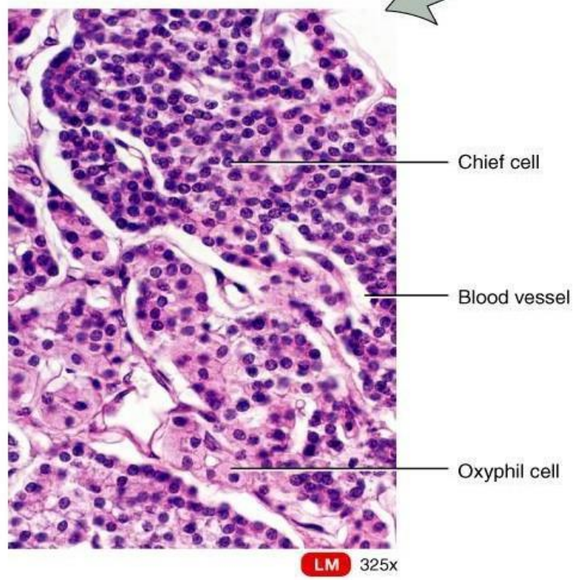
☺Blood calcium level directly controls secretion of both calcitonin and PTH via negative feedback

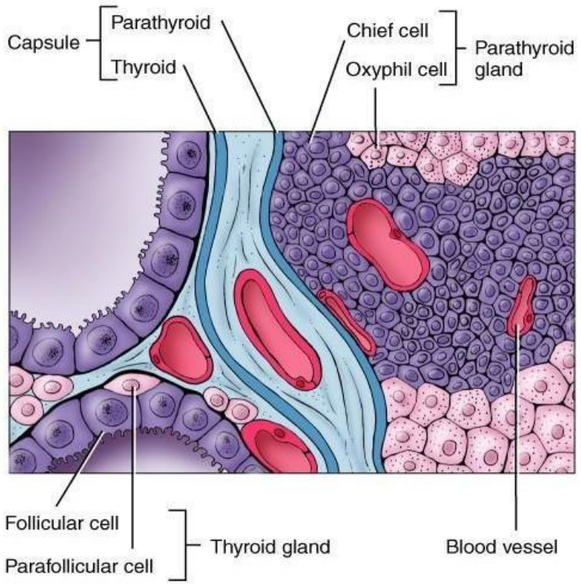
Parathyroid Glands

- ✓ Recall from previous lectures that **parafollicular cells** are located in the thyroid gland, but are not a part of the thyroid follicles. These cells secrete calcitonin,

During a thyroidectomy, the parathyroid glands may be accidentally removed, leading to hypocalcemia. This increases the excitability of the nerves and muscles. The most serious problem is the effect on the respiratory muscles, which can lead to respiratory complications.



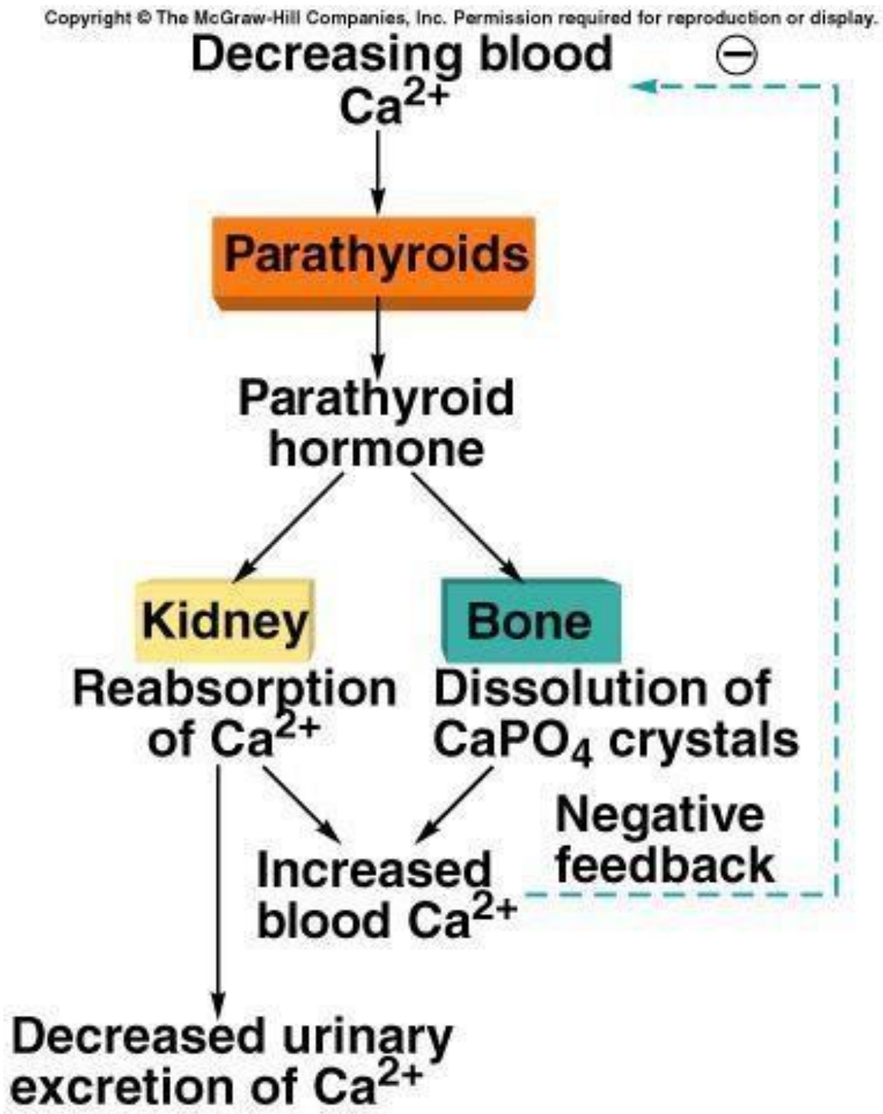




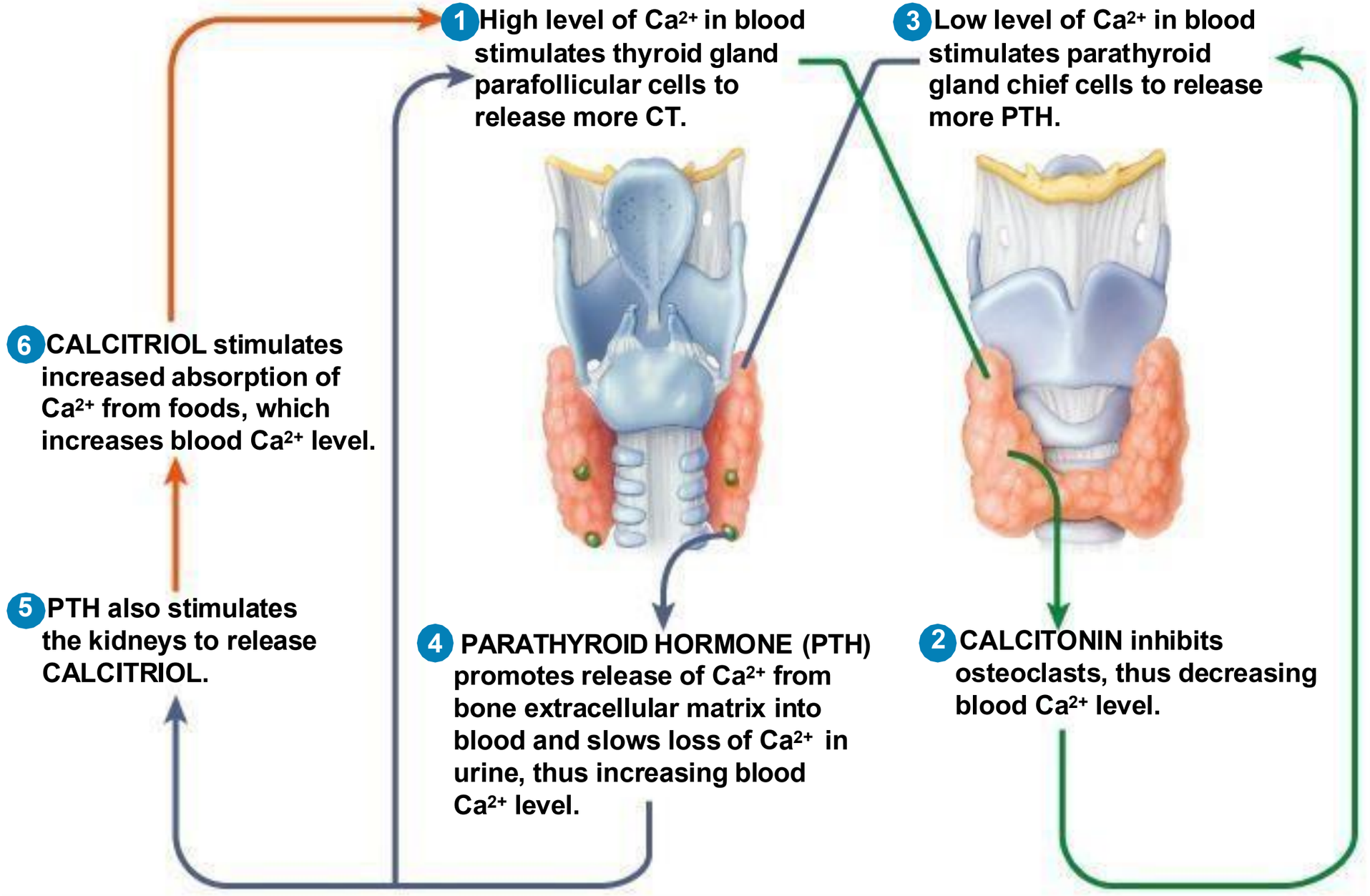
Parathyroid Glands

- 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.

- The main stimulus for parathyroid hormone (PTH) secretion is hypocalcemia.
- Important note: Vitamin D stimulates the absorption of both calcium and phosphate from the intestine, whereas parathyroid hormone (PTH) stimulates calcium reabsorption in the kidneys and phosphate excretion.



Roles of Calcitonin, Parathyroid hormone, Calcitriol in Calcium Homeostasis



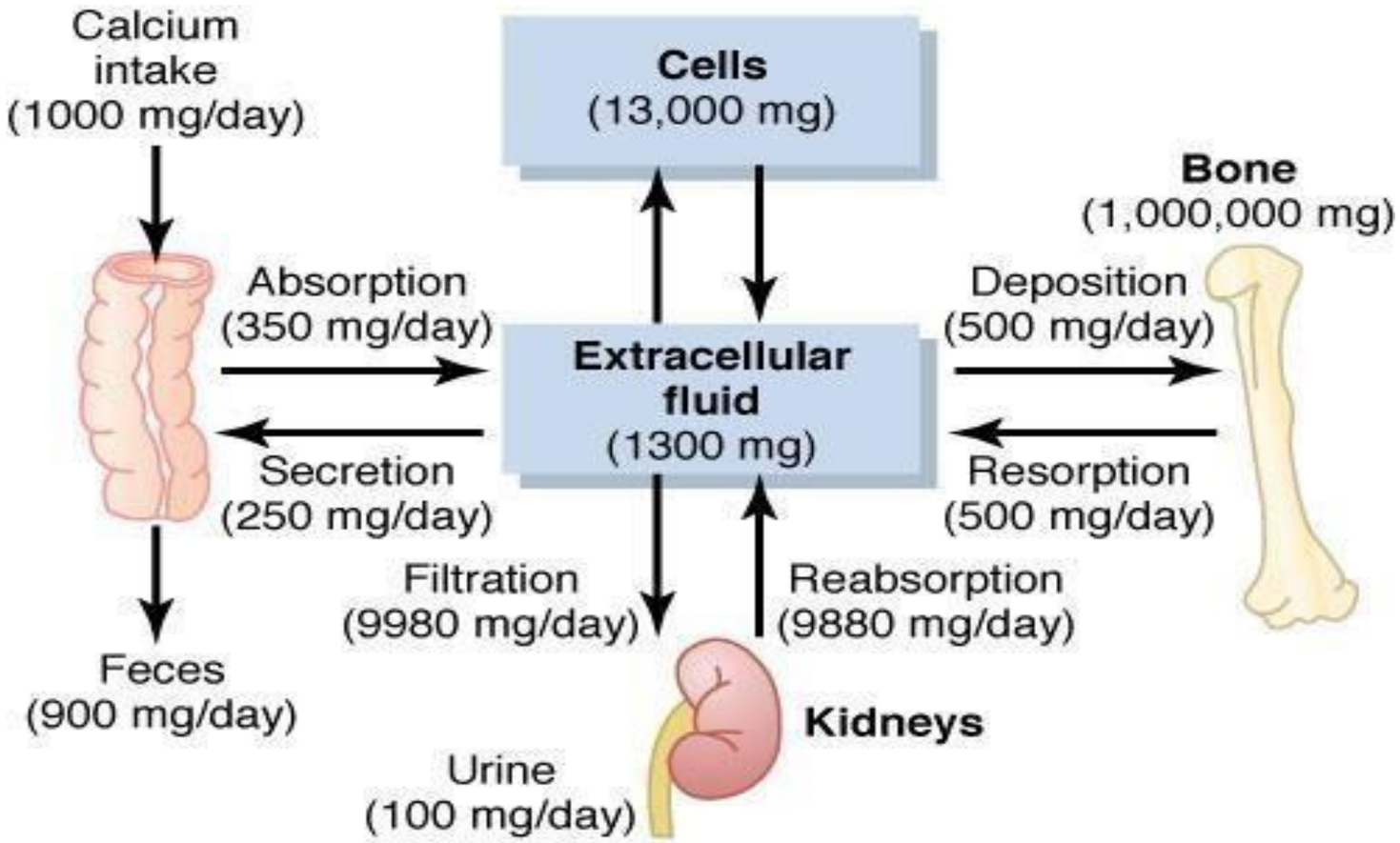
Calcitonin decreases blood calcium levels by retaining calcium in the bone matrix.

Hormonal Control of Calcium Metabolism

- PTH
- Vitamin D
- Calcitonin

❑ PTH and calcitonin have opposing effects. Vitamin D affects the GI to enhance Ca^{2+} absorption.

Calcium Metabolism



- The net amount of calcium absorbed in the GI is 100mg/day.
- The net amount of calcium excreted in urine after the reabsorption processes is 100mg/day.
- There's zero loss of calcium in bones (this is may be before the age of 45 , as beyond that bone resorption becomes more).
- Calcium moves from the inside of the cell to the outside and vice versa, based on the need.

Numbers in the diagram are **not** required. You only have to know how much the kidney secretes per day :)

[]= concentration

Calcium Homeostasis

- The main function of the PTH is to **increase** [Ca^{2+}] in the blood, hence why a low [Ca^{2+}] stimulates it. The normal total [Ca^{2+}] in the blood is ~10 mg/100 mL plasma, which translates to about 2.4-2.5 mmol/L plasma.

$$\frac{10\ mg}{100\ mL} = \frac{100\ mg}{1\ L}$$

Normal [Ca^{2+}]

$$\frac{100\ mg}{1\ L} \times \frac{1\ mol}{40000\ mg} = 2.5\ \frac{mMol}{L}$$

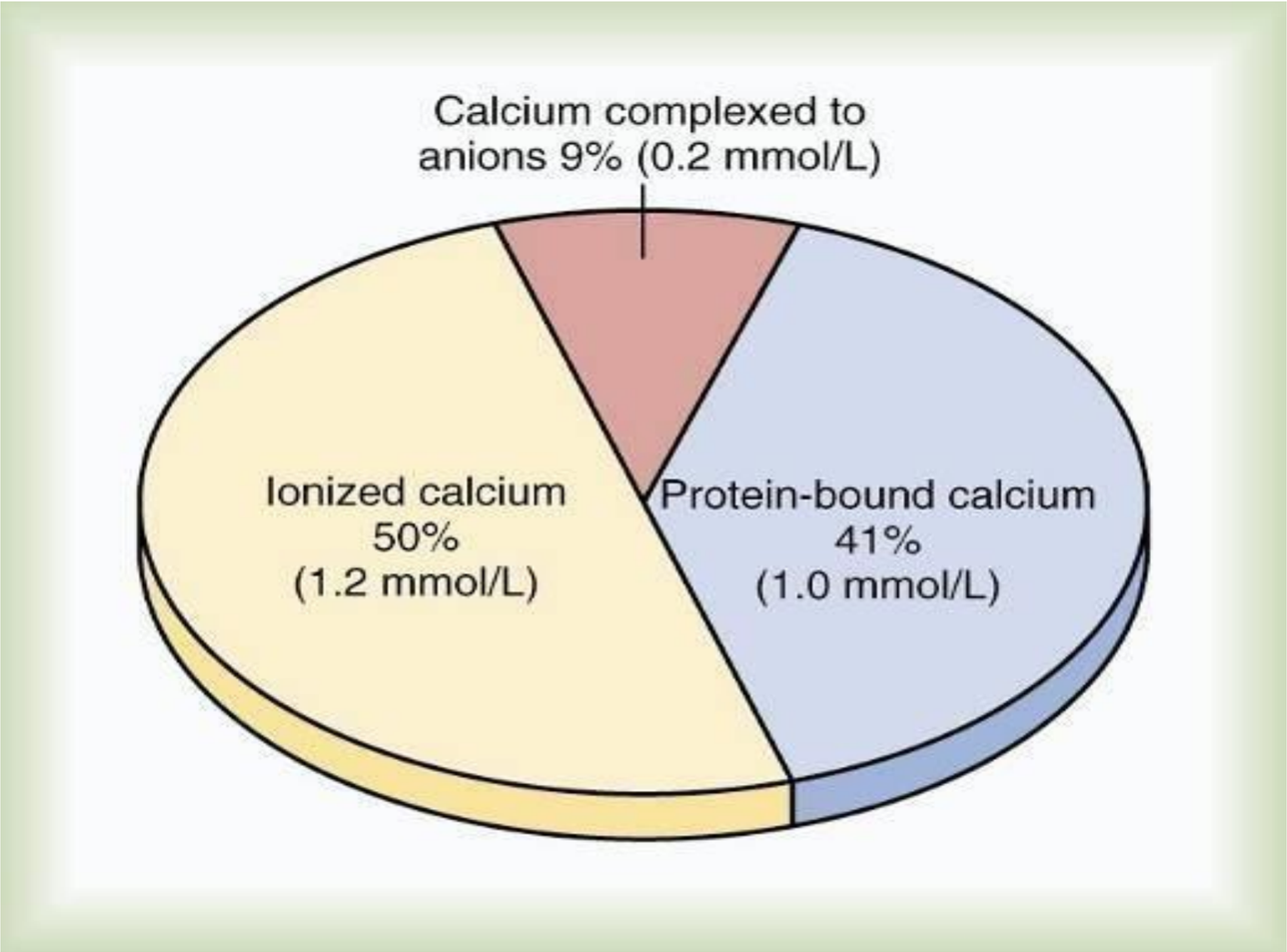
1 mol Ca = 40.078 g
1 g = 1000 mg

1 mol = 1000 mMol

- This 2.5 mmol/mL represents the total [Ca^{2+}] in the blood, which includes **ionic [Ca^{2+}]** and **bound calcium** (to albumin mostly). **Ionic calcium** which is the free, unbound calcium that's responsible for its effects on heart, nervous system, and bone formation[1]. It makes up around 50% of the total [Ca^{2+}] in the body, while bound calcium makes up the other 50% (1.25mmol). Calcium regulation targets **ionized calcium;** however, standard blood tests typically measure the **total [Ca^{2+}]**. Therefore, it is best to request a **protein (serum albumin) test** as well. This helps make a corrected value of the ionized Ca^{2+} levels. If protein (albumin) is low, total calcium levels may appear reduced even when ionized calcium levels are normal.

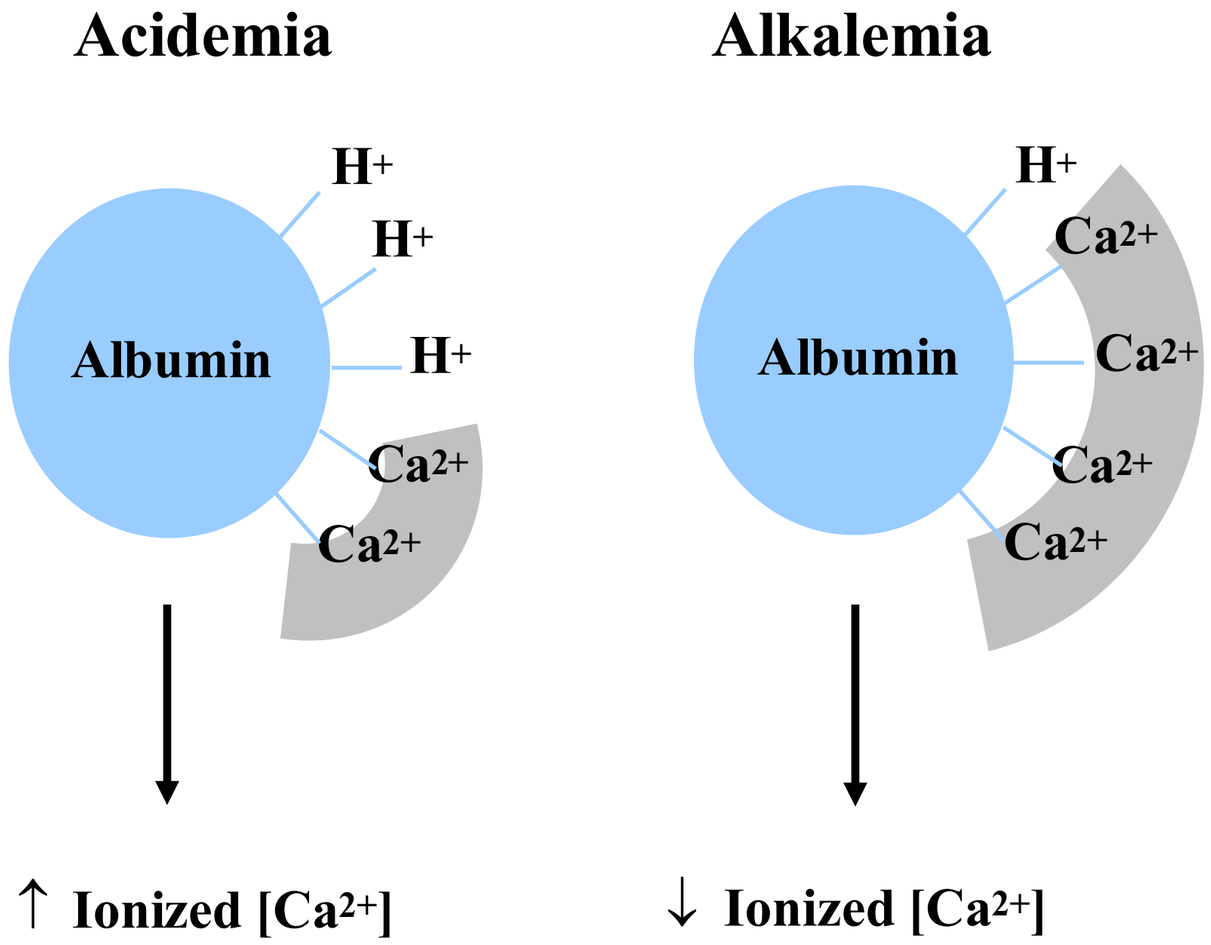
Distribution of Ionized Calcium in the Blood

- ✓ Recall that the intracellular $[Ca^{2+}]$ is 10^{-7} M, and 10^{-3} M extracellularly.

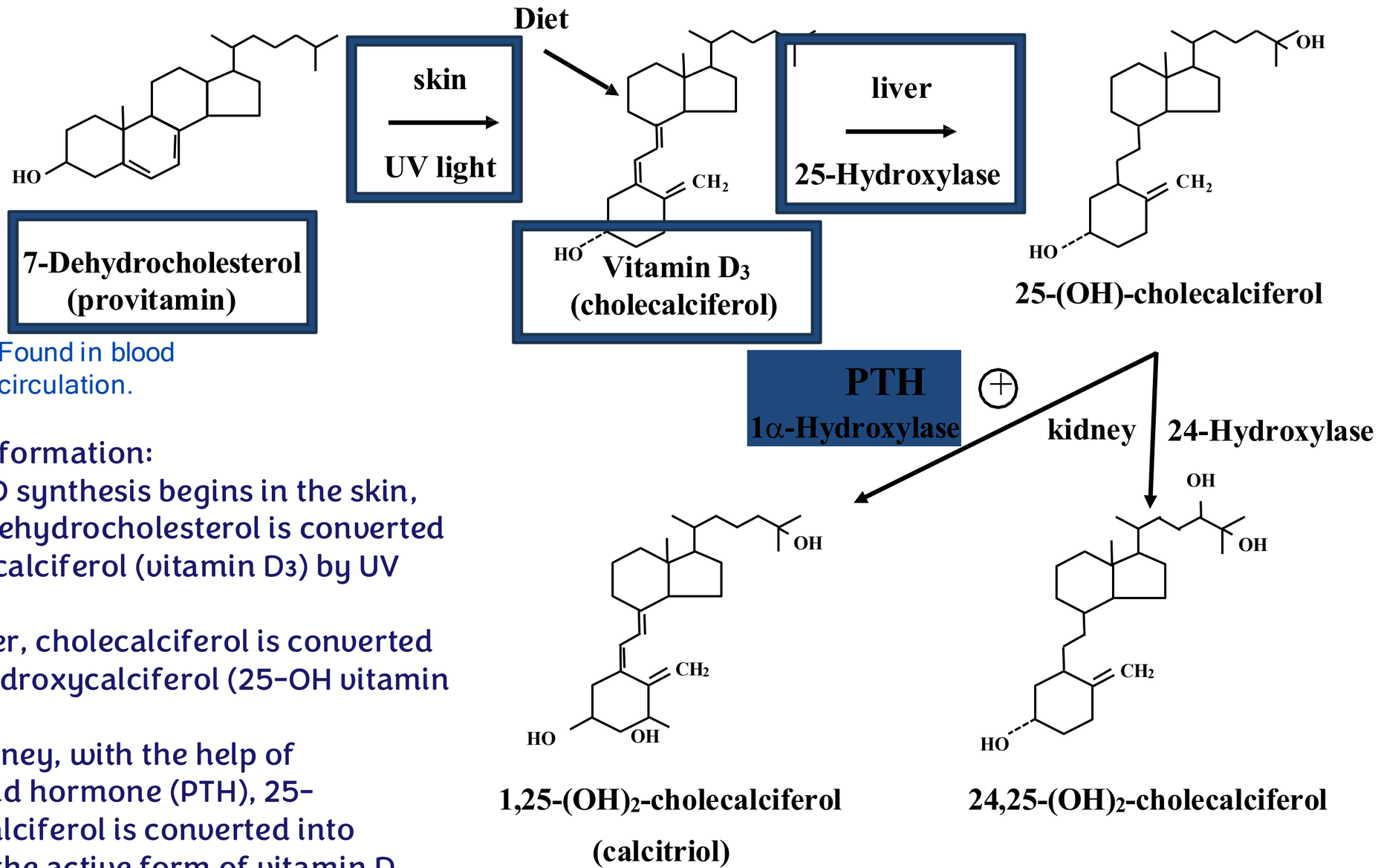


Effects of Acid-Base Disturbances on Ionized Calcium

- pH levels affect calcium binding to albumin. In the case of **acidosis** (low pH <7.35), calcium binds less to albumin resulting in a higher [ionized calcium]. On the other hand, **alkalosis** (high pH >7.45), more calcium will bind to albumin, decreasing the [ionized calcium]. This is important in diabetes and metabolic acidosis
  - Imagine this for better understanding, low pH means an abundance of hydrogen ions, making it more likely to find them bound to albumin, even competing with calcium for it. High pH means a lower [H^+], less competence and less chances of hydrogen binding to albumin.



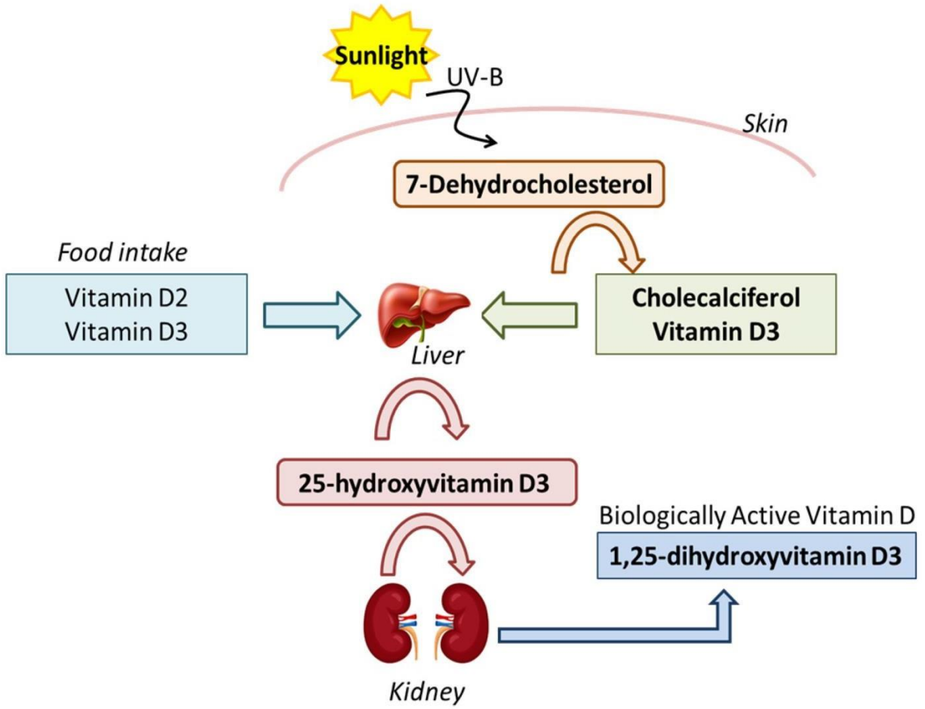
Formation and Hydroxylation of Vitamin D_3



Vitamin D formation:

- Vitamin D synthesis begins in the skin, where 7-dehydrocholesterol is converted into cholecalciferol (vitamin D3) by UV light.
- In the liver, cholecalciferol is converted into 25-hydroxycalciferol (25-OH vitamin D).
- In the kidney, with the help of parathyroid hormone (PTH), 25-hydroxycalciferol is converted into calcitriol, the active form of vitamin D.

- Sun exposure is recommended for vitamin D synthesis in the body.
- This is due to the fact that UV light converts the intermediate 7-dehydrocholesterol into vitamin D3, which then travels to the liver where it gets hydroxylated at the 25th carbon, forming 25-hydroxyvitamin D3.
- The kidney also has an enzyme, 1$^{\alpha}$- hydroxylase, that adds an OH to the 1st carbon to form **calcitriol**, or 1,25-dihydroxyvitamin D3. This enzyme is stimulated by the PTH.
- Calcitriol (active form of vitamin D) goes to the GI tract and increases calcium absorption from food, which raises blood calcium levels. PTH raises calcium levels in the blood directly through its effects on the bones and kidneys, and indirectly through vitamin D activation.



This diagram was added for better comprehension.

Vitamin D

- Vitamin D is a cholesterol derivative and is a steroid. This implies that it's receptor is present intracellularly, either cytoplasmic or intranuclear, and is a dimer of DNA and vitamin D-binding sites. In contrast, calcitonin and PTH are both peptide hormones with their receptors on the cell's surface. Another enzyme is present in the kidney, 24-hydroxylase which produces 24,25-$(OH)_2$-cholecalciferol, an inactive form of vitamin D. Even if it was present in the blood, it is physiologically irrelevant.

- Vitamin D deficiencies and malformations could arise because of kidney or liver diseases.

Vitamin D Actions

- **Intestine**
  - ↑ Ca^{2+} absorption
  - ↑ phosphate absorption
- **Bone**
  - ↑ mineralization (indirect effect) ➢ Due to high calcium levels.
  - ↑ bone resorption (direct effect)
- **Kidney**
  - ↑ Ca^{2+} reabsorption (weak effect)
  - ↑ phosphate reabsorption (weak effect)
  - Very high levels of vitamin D might affect reabsorption of calcium and phosphate in the kidney.

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

The active form of vitamin D (calcitriol) enters the cell because it is lipid-soluble. It binds to an intracellular receptor, and the complex translocates to the nucleus, where it stimulates the synthesis of proteins involved in calcium absorption. These proteins include calbindin, the calcium ATPase (Ca^{2+} pump), and the **Na^{+}/Ca^{2+} exchanger.

Calcium concentration is higher in the intestinal lumen, so Ca^{2+} enters the cell by passive diffusion through calcium channels, following its electrochemical gradient.

Inside the cell, calcium binds to calbindin, which transports it to the basolateral membrane.

- At the basolateral membrane, calcium leaves the cell by two transport mechanisms: A Ca^{2+}-ATPase (calcium pump), which uses ATP to actively transport calcium into the interstitial fluid against its concentration gradient.
- A Na^{+}/Ca^{2+} exchanger(like the one in the heart), which moves 3 Na^{+} into the cell in exchange for 1 Ca^{2+} leaving the cell.

Phosphate enters the cell through the Na^{+}/phosphate (NaPi) cotransporter, where phosphate is absorbed together with sodium.

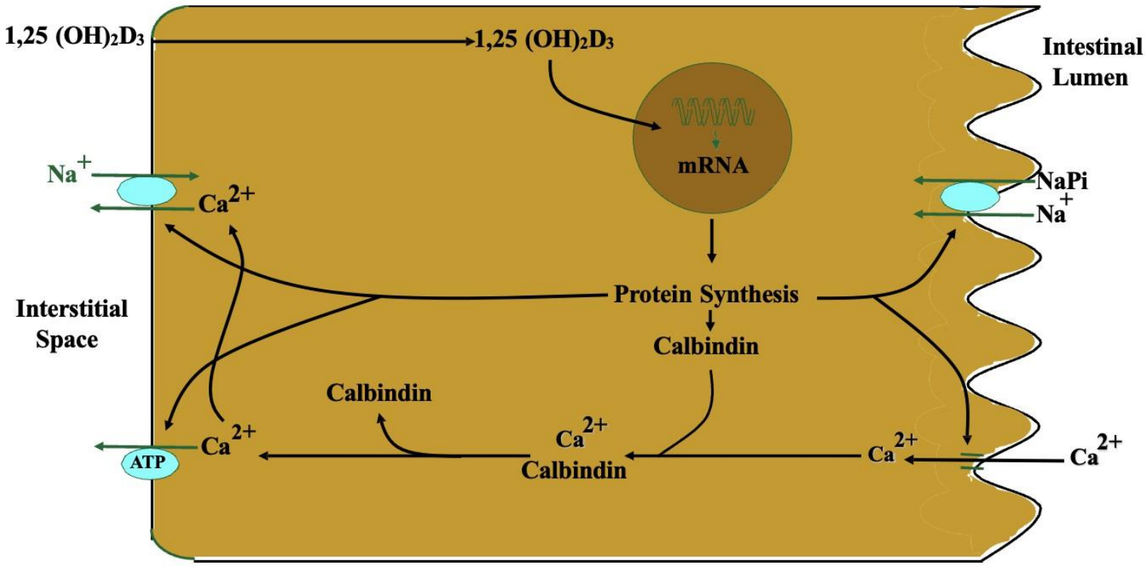
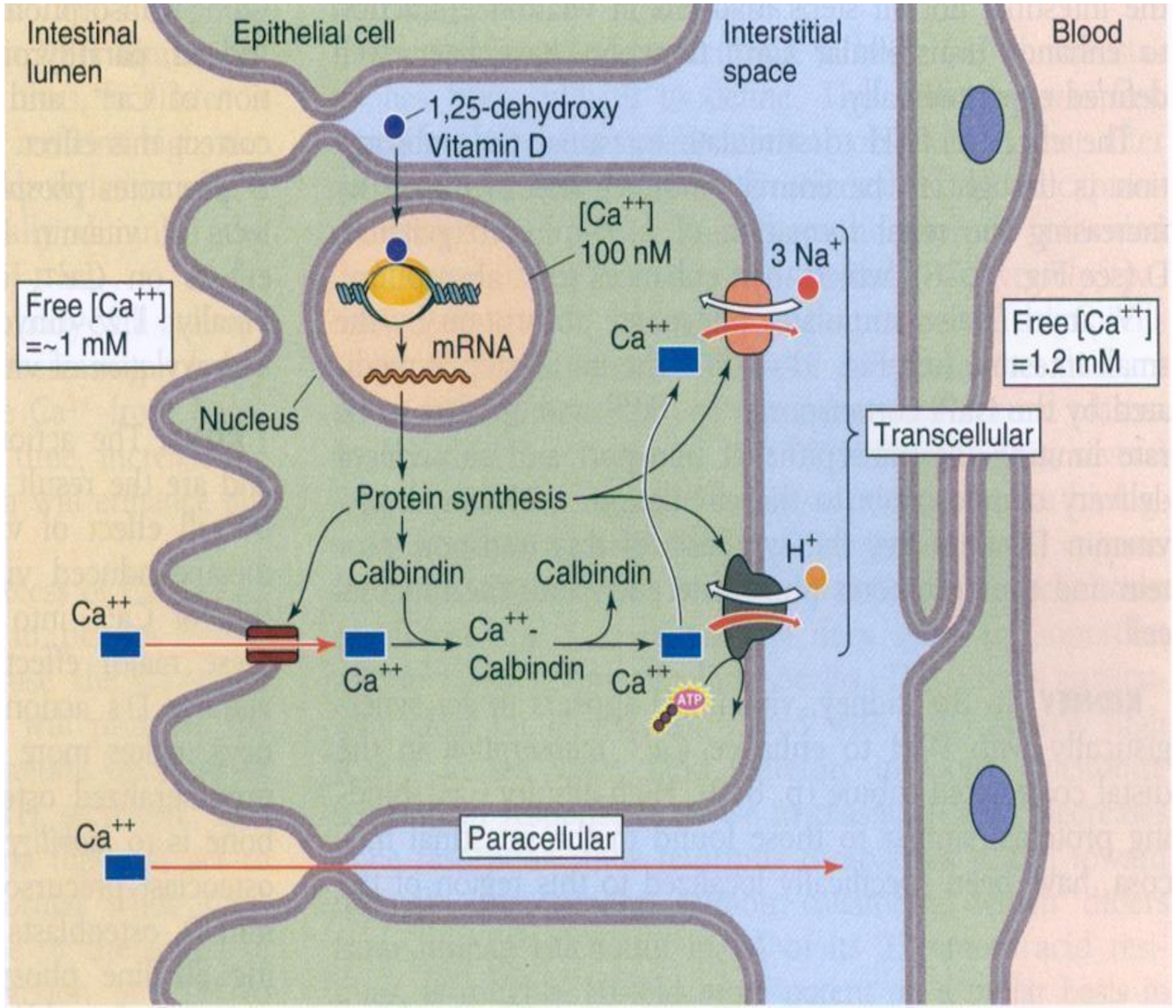


Figure of an intestinal epithelial cell.

Intestinal Absorption of Calcium

- A third type of receptor that might be present at the basolateral surface is the Ca2+/H+ ATPase. In the intestines, the duodenum in this case, there are intercellular spaces, or a *paracellular pathway,* that allow for fluid and ion absorption and movement according to the osmotic pressure. The interstitial space has high sodium and potassium concentrations, drawing the fluids into that direction (left → right).



PTH Actions

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

The main stimulus for PTH secretion is **hypocalcemia (decreased plasma calcium concentration).**

PTH receptors are found on **osteoblasts and osteocytes**. When PTH binds to these cells, it increases **osteolysis** (rapid release of calcium from bone) and indirectly increases the **bone resorption activity of osteoclasts**, leading to the release of calcium into the extracellular fluid.

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

Blood is filtered through the kidney by the **Glomerular Filtration Rate (GFR)**. Since the filtrate contains almost all plasma components (except large proteins), calcium is also filtered into the renal tubules.
PTH acts to **increase calcium reabsorption**, so less calcium is lost in urine.
At the same time, it **increases phosphate excretion** (phosphaturia).

- The reason phosphate is important is that **inside cells**, the major: **Cation:** Potassium (K^{+})
- **Anions:** Proteins and phosphate.

When phosphate leaves the extracellular fluid and is excreted, more calcium remains free in the plasma instead of binding with phosphate.
The doctor also mentioned that **sodium and phosphate are usually reabsorbed together in the proximal tubule**, so decreasing phosphate reabsorption also decreases its accompanying sodium reabsorption.

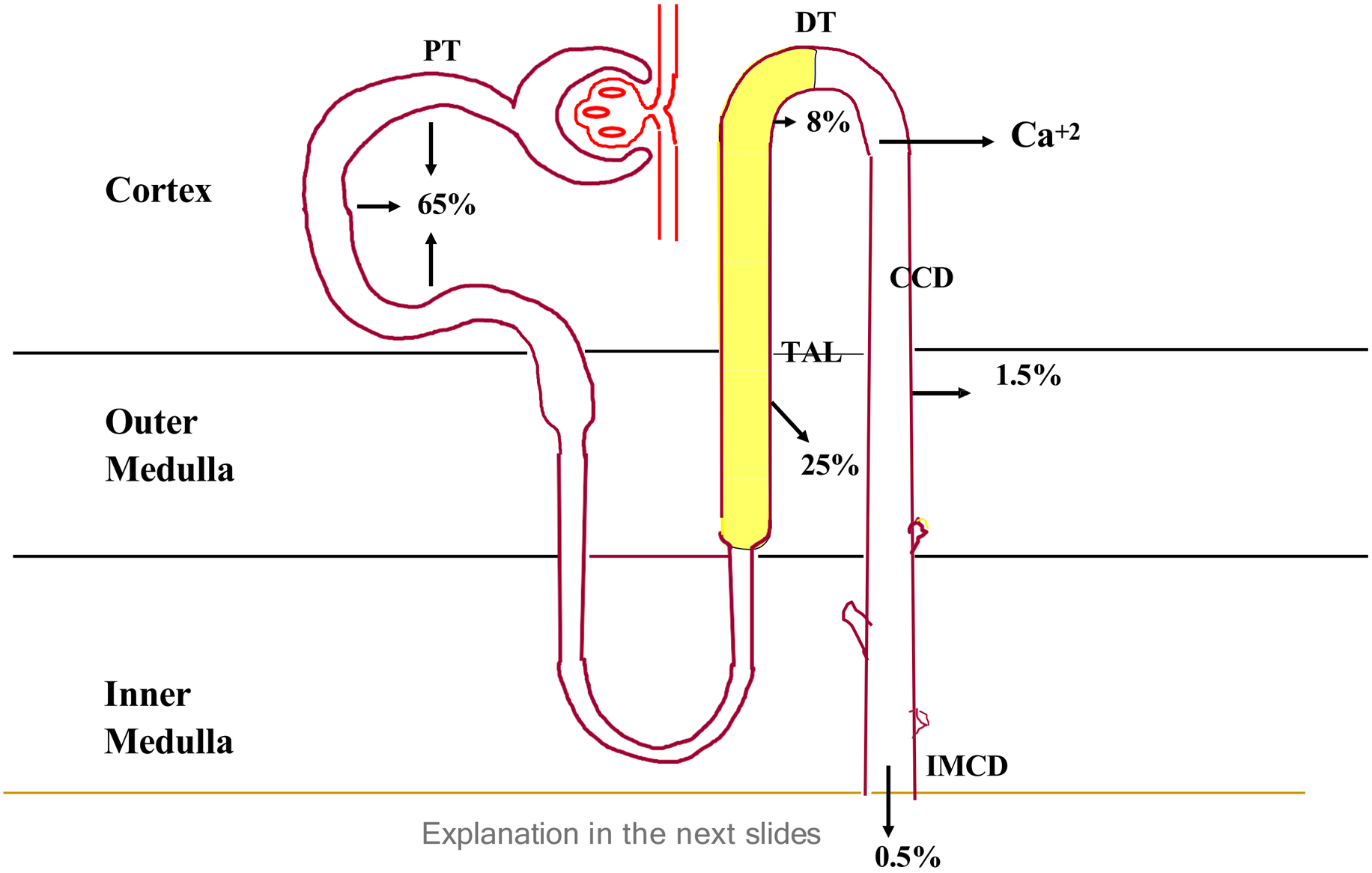
- ***Intestine***
  - ↑ Ca^{2+} absorption
  - ↑ phosphate absorption

PTH does **not** act directly on the intestine.

- Instead, it increases the formation of **active Vitamin D**, which then increases intestinal absorption of both: Calcium
- Phosphate

This is therefore an **indirect effect** of PTH.
The protein whose synthesis increases in intestinal cells is **Calbindin**, which facilitates calcium absorption.

Tubular Effects of PTH



Explanation in the next slides

PTH and Vitamin D

Another important action of PTH is increasing the formation of **active Vitamin D**.

- Vitamin D activation occurs in **two hydroxylation steps**: **Liver:** converts Vitamin D into **25-Hydroxy Vitamin D (25-OH Vitamin D or Calcidiol).**
- **Kidney:** converts 25-OH Vitamin D into **1,25-Dihydroxy Vitamin D ($1,25\text{-}(OH)_2$ Vitamin D or Calcitriol).**

The **second step** (1α-hydroxylation in the kidney) is stimulated by **PTH**.

Tubular Effects of PTH

- Approximately 65% of fluid reabsorption occurs in the proximal tubule, a process known as obligatory reabsorption. During this process, 65% of calcium is also reabsorbed. The absorption is isotonic, meaning that the osmolality and the calcium concentration in the filtered fluid is the same as in the plasma. However, in the proximal tubule, all glucose and any amino acids that might have leaked are reabsorbed.

- About **25%** is reabsorbed in the **Loop of Henle**.

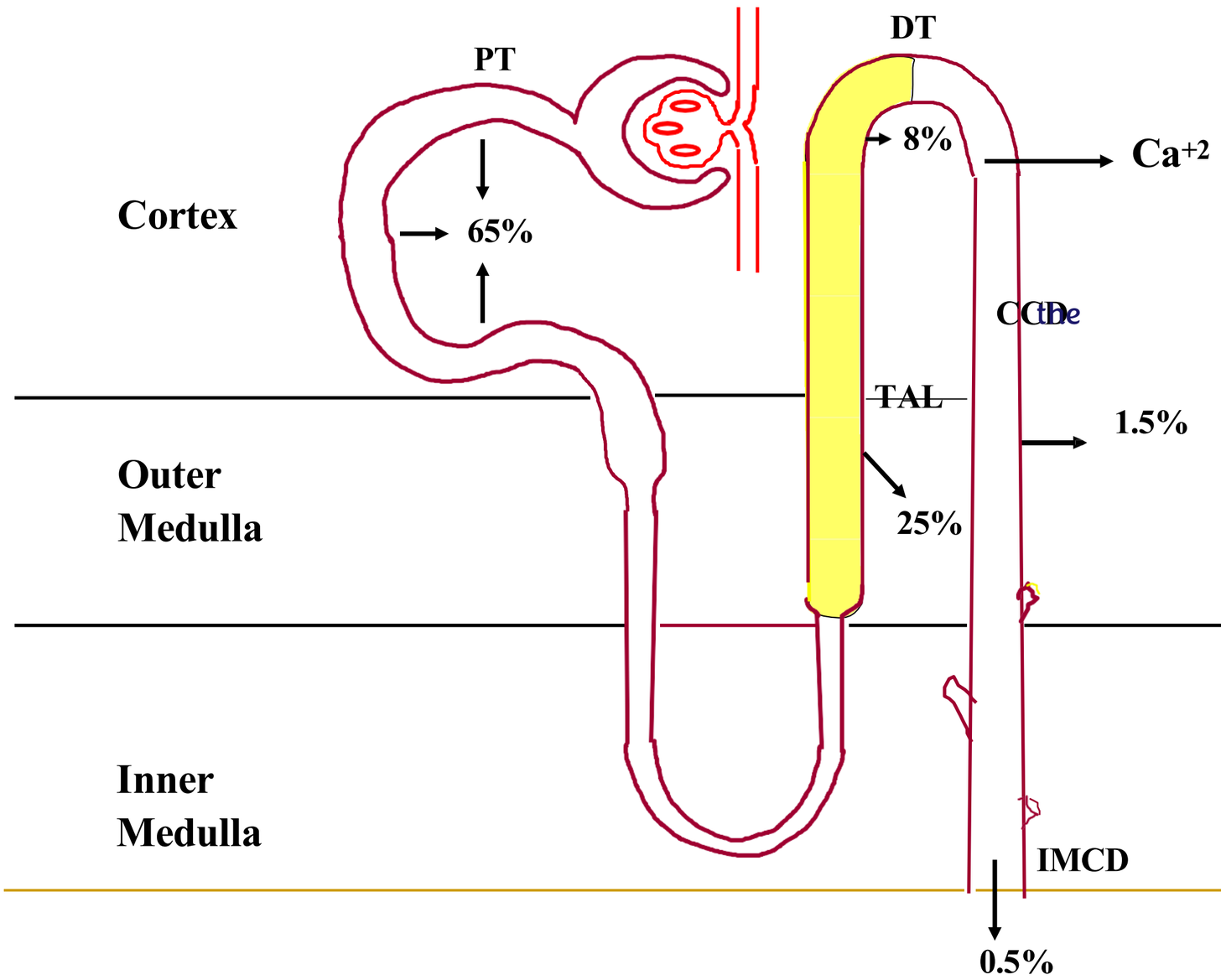
Therefore, nearly **90%** of filtered fluid has already been reabsorbed before reaching the distal nephron.
The doctor compared this to water regulation by ADH:
Only about **10%** of filtered water reaches the collecting ducts, where ADH determines the final amount excreted.
He then applied the same idea to calcium:
About **90% of filtered calcium is already reabsorbed**, while the remaining portion is under hormonal regulation, mainly by **PTH**.

Glucose reabsorption occurs through secondary active transport via the glucose-sodium co-transporter, in addition to primary active transport and facilitated diffusion. All these transport mechanisms have a specific Vmax and Tmax values, meaning they have a transport maximum. This explains why glucose appears in the urine of diabetic patients.

For instance, in a healthy individual, if plasma glucose concentration is 200 mg per 100 ml, the transporters can reabsorb all the glucose. In contrast, in a diabetic patient, the plasma glucose concentration exceeds 200 mg per 100 ml, all the transporters are saturated. As a result, the excess glucose is excreted in the urine.

It's important to note that glucose reabsorption only occurs in the proximal tubule. If glucose passes beyond this segment, it will inevitably be excreted in the urine. Furthermore, unabsorbed glucose within the tubule creates osmotic pressure, drawing water into the tubular lumen and leading to polyuria—a condition also known as osmotic diuresis.

Tubular Effects of PTH

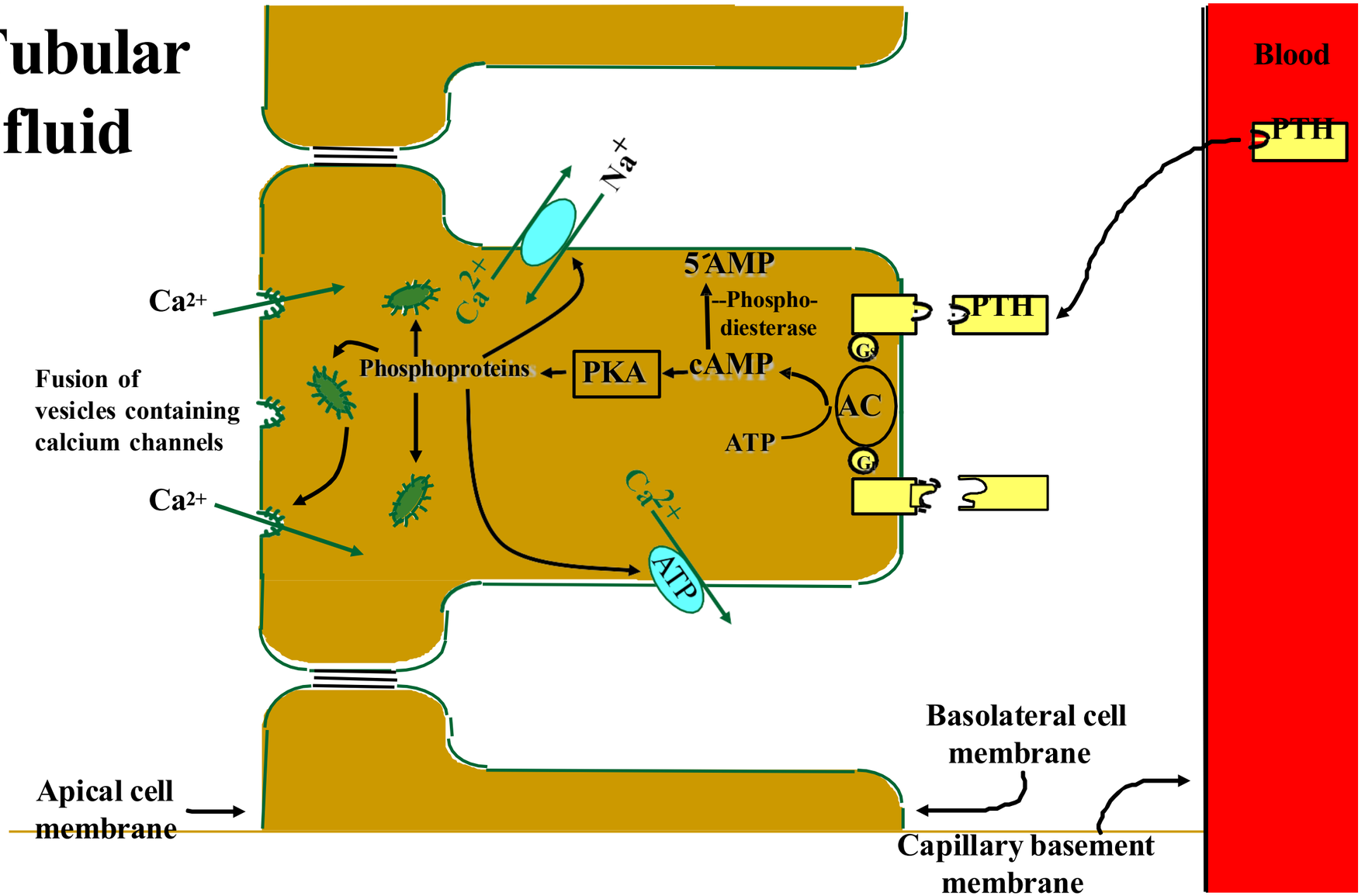


In the ascending and descending limbs of the loop of Henle, 25% of calcium is reabsorbed. The regulation of calcium reabsorption occurs in the distal tubule, where parathyroid hormone (PTH) exerts its effect. In the absence of PTH, 8% of the filtered calcium will be excreted. This indicates that only 8% of calcium reabsorption in the late distal tubule is under the control of PTH.
Recall that ADH exerts its regulatory effect in the collecting duct.

In the thick ascending limb of the loop of Henle, primary reabsorption is of sodium, chloride, and potassium.
Recall from biochemistry last summer: we learned that enzymes have a Vmax, and similarly, hormones have binding sites that can become saturated.

Therefore, when giving a hormone to a patient, it must be given at a dose below its Tmax. Any amount above the Tmax provides no additional benefit and only increases the cost for the patient.
We must also consider Km, which represents the hormone's affinity and is the concentration at which half of the maximum binding is achieved.

Cellular Actions of PTH in the TAL & Distal Tubule



Explanation in the next slide ☺

Cellular Actions of PTH in the TAL & Distal Tubule

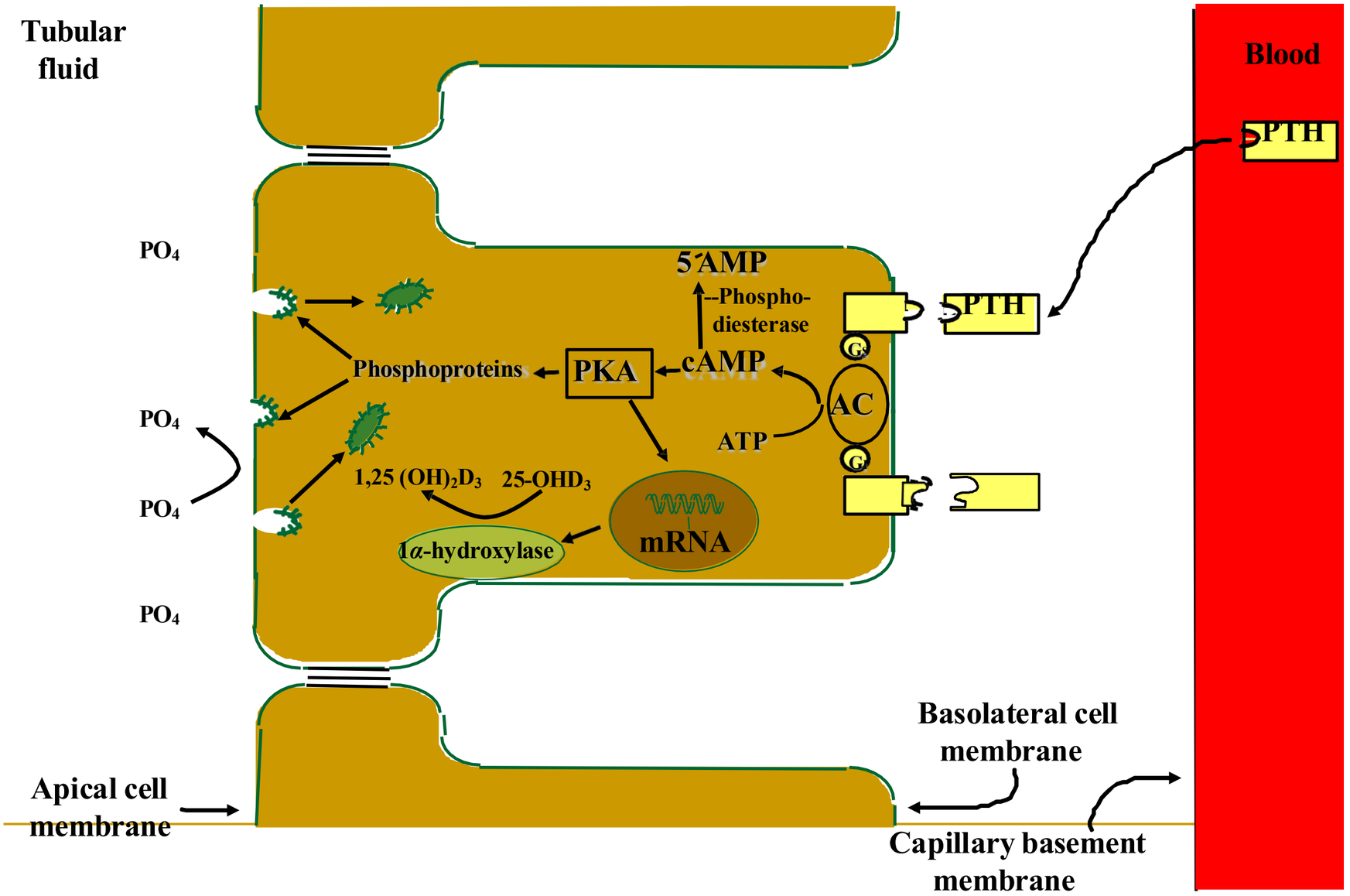
PTH in the blood acts on the basolateral membrane by binding to its G-protein-coupled receptor. (Remember: PTH is an 84-amino-acid peptide so it cannot enter the cell, and the major active portion is the first 34 amino acids—so synthetic PTH can consist of just the first 34 amino acids). Instead, it binds to a G-protein coupled receptor (GPCR) on the cell membrane.

After binding to its receptor, PTH activates adenylate cyclase, which converts ATP to cAMP. cAMP then activates protein kinase A, which phosphorylates phosphoproteins. These phosphorylated proteins function as channels that translocate to the membrane, increasing calcium reabsorption according to the electrochemical gradient. The intracellular calcium concentration is about 10^{-7}, while the concentration in the tubular fluid is much higher. Since the filtrate in the tubule is the same as plasma (except for lacking proteins), the calcium concentration there is similar to that of plasma (almost 10^{-3}) allowing calcium to enter the cell by simple diffusion.

Calcium then exits the cell into the bloodstream through two mechanisms: a calcium-sodium exchanger (which exchanges 3 sodium ions for 1 calcium ion) and a calcium pump located in the membrane.(electrogenic transporter)

As mentioned in earlier lectures, the action of cAMP is terminated by phosphodiesterase, which converts cAMP into AMP. Similarly, if a hormone acts through cGMP, a cGMP-specific phosphodiesterase will terminate its action.

Cellular Actions of PTH in the Proximal Tubule



Explanation in the next slide ☺

Cellular Actions of PTH in the Proximal Tubule

In the proximal tubule, PTH acts on phosphate but NOT on calcium.

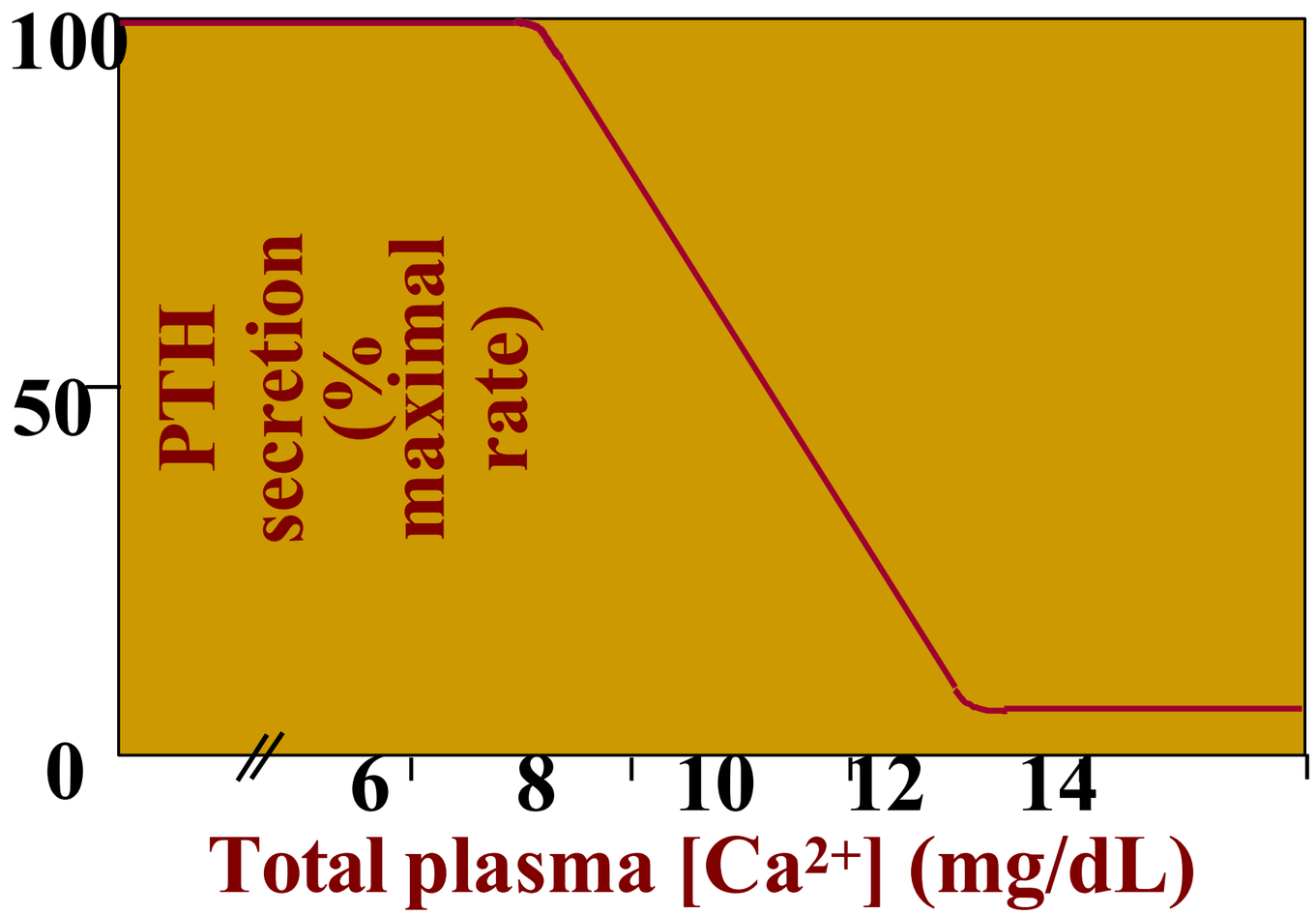
Similar to its mechanism for calcium, PTH binds to a G-protein-coupled receptor, which activates protein kinase A (PKA). PKA then phosphorylates specific proteins that increase phosphate excretion. Therefore, in the kidney, PTH promotes calcium reabsorption and phosphate excretion.

The concentration of phosphate inside the cell is much higher than outside. The main intracellular anions are phosphate plus proteins, while the main intracellular cation is potassium. Extracellularly, the main anion is chloride, and the main cation is sodium.
Therefore:
↑ Urinary phosphate
↓ Plasma phosphate

In addition, PTH, through activation of PKA, influences mRNA to stimulate the induction of 1α-hydroxylase in the proximal tubule. This enzyme converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol.

Besides activating the existing enzyme, Protein Kinase A also stimulates the nucleus to increase transcription and translation of more 1α-hydroxylase enzyme.
Therefore, 1α-hydroxylase is an inducible enzyme, and PTH increases both its activity and its synthesis.

Plasma [Calcium] & PTH Secretion



PTH increases when the calcium conc. decreases and when the calcium conc. Increases it inhibits PTH.

Remember that the main controller of the insulin and glucagon secretion is the conc. of glucose, similarly PTH is mainly controlled by the conc. of calcium, so they have approximately the same curve.

Calcitonin

A 32 amino acid peptide secreted from the parafollicular cells from the thyroid gland .

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

Resorption of bone is decreased, osteoblast activity is increased.

✓ Causes of abnormality in calcitonin secretion:

- thyroidectomy
- C-cell tumors

The function of the osteoblast is to cause mineralization of bone, meaning that more calcium and phosphate are deposited into the bone matrix, resulting in increased bone formation.
The doctor emphasized that Calcitonin is not an important hormone for chronic regulation of plasma calcium. Its role is relatively minor in humans and is considered more important in animals.
For this reason, after thyroidectomy, removal of calcitonin usually does not produce a significant disturbance in calcium homeostasis.

Rickets-Osteomalacia

- **Vitamin D deficiency**
  - –Dietary
  - –Deficient synthesis
    - Mainly the problem is in the kidney, it might be due to decreased sunlight exposure or liver dysfunction, but the liver cells regenerate more easily, unlike the kidney which has limited regenerative capacity, that's why kidney dysfunction is typically the main cause.
- **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) ✓ Remember a hormone needs its receptor to work.

Continued in the next slide…

1. Decreased PTH
Since PTH stimulates 1α-hydroxylase, decreased PTH leads to decreased production of active Vitamin D.

2. Liver disease
Example:
Cirrhosis
The liver performs the 25-hydroxylation step.
If liver function is impaired, less 25-OH Vitamin D is produced.

3. Kidney disease
The kidney performs the 1α-hydroxylation step.
If the renal tubules are diseased or dysfunctional, they cannot convert:
25-OH Vitamin D
↓
1,25-$(OH)_2$ Vitamin D
Therefore active Vitamin D decreases.

4. Hereditary disorders
The doctor mentioned Pseudo Vitamin D Deficiency Rickets (Vitamin D-dependent Rickets Type I).
In this condition there is a deficiency of 1α-hydroxylase.
Even if PTH is present, there is no functional enzyme, so active Vitamin D cannot be formed.

Then he discussed another hereditary condition:
Vitamin D-dependent Rickets Type II
Here the problem is not the hormone, but the receptor.
Vitamin D may be present in normal or even high concentration, but the receptor is absent.
The doctor repeated an important concept:
A hormone without its receptor has no effect, and a receptor without its hormone also has no effect.

Example Given by the Doctor
The doctor gave an analogy using testosterone.
A genetic male (XY) produces testosterone normally.
However, if androgen receptors are absent, the tissues cannot respond.
Therefore the individual develops a female phenotype despite having normal or high testosterone concentrations.
This condition is called Testicular Feminization Syndrome (Androgen Insensitivity Syndrome).
It is usually discovered around puberty because the patient presents with:
Primary amenorrhea.
No uterus.
No ovaries on ultrasound.
Karyotyping reveals an XY chromosome pattern.
The same principle applies to Vitamin D.
Vitamin D may be present, but if its receptor is absent, its biological actions cannot occur.

Other Causes of Vitamin D Deficiency
The doctor continued with additional causes.
Chronic renal failure
The damaged renal tubules cannot convert:
25-OH Vitamin D
↓
1,25-$(OH)_2$ Vitamin D.

Phosphate depletion
Phosphate depletion may occur because of poor dietary intake or excessive renal phosphate loss.
The doctor mentioned this as another factor affecting Vitamin D metabolism.

Rickets-Osteomalacia

- **Chronic renal failure**

✓ Deficiency in α1- hydroxylase enzyme, so no activation of vitamin D. Also, difficulty in reabsorbing calcium from the kidney.

- **Phosphate depletion**

– Dietary
–Renal

✓ As vitamin D increases the absorption of calcium and phosphate from food , deficient vitamin D will cause phosphate and calcium depletion.

In children, because the epiphyseal plates are still open and the bones are soft, weight bearing causes bowing (bending) of the legs.
In adults, the growth plates are already closed, so instead of bowing, there is defective mineralization of bone, making bones fragile and predisposing them to fractures.

Treatment of Rickets-Osteomalacia

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

Possible treatments include:
Giving Vitamin D precursor and allowing the liver and kidney to convert it into active Vitamin D.
Giving the active form directly (1,25-Dihydroxy Vitamin D (Calcitriol)).
Calcium supplementation.
Increasing exposure to sunlight.

Osteoporosis

- Aging
  - ↓ estrogen
  - ↓ testosterone
  - ↓ GH

✓ It could occur in females or males. In females, it usually occurs after the age of menopause as there is no estrogen which is very protective when present .

✓ Another contributing factor is aging itself, during which Growth Hormone (GH) decreases.

- ↑ Glucocorticoids

osteoporosis in cases of elevated glucocorticoids is protein breakdown

- Immobilization
- (↓ Vitamin D + Ca^{2+})*

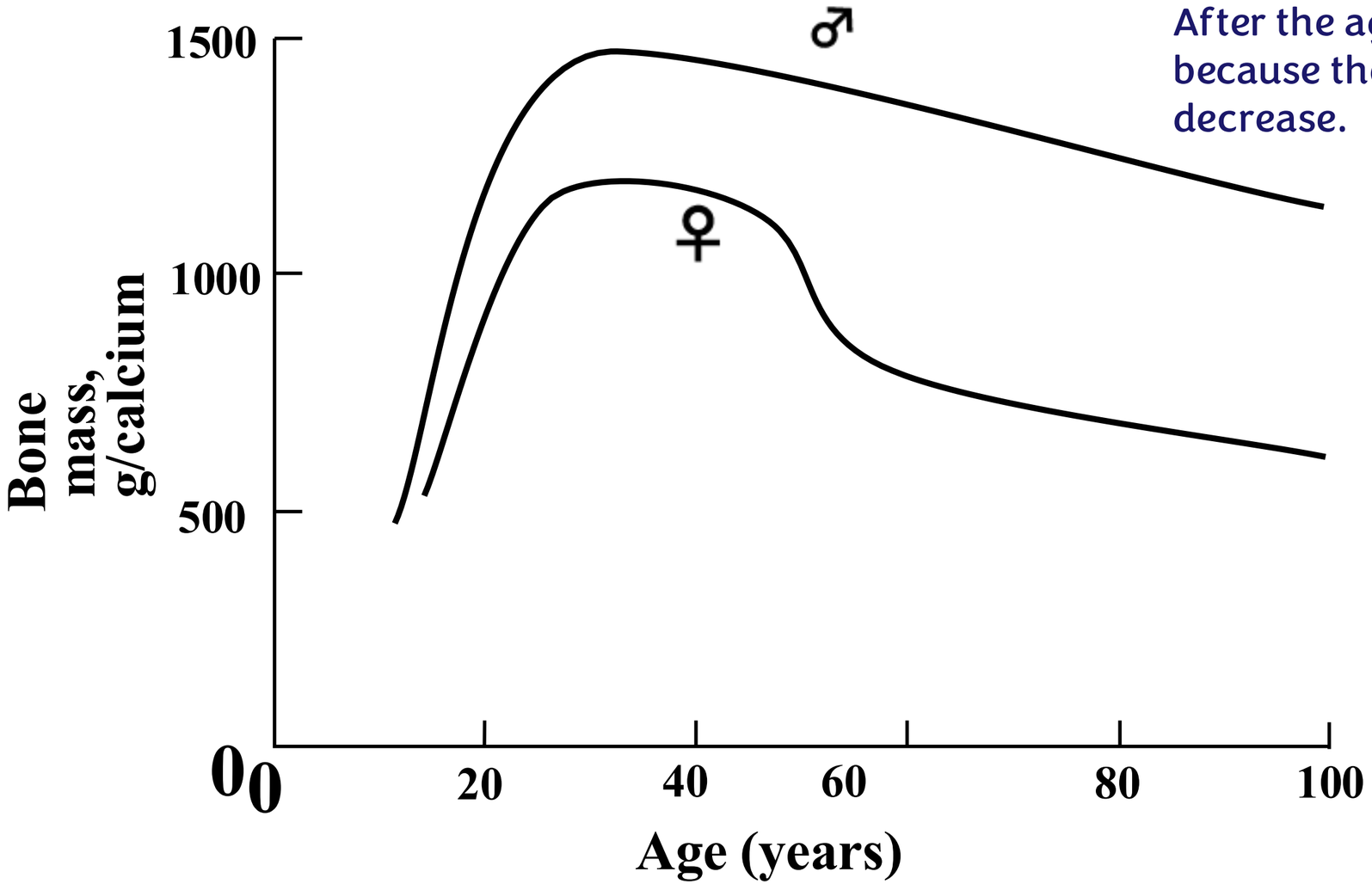
✓ Movement strengthens the bone.

*secondary response

✓ Patients receiving pharmacological doses of glucocorticoids (such as hydrocortisone/prednisolone) are at increased risk of osteoporosis.

The doctor emphasized that physiological concentrations of glucocorticoids do not cause osteoporosis.
However, prolonged therapeutic doses increase protein breakdown, leading to loss of bone mass.
He gave examples of patients with:
Rheumatoid arthritis.
Lupus erythematosus.
Autoimmune diseases.
These patients commonly receive long-term glucocorticoid therapy.
Therefore, they should undergo bone density assessment every 2–3 months (as mentioned by the doctor) to monitor for osteoporosis.

Time-Dependent Changes in Bone Mass



After the age of 40, bone mass decreases because the level of sex hormones decrease.

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

1) Surgical removal of the parathyroid can occur either due to a tumor within the parathyroid itself, or unintentionally during thyroidectomy, although the surgeon tries to be cautious.

Sometimes during thyroidectomy, the parathyroid glands are accidentally removed.
As a result:
↓ PTH
↓ Formation of active Vitamin D (1,25-$(OH)_2$ Vitamin D)
↓ Calcium reabsorption from the kidney
↓ Intestinal calcium absorption
-> Hypocalcemia
At the same time, because there is no PTH, phosphate excretion decreases.
Therefore:
Plasma phosphate increases (Hyperphosphatemia).
Urinary phosphate decreases.
Urinary cyclic AMP also decreases because PTH normally stimulates cAMP production in the kidney.
So the findings become:
↓ Plasma calcium
↑ Plasma phosphate
↓ Urinary phosphate
↓ Urinary cAMP

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

2)In response to low calcium in Vitamin D deficiency or Chronic renal failure, PTH is increased.

The primary problem is decreased Vitamin D.
As compensation, the parathyroid gland secretes more PTH.
Therefore:
↓ Vitamin D -> ↑ PTH
(Secondary Hyperparathyroidism)
The increased PTH produces several effects.
First: It increases bone resorption, releasing calcium from bone.
Second: It increases phosphate excretion in urine.
Third: It increases urinary cyclic AMP, because PTH acts through the cAMP signaling pathway.
Plasma calcium may remain normal for a long time,Why?
Because many mechanisms are working together to maintain calcium concentration within the normal range.
Only when these compensatory mechanisms fail does plasma calcium begin to decrease.
Meanwhile, because PTH increases phosphate excretion -> Plasma phosphate decreases.

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

3)Chronic Renal Failure
Active Vitamin D decreases because the damaged kidney cannot convert 25-OH Vitamin D -> 1,25-$(OH)_2$ Vitamin D.
This causes Hypocalcemia.
Hypocalcemia stimulates: ↑ PTH
So plasma PTH becomes elevated.
Normally, high PTH should increase phosphate excretion.
However, this does not happen.
The doctor explained why.
The kidney itself is not functioning properly.
The GFR decreases.
If GFR decreases,
Less phosphate is filtered.
Less phosphate reaches the urine.
Less phosphate is excreted.
Phosphate accumulates in plasma.
Therefore, despite high PTH:
Plasma phosphate increases.
Plasma calcium decreases.
The problem is kidney failure, not failure of PTH secretion.

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%, ♀ ♂

Very rare condition

Primary Hyperparathyroidism

The parathyroid gland becomes overactive.

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

* Primary disturbance

If PTH increases calcium reabsorption in the kidney, why do some patients with hyperparathyroidism still have increased calcium in the urine?

PTH indeed **increases calcium reabsorption**.

However, in primary hyperparathyroidism,

the amount of calcium entering the blood from:

- Bone resorption.
- Increased intestinal absorption.

becomes extremely large.

Therefore, the filtered load of calcium becomes much higher than normal.

Even though the kidney reabsorbs a larger percentage,

the total filtered amount is so high that **the excess calcium still appears in urine (hypercalciuria).**

In other words:

The kidney tries to conserve calcium,

but once plasma calcium becomes excessively high,

it cannot reabsorb all of the filtered calcium.

So both statements are true:

- **PTH increases calcium reabsorption.**
- **Urinary calcium may still increase in hyperparathyroidism because the filtered load is enormous.**

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 → High extracellular calcium makes voltage-gated sodium channels harder to open.Therefore, the threshold for generating an action potential increases
    And a stronger stimulus is required to excite nerves and muscles.
    As a result: Muscle weakness, Reduced reflexes, Decreased excitability.
    - Reduces excitability
  - Hypocalcemia
    - Brings about overexcitability of nerves and muscles
    - Severe overexcitability can cause fatal spastic contractions of respiratory muscles → Low extracellular calcium makes sodium channels easier to open.
      The threshold potential decreases.
      Even a small stimulus can generate an action potential.
      As a result: Tetany, Muscle spasms, Respiratory failure(Death if untreated.)
      Therefore, severe hypocalcemia is considered a **medical emergency**.

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

The complete pathway of Vitamin D synthesis:

The pathway begins in the skin.
7-Dehydrocholesterol
↓
Exposure to **sunlight (UV radiation)**
↓
Cholecalciferol (Vitamin D_3)
↓
Transport to the **liver**
↓
25-Hydroxylation
↓
25-Hydroxy Vitamin D (Calcidiol)
↓
Transport to the **kidney**
↓
1α-Hydroxylation (stimulated by PTH)
↓
1,25-Dihydroxy Vitamin D (Calcitriol)
↓
Active Vitamin D

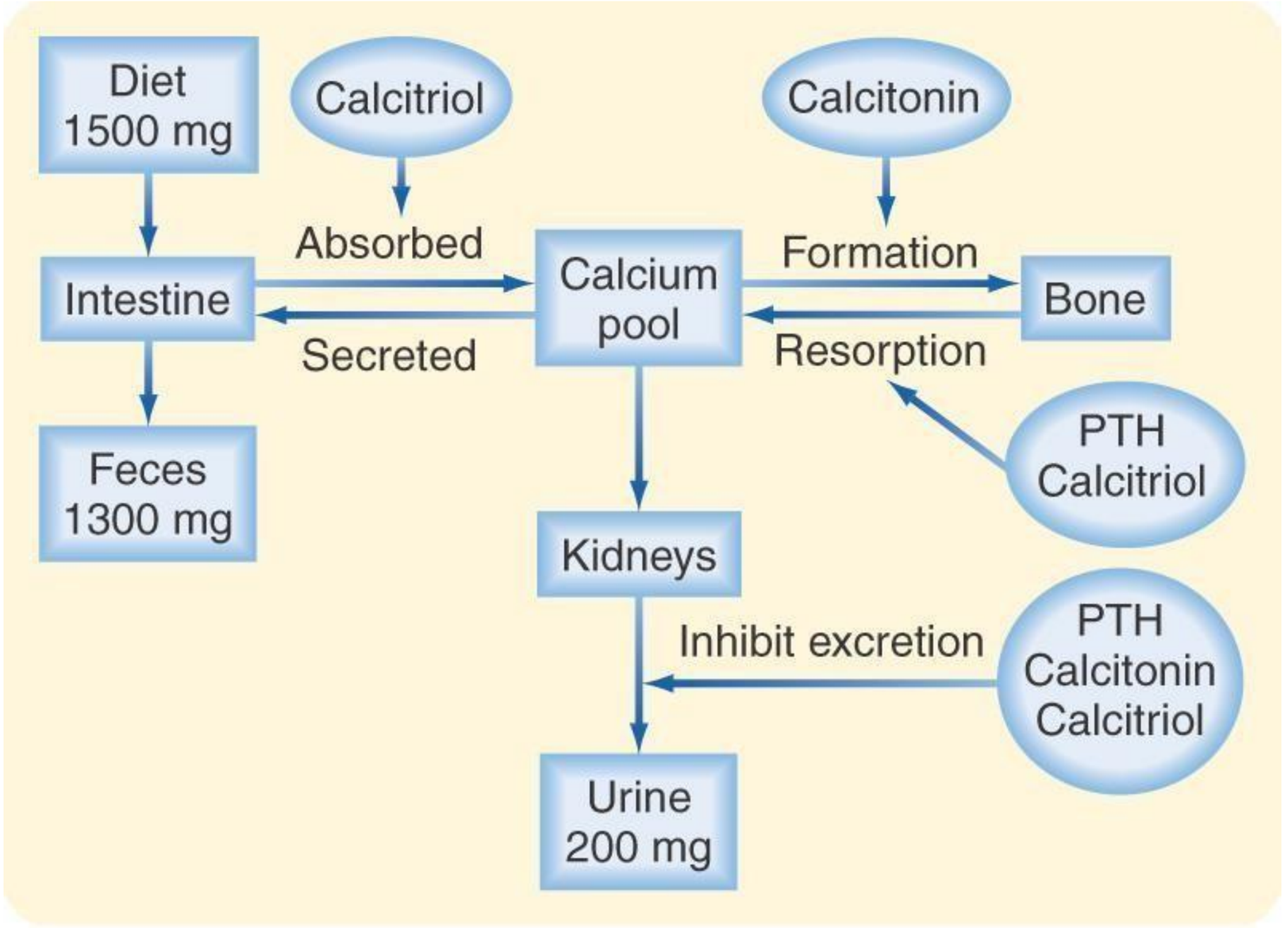
Endocrine Control of Calcium Metabolism

- Calcitonin

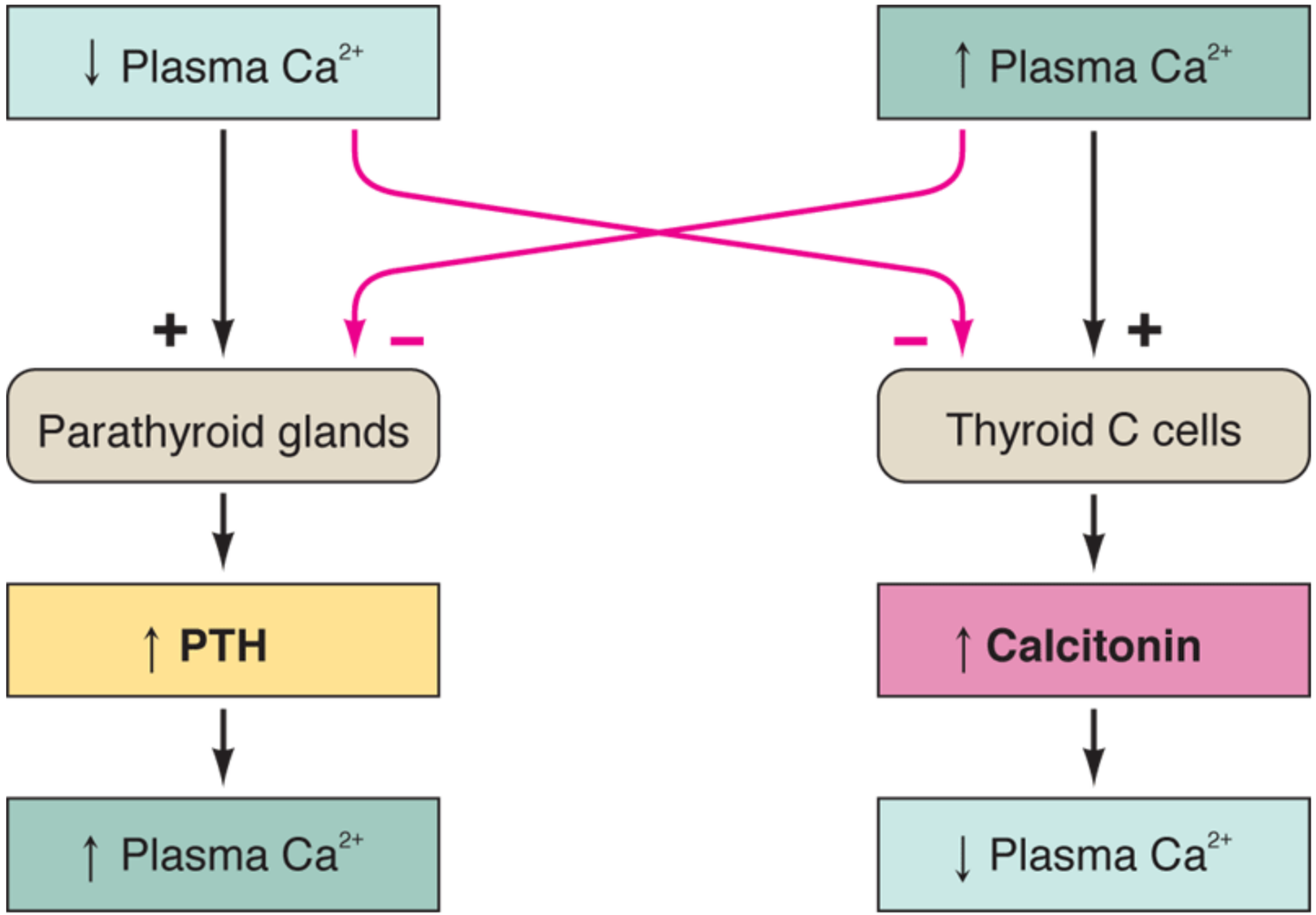
Parafollicular cells

  - Hormone produced by C cells of thyroid gland
  - Negative-feedback fashion Acute regulation of calcium NOT chronic.
    - Secreted in response to increase in plasma Ca^{2+} concentration
  - Acts to lower plasma Ca^{2+} levels by inhibiting activity of bone osteoclasts Stimulant high calcium
  - Unimportant except during hypercalcemia

- Since calcitonin is a peptide, it works through G-protein coupled receptor and cAMP.

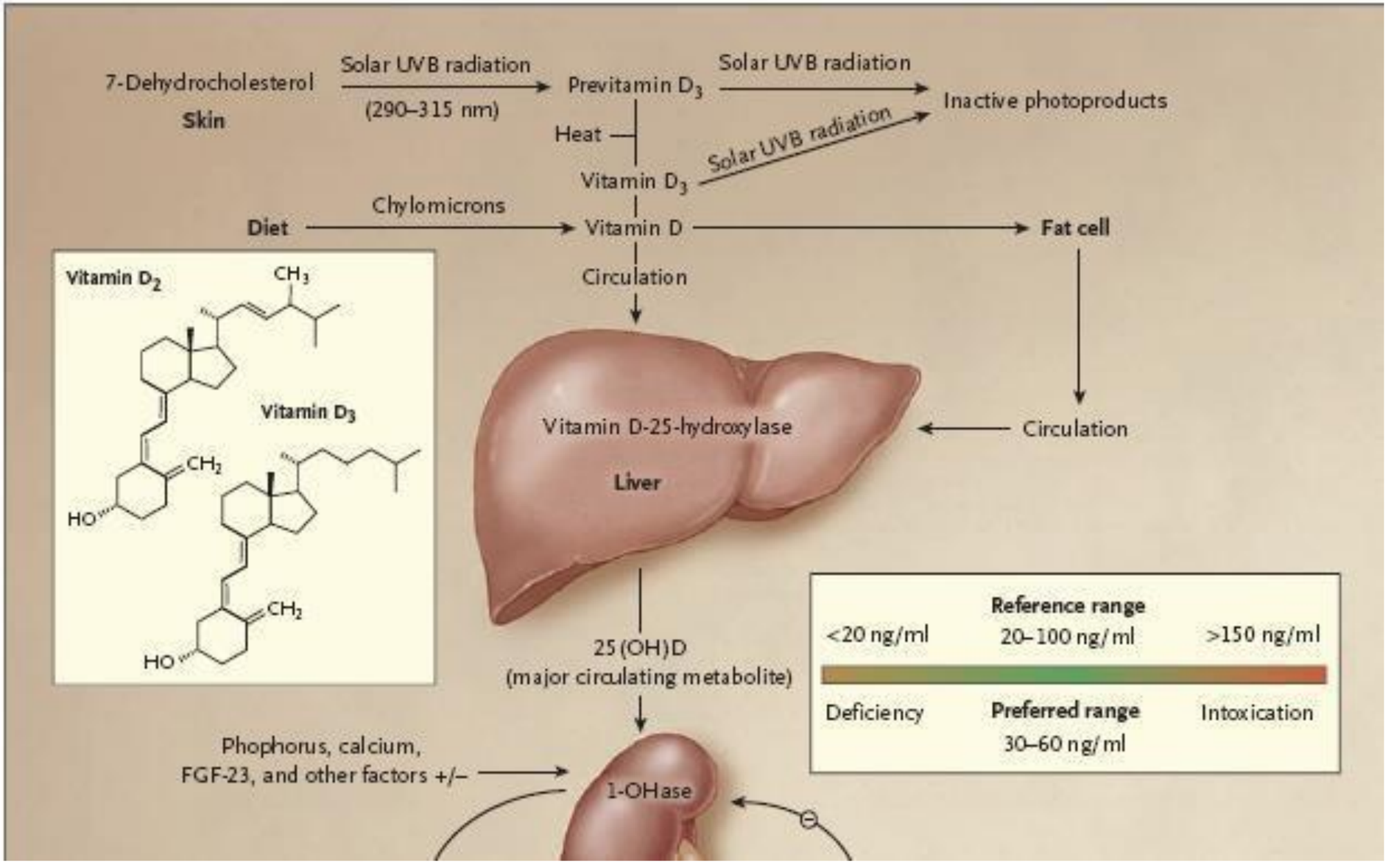


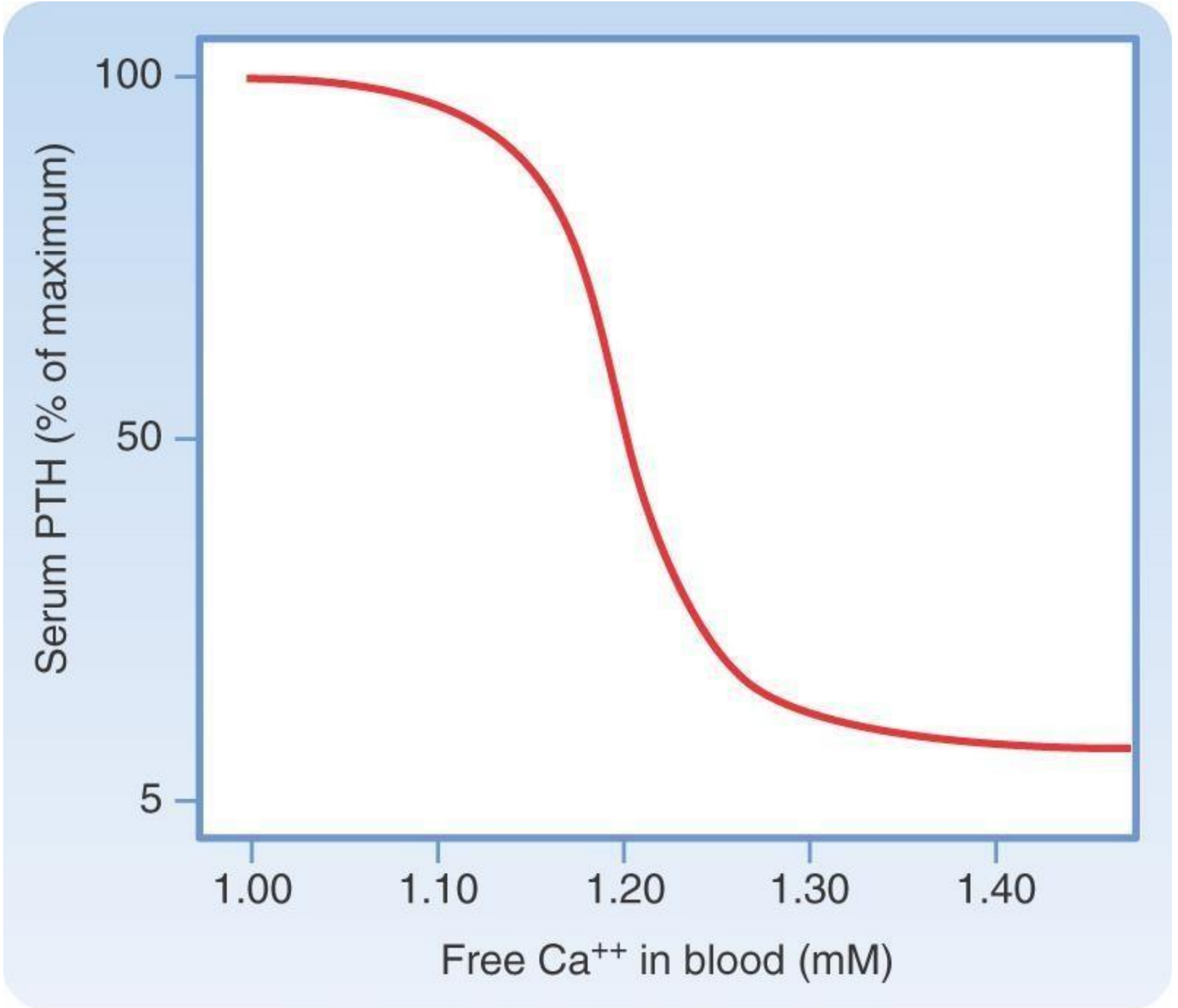
Negative-feedback Loops Controlling Parathyroid Hormone (PTH) and Calcitonin Secretion



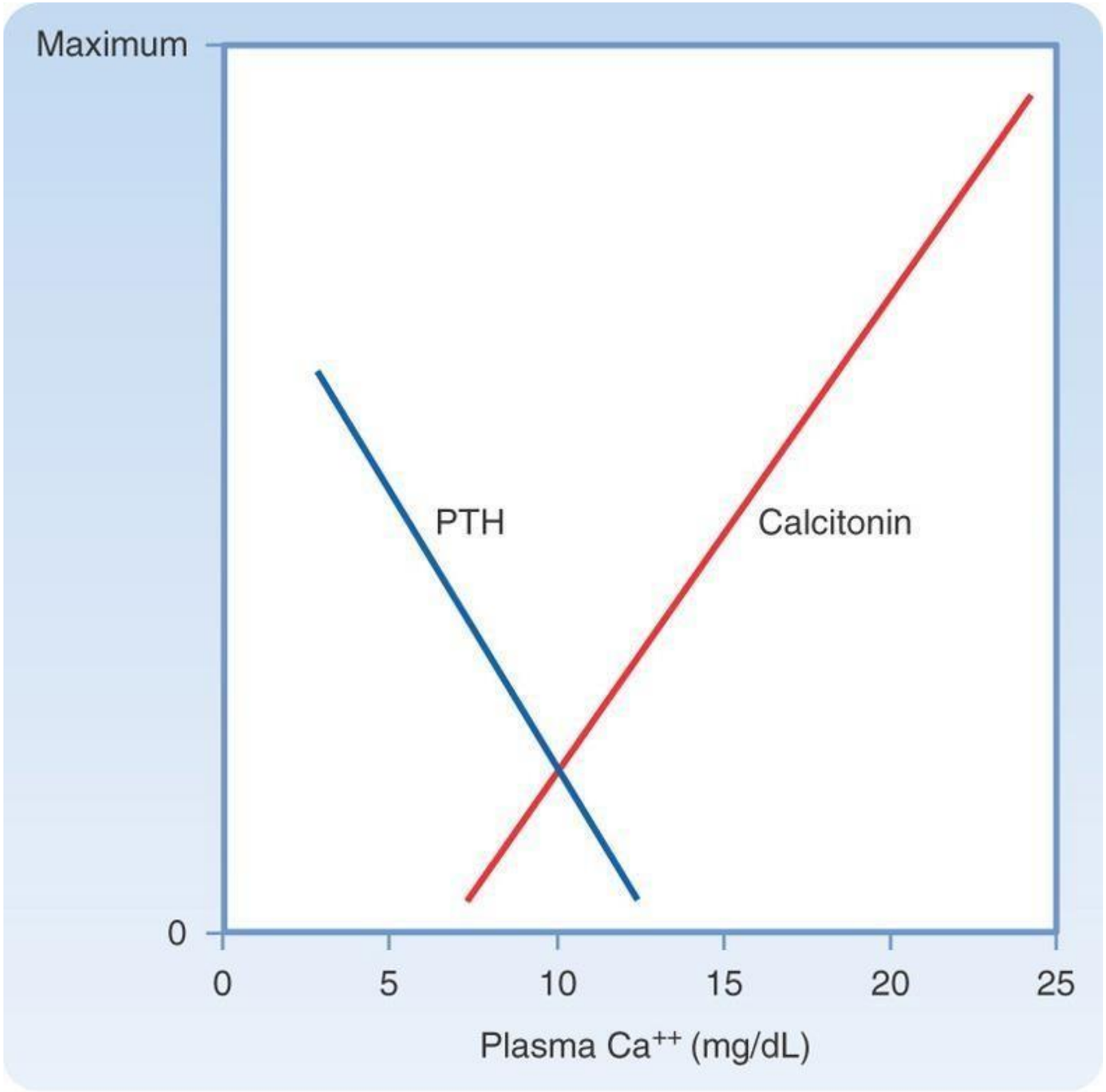
Calcium Disorders

- **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 D3
Solar UVB radiation
Inactive photoproducts
Heat
Vitamin D3
Solar UVB radiation
Chylomicrons
Diet
Vitamin D
Fat cell
Circulation
Vitamin D2
CH3
Vitamin D3
CH2
HO
CH2
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.)

- ✓ More calcium stimulates calcitonin.
- ✓ Less calcium stimulates PTH.

Thank You

Physiology Quiz

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			