Hormonal control of calcium metabolism Part I

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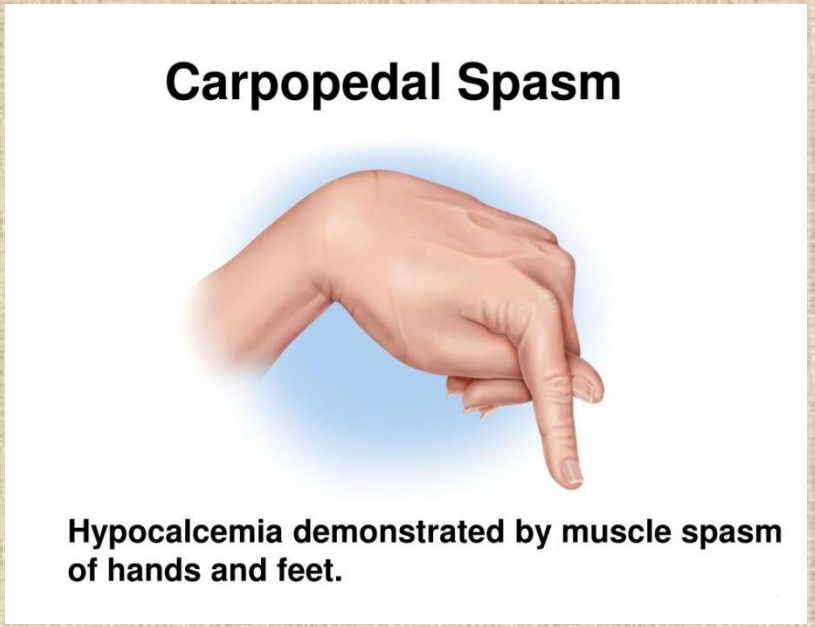
Lecture objectives:

- Assess the physiological importance of ionized calcium in different physiological functions
- Illustrate calcium compartments in the body
- Illustrate calcium and phosphate absorption, metabolism and excretion
- Describe the role of vitamin D in calcium and phosphate absorption
- Outline the effect of calcium ion concentration on the regulation of the active form of vitamin D levels

Calcium homeostasis

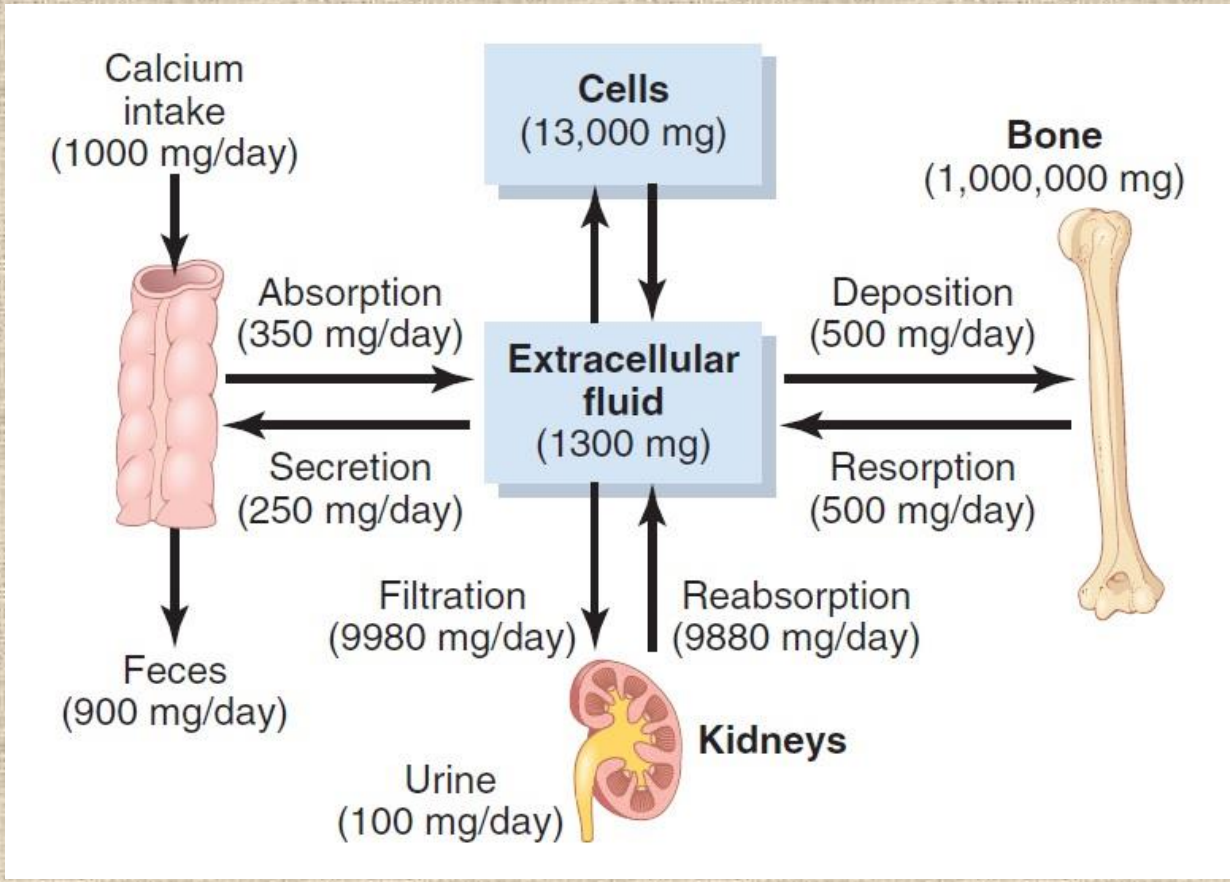
- Extracellular ionized calcium (Ca) concentration is regulated very precisely. Its normal value in plasma is 9.4 mg/dl (8.5-10.5 mg/dl). Calcium is essential for contraction of skeletal, cardiac, and smooth muscle. It is also essential for blood clotting and transmission of impulses.
- Hypercalcemia → depression of the nervous system with sluggish CNS reflexes when concentration reaches to 12 mg/dl. Decrease of the QT interval of the heart, constipation, and loss of appetite can occur too.
- Hypocalcemia → excitement of the nervous system because of increased neuronal membrane permeability to Na^+, even spontaneous discharge of neurons can take place → **Tetany** or **Seizures** when concentration goes down to 6 mg/dl.



Hypocalcemia demonstrated by muscle spasm of hands and feet.

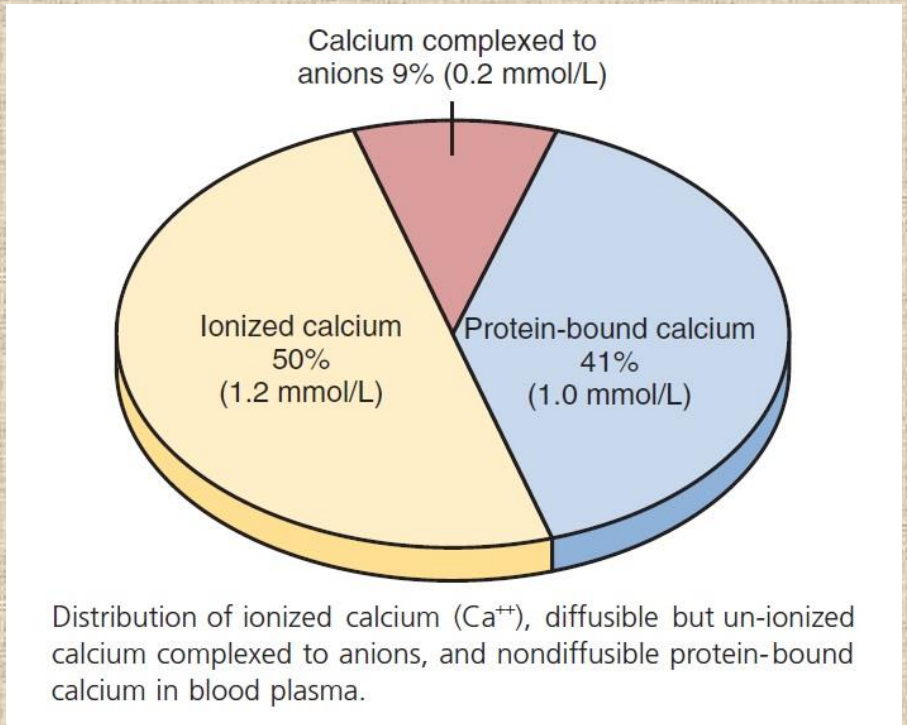
Calcium homeostasis (Cont.)

- Calcium level is determined by
  (1) Ca absorption from the GIT
  (2) Renal excretion of Ca
  (3) Bone uptake and release of Ca



Calcium homeostasis (Cont.)

- The bones serve as the **body reservoir** of Ca as it contains 99% of body Ca in the form of phosphate and hydroxide salts, predominantly as hydroxyapatite. Bones contain exchangeable Ca that is in equilibrium with extracellular Ca. The bone releases Ca when extracellular fluid concentration decreases and stores excess Ca. Bones store 85% of body's phosphate as well.
- In plasma, 41% of Ca is bound to plasma proteins, 9% are incorporated in compounds as citrates and phosphates, i.e. not ionized, and 50% as free ionized form (Ca^{2+}). The ionized form is the part responsible for the biological effect of Ca.



Distribution of ionized calcium (Ca^{++}), diffusible but un-ionized calcium complexed to anions, and nondiffusible protein-bound calcium in blood plasma.

Phosphate homeostasis

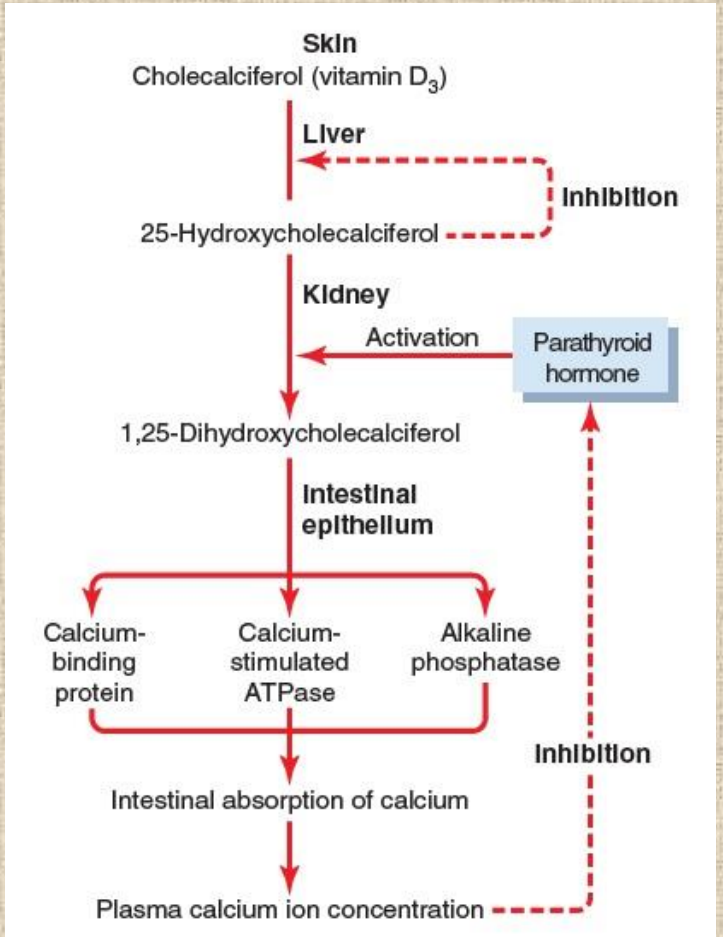
- In plasma, inorganic phosphate is in the form of $(HPO_4)^{2-}$ or $(H_2PO_4)^{-}$. Both are parts of the buffer system. In acidosis $(H_2PO_4)^{-}$ rises and $(HPO_4)^{2-}$ decreases and vice versa. Both phosphate ions represent a total of inorganic phosphorous of about 4 mg/dl (3-4 mg/dl in adults and 4-5 mg/dl in children). Changes in plasma phosphate level do not cause major immediate effects.
- Divalent cations (such as Ca^{2+}) are poorly absorbed from the intestine. However, Vit D promotes Ca^{++} absorption. About 350 mg of Ca is ingested/day while 250 mg/day is lost with GIT juices and sloughed mucosal cells. Almost all the dietary phosphate is absorbed from the gut and excess is excreted in the urine.

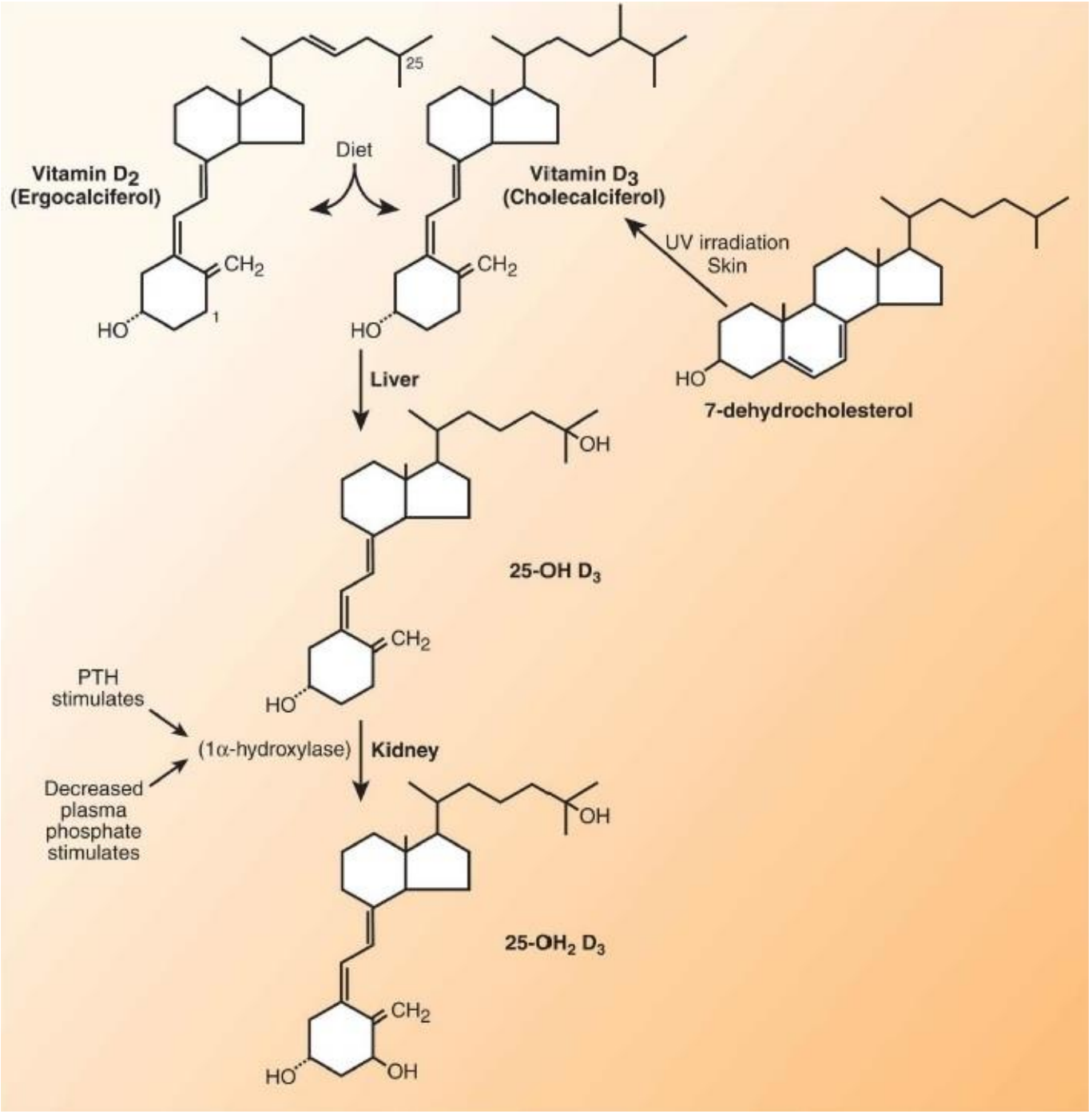
Calcium and Phosphate metabolism and excretion

- About 100 mg/day of ingested Ca (10%) is excreted in the urine.
- Normally, the renal tubules reabsorb 99 percent of the filtered calcium, and approximately **90%** of the calcium in the glomerular filtrate is reabsorbed in the proximal tubules, loops of Henle, and early distal tubules.
- In the late distal renal tubule and early collecting ducts, reabsorption of the remaining **10%** is of Ca is very selective. In this part of the renal tubule Ca reabsorption is inversely proportional to Ca ion concentration in the blood. The most important factor controlling this reabsorption is **parathyroid hormone (PTH)**.
- Renal phosphate excretion is controlled by an ***overflow mechanism***. That is, excretion is directly proportional to plasma phosphate concentration and rate of phosphate filtration by the kidneys. However, PTH can greatly increase phosphate excretion by the kidneys.
- The concentration of Ca and phosphate in extracellular fluid are high enough to cause their precipitation in all cells as crystalline salts known as **hydroxyapatite** [$Ca_{10}(PO_4)_6(OH)_2$]. However, this precipitation occurs in bones only because plasma and other tissues of the body have inhibitors that prevent such precipitation: one such inhibitor is **pyrophosphate**.
- In the bones, osteoblasts supposedly secrete a substance to neutralize crystallization inhibitors. Ca precipitation can occur in non-bony tissues (e.g. arterial walls and old clots) when inhibitor factors disappear from the tissue.
- The exchangeable Ca in bones forms the first line of defense against Ca level changes to maintain Ca homeostasis. The hormonal control (PTH and Calcitonin) represents the second line of defense.

Vitamin D

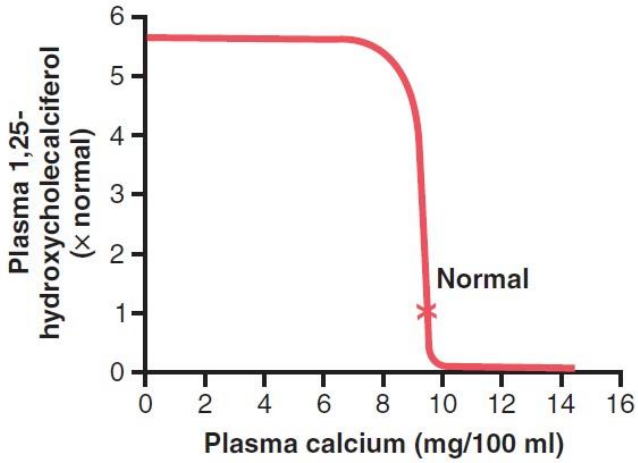
- Vitamin D-3 (cholecalciferol) is formed in the skin when a cholesterol precursor, 7-dehydroxycholesterol, is exposed to ultraviolet light. Dietary vitamin D-2 (ergocalciferol) is identical to the cholecalciferol formed in the skin, except for the substitution of one or more atoms that do not affect their function.
- This vitamin increases Ca absorption from the intestinal tract. It should be first converted to the active form 1,25-dihydroxycholecalciferol by the liver and the kidneys.
- Vit D conversion to 25-hydroxycholecalciferol occurs in the **liver**. This compound has a feedback inhibitory effect on conversion reactions. Non-converted vitamin D-3 can be stored in the liver for many months for future use.
- 1,25–dihydroxycholecalciferol is formed in the proximal tubules of the **kidney**, and acts as a hormone and leads to the formation of ***calbindin***, a calcium-binding protein within the distal renal tubule and intestinal epithelial cells for several weeks. Calbindin facilitates the cytosolic diffusion of Ca^{2+} from the apical influx to the basolateral efflux sites.
- Vitamin D also promotes intestinal absorption of phosphate ion, although the exact mechanism is unclear. Negatively charged phosphate ion may passively flow through the intestinal cell because of flux of the positively charged calcium ion.




Vitamin D2
(Ergocalciferol)
Diet
Vitamin D3
(Cholecalciferol)
UV irradiation
Skin
7-dehydrocholesterol
Liver
25-OH D3
PTH
stimulates
(1α-hydroxylase)
Kidney
Decreased
plasma
phosphate
stimulates
25-OH2 D3

Vitamin D (cont.)

- The plasma concentration of 1,25-dihydroxycholecalciferol is inversely affected by the concentration of calcium in the plasma. This effect could be mediated indirectly by the inhibitory effect of calcium on PTH secretion.
- Vit D increases Ca and phosphate reabsorption by renal tubules thereby decreases excretion of these substances in the urine, and promoting the retention of both ions in the body. However, this effect is <u>weak</u>.



Effect of plasma calcium concentration on the plasma concentration of 1,25-dihydroxycholecalciferol. This figure shows that a slight decrease in calcium concentration below normal causes increased formation of activated vitamin D, which in turn leads to greatly increased absorption of calcium from the intestine.

- Vit D promotes bone calcification (in small quantities), the mechanism is unknown. Toxic doses of Vit D cause the opposite, i.e. resorption of bone. As such Vit D plays a synergistic role with PTH in stimulating osteoclast proliferation and bone resorption.
- Deficiency of vitamin D may occur in winter due to less exposure to sunlight. Deficiency of vitamin D causes rickets in children and osteomalacia in adults.
- The recommended daily allowance of vitamin D is 200 U for adults and 400 U for children, pregnant women, and lactating women. Vitamin D is a lipid soluble vitamin similar to A, D, E, and K, and can be stored in tissues. Excess vitamin D may lead to problems such as calcinosis (calcification of soft tissues), deposition of Ca^{2+} and PO_4 in the kidney, and increased plasma Ca^{2+} levels, resulting in cardiac arrhythmia.

Test Question:

Q. 1,25-Dihydroxycholecalciferol can be formed in the body by metabolism of cholesterol. Which of the following is not either directly or indirectly involved in formation of 1,25-dihydroxycholecalciferol?

A. Bone
B. Skin
C. Kidney
D. Liver
E. Both kidney and liver