Hormones Affecting calcium homeostasis

Hormones Affecting calcification

- Calcium in the body:
  - Fifth most abundant element in the body.
  - A 70 kg adult contain approximately 1 kg of calcium.
  - 99% of calcium is located in the bones, teeth.
  - The remaining 1% present in cells and plasma.
  - Calcium in plasma:
    - 50% bound to proteins.
    - 46% complexes with counter ions.
    - 4% free ions. This fraction regulated by hormones.
- Daily Requirements:
  - Ranging from 400 mg in infants to 1200 mg in pregnant and lactating women.
- Absorption and Excretion:
  - About 1/3 of the ingested calcium is absorbed through the intestine.

- Calcium absorption increased by:
  - Vit D.
  - PTH.

- Calcium absorption decreased by:
  - Glucocorticoids.

- Physilogical functions:
  - Increase neuromuscular excitability.
  - Important for contraction of vascular and other smooth muscles.
  - Essential for excitation and contraction of cardiac muscles.
  - Essential for bone growth.
  - Important for maintaining mucosal and cell membranes.
  - Involved in blood coagulation.

Role of Calcium in Bone Formation

- Adequate calcium supply is required for bone formation, as calcium and phosphate are the minerals which make up bone.
- Bone is mineralized by the precipitation of calcium and phosphate in a basic environment.
- Without calcium, → decreased bone mineralization and strength.

Intake, Storage and Excretion of Calcium

- Calcium is one of the **most abundant mineral** in the body.
- The amount of calcium in the body is a balance between **intake, storage**, and **excretion**.
- This balance is controlled by transfer of calcium between three organs: **intestine, bone, and kidney.**

Intake of Calcium

- About 1000 mg of calcium is ingested per day.
- About 200 mg of this is absorbed into the body.
- Absorption occurs in the **small intestine**, and requires **vitamin D**

Storage of Calcium

- The primary site of storage is **our bones** (about 1000 grams).
- Some calcium is stored within cells **(endoplasmic reticulum and mitochondria).**
- Bone is produced by **osteoblast** cells that produce collagen, which is then mineralized by calcium and phosphate **(hydroxyapatite).**
- Bone is demineralized (broken down) by **osteoclasts**, which secrete acid, causing the release of calcium and phosphate into the bloodstream.
- There is constant exchange of calcium between bone and blood.

Excretion of Calcium

- The major site of calcium excretion in the body is the **kidneys**.
- The rate of calcium loss and reabsorption at the kidney can be regulated.
- Regulation of absorption, storage, and excretion of calcium results in maintenance of calcium homeostasis.

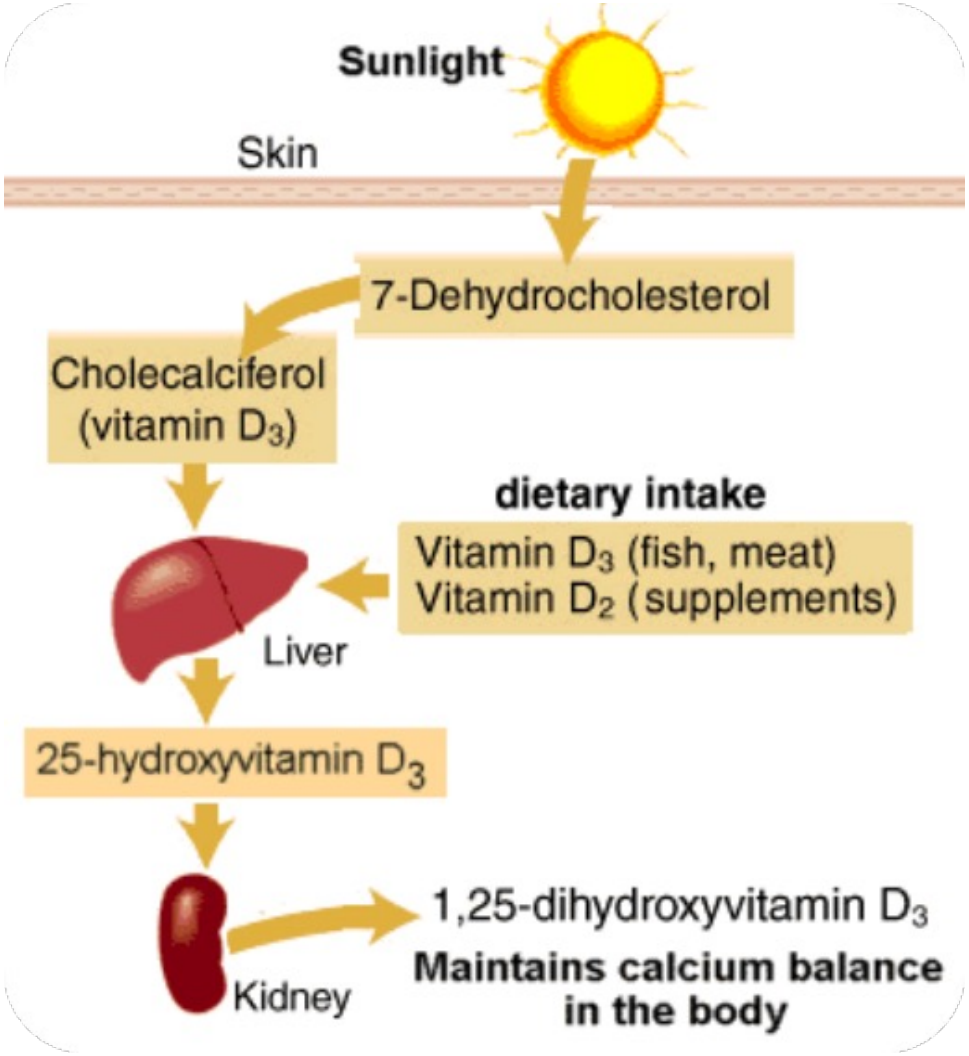
Calcium regulating hormones & Metabolic Bone Disease

There are 3 main hormones which regulate calcium balance:

- **Vitamin D**
- **Parathyroid hormone (PTH)**
- **Calcitonin**

(**1 & 2 act to ↑ calcium**; **3 ↓ calcium concentrations**)

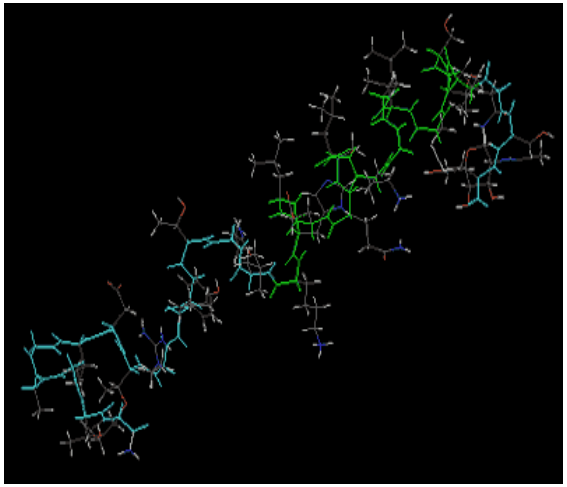
NOTE: Although Vitamin D is considered a vitamin, it has been attributed that it would be better classified as a hormone



Vitamin D binds to nuclear receptors, & promotes synthesis of proteins involved in calcium absorption in the gut

1- Calcitonin

- Site of Secretion: Is secreted from the parafollicular or C-cells of the thyroid gland
- Structures: Peptide Hormones composed of 32 amino acid in single chain.



- Regulations:
  - By calcium ion concentration:
    - When calcium ion concentration in plasma increase calcitonin concentration increase (and Vic versa).
    - When calcium ion concentration in plasma decrease calcitonin concentration decrease.

Physiological Functions of Calcitonin :

- Hypocalcemia effect (decease calcium level in blood)
- Acts through G-protein mechanism increasing cyclicAMP (receptors are located on renal tubule cells and osteoclasts)

- In *bone:*

- it suppresses the release of calcium & phosphate from bones
- Stimulate bone formation.
- Direct inhibition of bone resorption (break down).

- In *Kidneys*:

- It inhibits calcium & phosphate reabsorption in kidneys

- It opposes action of PTH

Actions of Calcitonin

- The major action of calcitonin is on bone metabolism.
- Calcitonin inhibits activity of osteoclasts, resulting in decreased bone resorption (and decreased plasma calcium levels).
- Calcitonin **inhibits the activity of osteoclasts, which are cells that break down bone**. When osteoclasts break down your bone, the calcium from your bone is released into your bloodstream. Therefore, the temporary blocking of osteoclasts by calcitonin reduces the amount of calcium that enters your blood.

- Calcitonin may also have **minor effects on the kidney**:
  - increased calcium excretion
  - increased H+ secretion / K+ retention

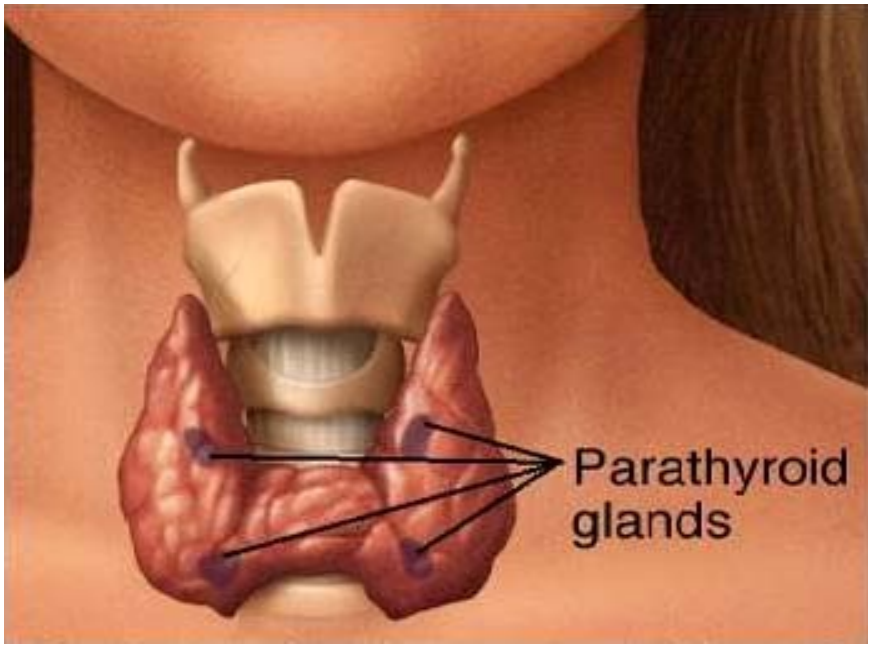
What is the Role of Calcitonin in Humans?

1. Removal of the thyroid gland has no effect on plasma calcium levels!
2. Excessive calcitonin release does not affect bone metabolism!
3. Other mechanisms are more important in regulating calcium metabolism (ie, PTH and vitamin D).

The effects of calcitonin counter the effects of parathyroid hormone, a substance secreted by the parathyroid glands that acts to increase serum calcium concentrations.

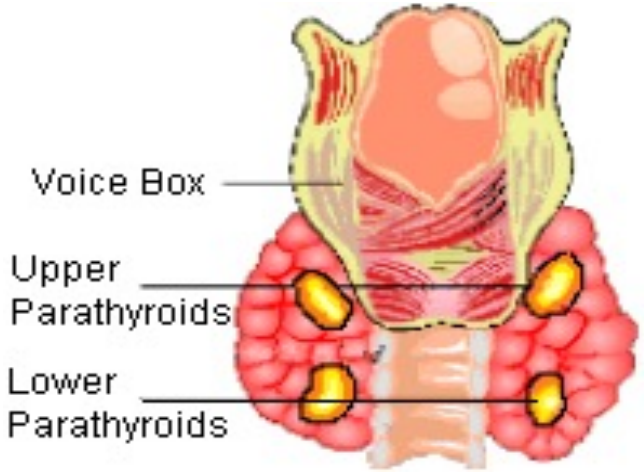
2-Parathyroid Hormone

- Parathyroid hormone (PTH) is produced by the four parathyroid glands, on the posterior aspect of the thyroid gland.
- It is THE MAJOR regulator of calcium homeostasis in humans.



2- Parathyroid Hormone (PTH)

- **Site of Secretion:**
  - Parathyroid gland.



- **Structure:**
  - Peptide Hormones composed of **84 amino acid in single chain** formed from a prohormone (90 amino acids)..

- The immediate precursor for proPTH (90 amino acids) is the 115-aminoacid preproPTH.
- PreproPTH differs from proPTH by having an additional 25-amino-acid amino terminal extension.
- PTH 1–34 has full biologic activity, and the region 25–34 is primarily responsible for receptor binding.

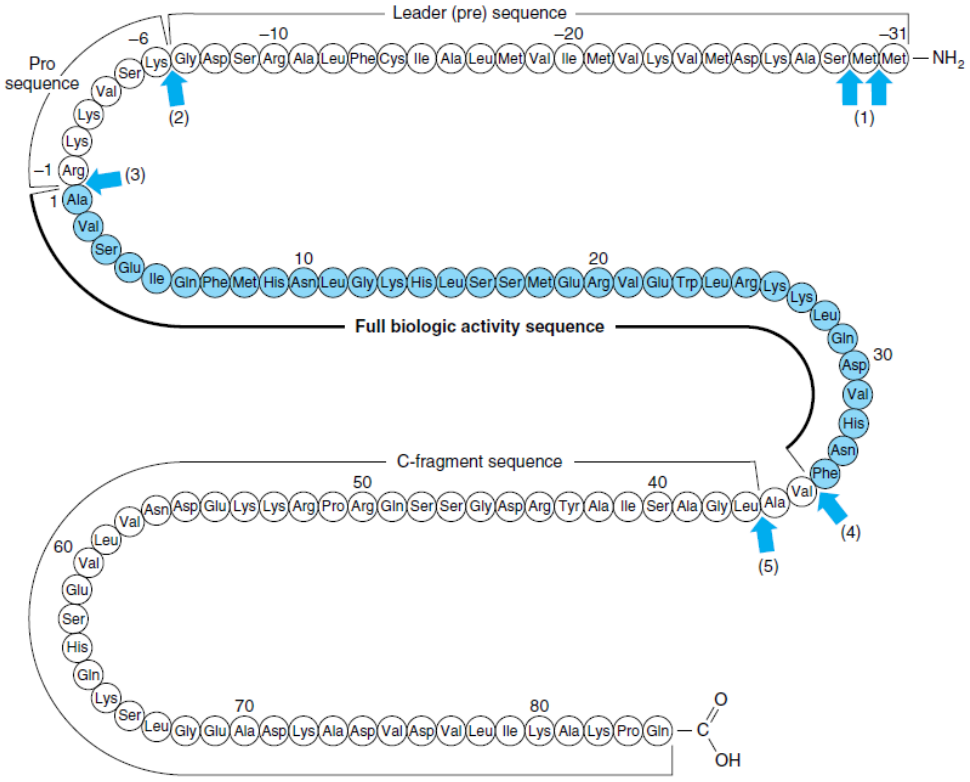


Figure 42–13. Structure of bovine preproparathyroid hormone. Arrows indicate sites cleaved by pro-

Regulation:

- The biosynthesis of PTH and its subsequent secretion are regulated by the plasma ionized calcium (Ca^{2+}) concentration

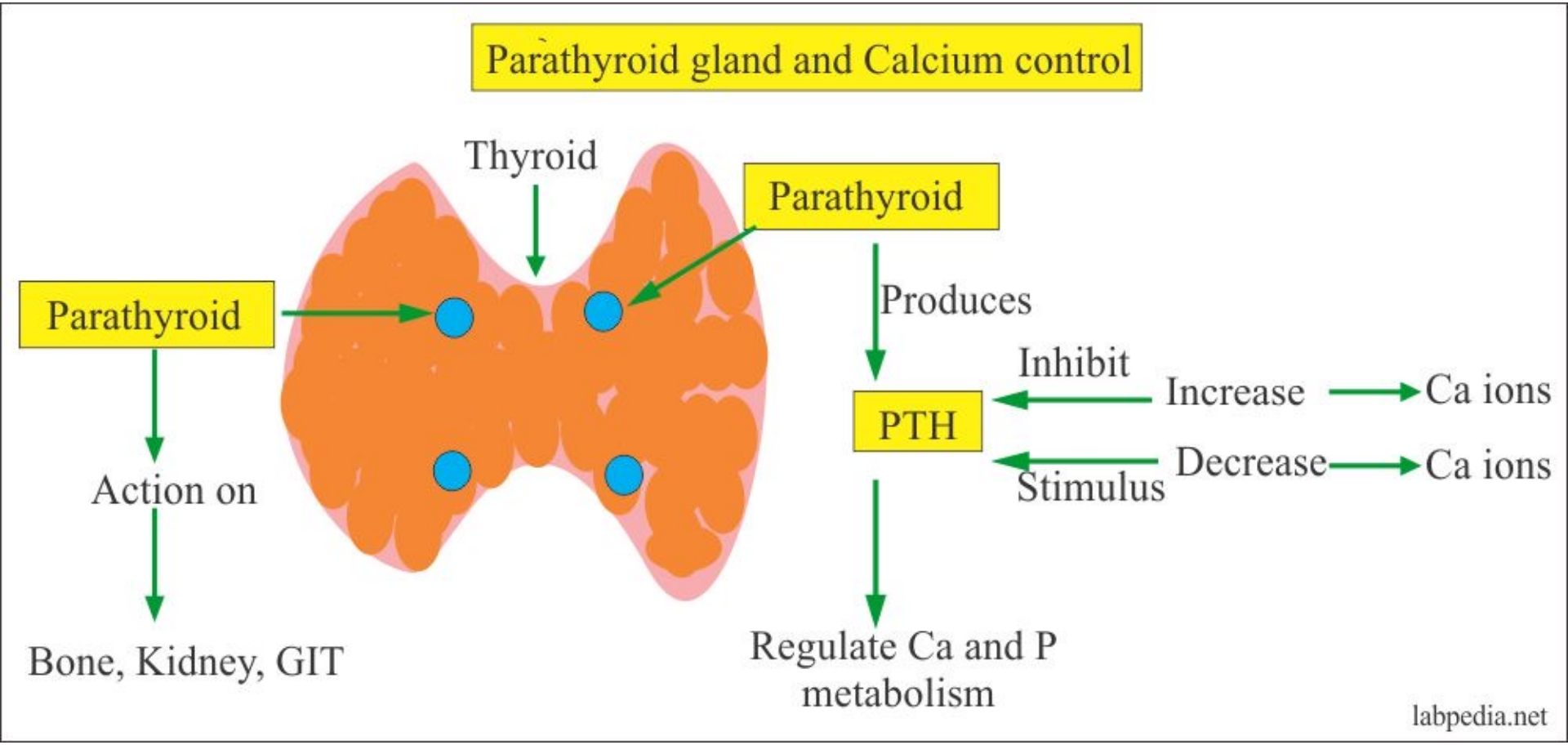
- An acute decrease of Ca^{2+} results in a marked increase of PTH mRNA, and this is followed by an increased rate of PTH synthesis and secretion
  - When calcium ion concentration in plasma decrease PTH concentration increase (and Vic versa).
  - When calcium ion concentration in plasma increase PTH concentration decrease.

Regulation of PTH Secretion

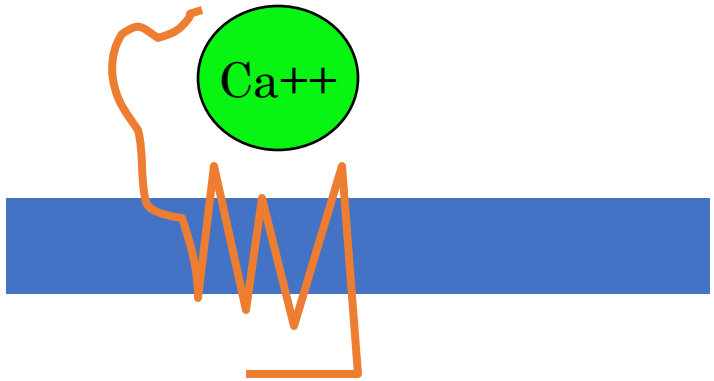
- **PTH cells** contain **a receptor for calcium**, coupled to a G protein.
- **Result of calcium binding**: decreased cyclic AMP,

  decrease PTH release.
- **Low calcium results in higher cAMP**, increase **PTH release**.
- Ionized calcium has **a negative feedback** on
- parathyroid hormone (PTH) production.
- Normal total blood calcium levels are 10mg/dl

  * Also, **vitamin D inhibits PTH release** (negative feedback).


Parathyroid gland and Calcium control
Thyroid
Parathyroid
Parathyroid
Produces
Inhibit
Increase
Ca ions
PTH
Decrease
Ca ions
Stimulus
Action on
Bone, Kidney, GIT
Regulate Ca and P metabolism
labpedia.net

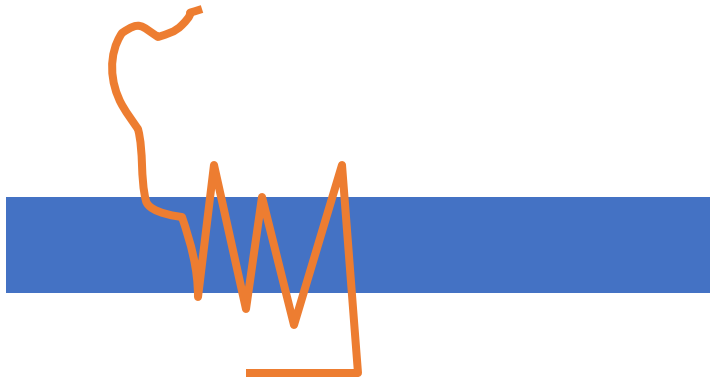
Calcium Receptor, cAMP, and PTH Release



decreased cAMP

decreased PTH release

Calcium Receptor, cAMP, and PTH Release



increased cAMP

increased PTH release

Mechanism of Action of PTH

- PTH binds to a **G protein-coupled** receptor.

- Binding of PTH to its receptor activates TWO signaling pathways:
  - increased **cyclic AMP** → activation of **PKA**
  - increased **phospholipase C** → activation of **PK C**

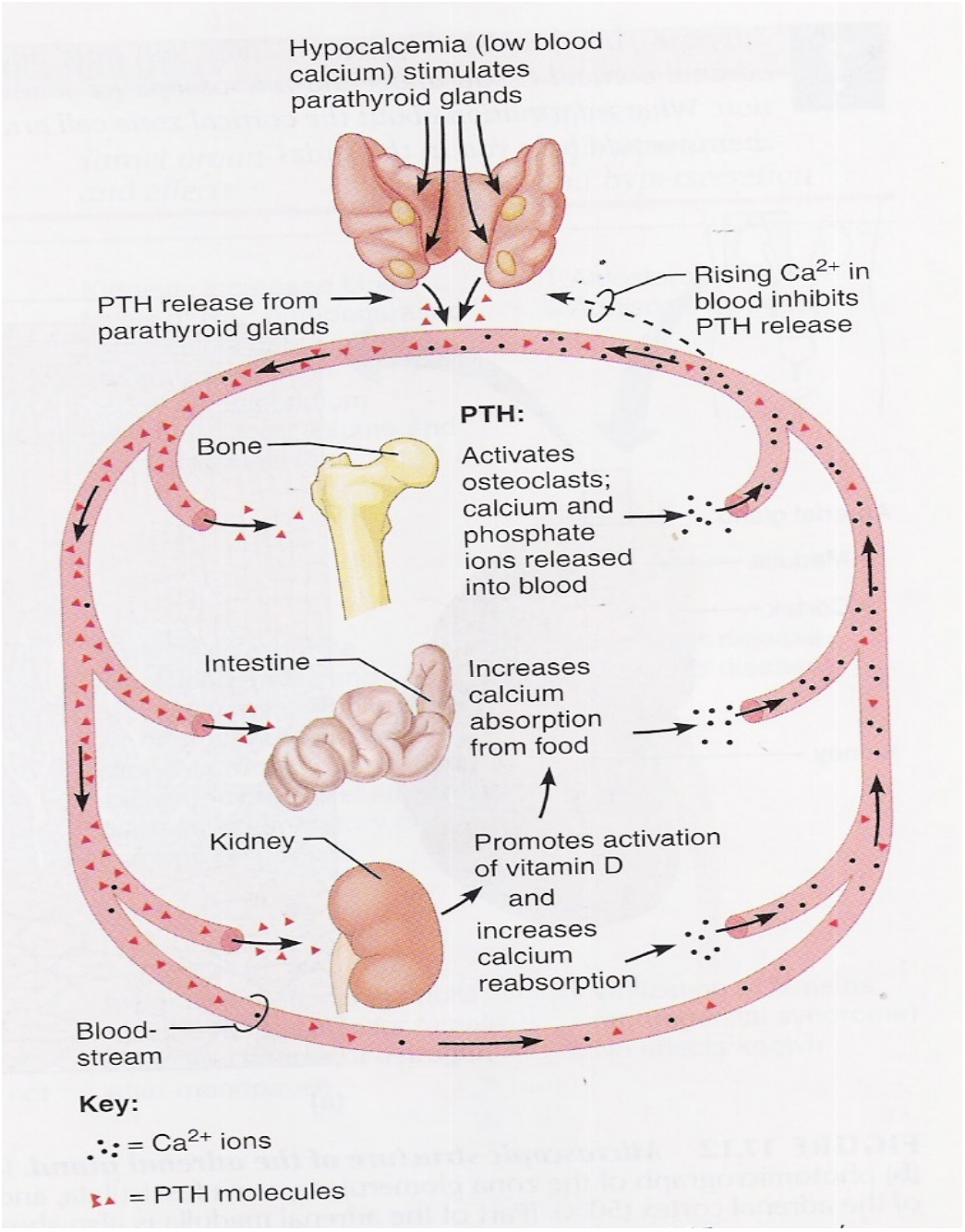
- Activation of **PKA** ⟹ **decrease bone mineralization** (bone formation)

- Both **PKA and PKC** activity ⟹ **increased reabsorption of calcium** by **the kidneys**

Physiological Functions:

- Stimulate mobilization (release) of calcium from bones. (stimulate osteoclast activity)
- Increase absorption of calcium from gastrointestinal tract (indirectly through increased production of the active metabolite of vitamin D3 by the kidney required for calcium absorption from the small intestine).
- Decrease calcium excretion and enhance its reabsorption by the kidney.
- Also get increased excretion of phosphate (other component of bone mineralization), and decreased excretion of hydrogen ions (more acidic environment favors demineralization of bone)
- Decrease calcium concentration in milk and saliva.

NET RESULT: increased plasma calcium levels (Hypercalcemic effect)


Hypocalcemia (low blood calcium) stimulates parathyroid glands
PTH release from parathyroid glands
Rising Ca^{2+} in blood inhibits PTH release
PTH:
Bone
Activates osteoclasts; calcium and phosphate ions released into blood
Intestine
Increases calcium absorption from food
Kidney
Promotes activation of vitamin D and increases calcium reabsorption
Blood-stream
Key:
= Ca^{2+} ions
= PTH molecules

The Role of Vitamin D in Calcium Homeostasis

- The active metabolite of vitamin D is required for efficient absorption of calcium in the small intestine (major effect).
- In addition, vitamin D may have a minor effect on bone resorption (and is required for the effects of PTH on bone).

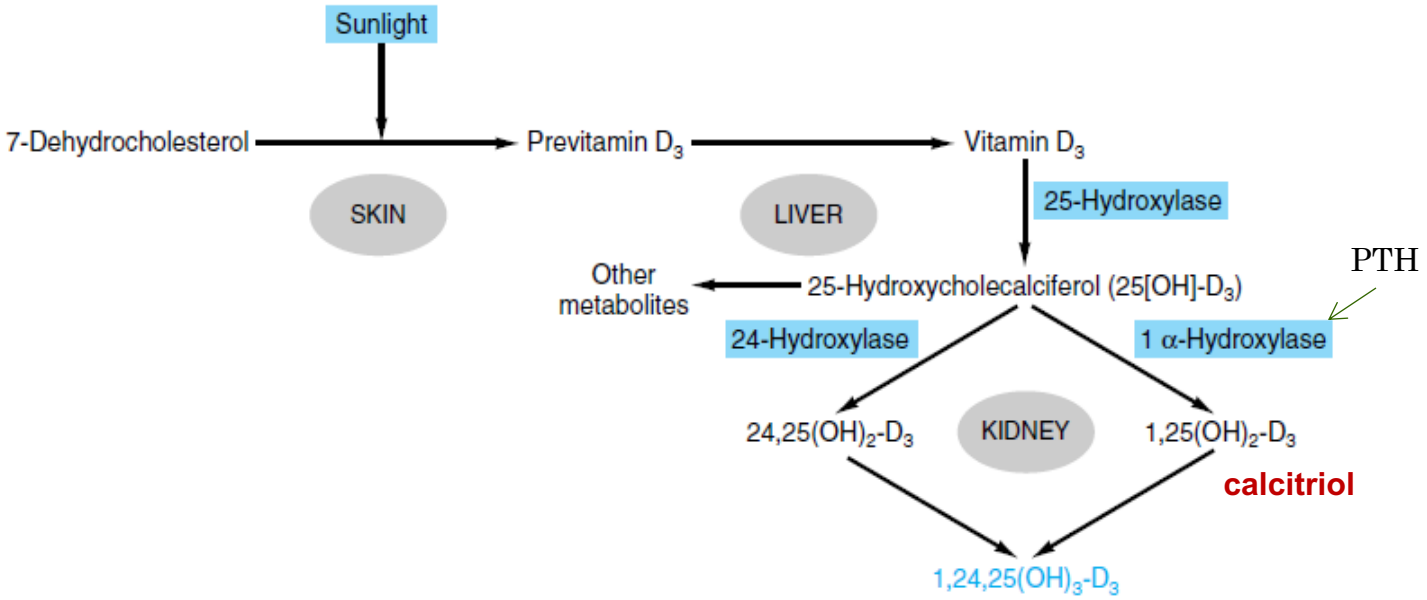
Sources and Metabolism of Vitamin D

1. The production of the active metabolite of vitamin D requires the actions of three major organ systems, **the skin, liver, and kidney**.
2. Vitamin D3 (**cholecalciferol**) is produced in the **skin** upon exposure to the sun. It is also found in **foods** (fish liver oil, egg yolk).
3. A specific transport protein called **the vitamin D-binding protein** (VDBP), a carrier protein in the plasma, **binds** vitamin D3, moves vitamin D3 from the **skin or intestine** to the **liver**, where it undergoes 25-hydroxylation,

- Cholecalciferol then is hydroxylated in the liver, to form 25-hydroxycholecalciferol (weak), it is the major form of vitamin D found in plasma, and is transported to the kidney by the VDBP(vitamin D binding protein).

- 25-hydroxycholecalciferol is then 1-hydroxylated in the kidney (mitochondria of the renal proximal convoluted tubule)to form the active metabolite, 1,25dihydroxycholecalciferol (calcitriol) which is the most potent naturally occurring metabolite of vitamin D.

- By binding to VDBP, calcitriol is transported to various target organs.



Regulation of Vitamin D Metabolism

- **PTH increases 1-α hydroxylase activity,** increasing production of active form of vitamin D that:

✓ Increases calcium absorption from the intestines,

✓ increases calcium release from bone increasing **osteoclast** number

✓ and decreases loss of calcium through the kidney(increase calcium reabsorption from kidney).

increased calcium levels

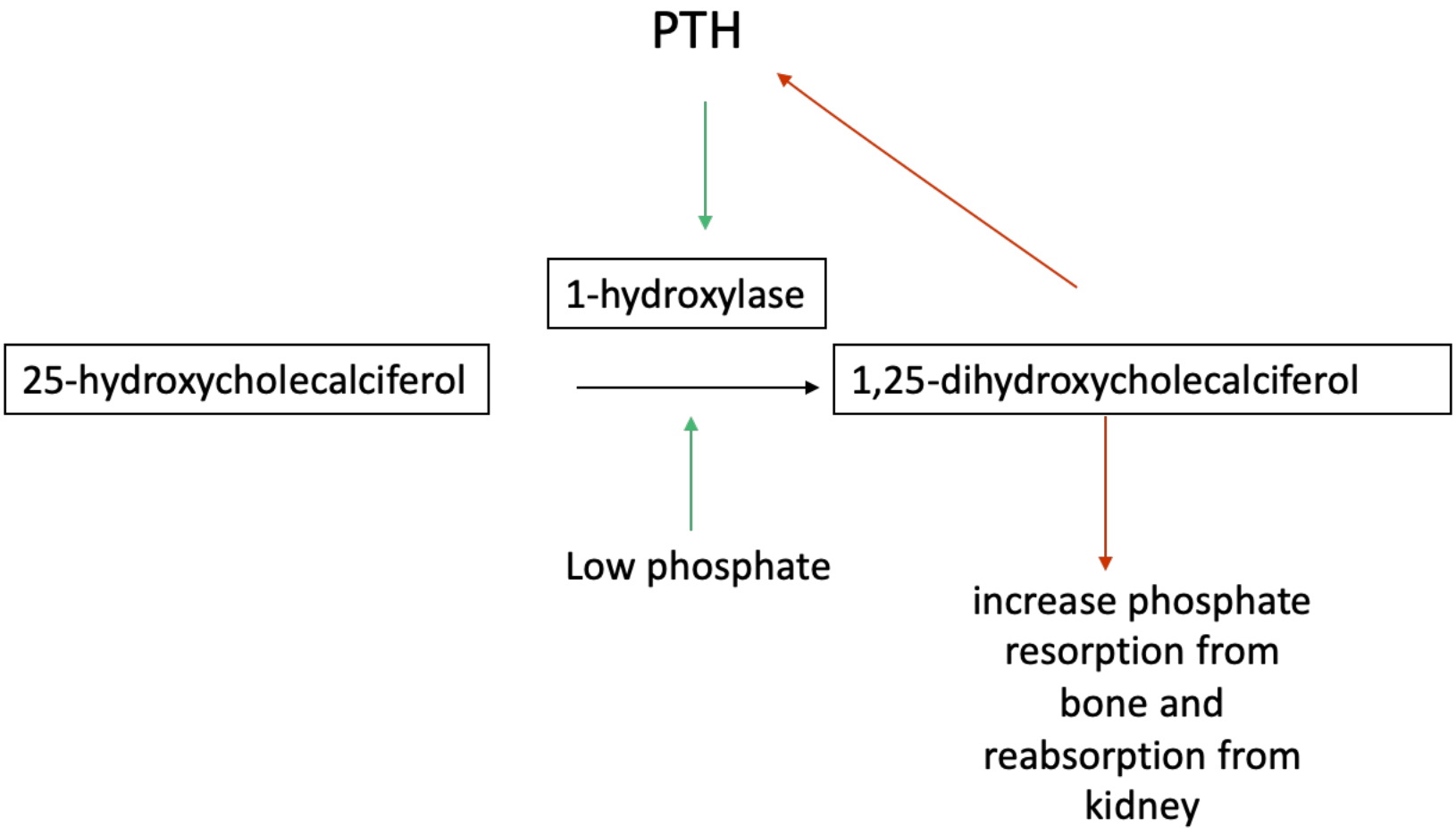
- As a result of increased calcium levels , PTH secretion decreases decreasing ⟶ 1-α hydroxylase activity (**negative feedback**).

- **Low phosphate** concentrations **also increase**

  1-α hydroxylase activity ⟶ 1, 25 $(OH)_2$ D_3 increases phosphate resorption from bone and reabsorption from kidney

- Vitamin D maintaining **calcium and phosphate levels** **for** **bone formation** **and** proper functioning of **parathyroid hormone** **to maintain serum calcium levels**

Regulation of Vitamin D by PTH and Phosphate Levels



Mechanism of Action of Vitamin D

- Vitamin D interacts with an intracellular receptor which acts as a transcription factor that modulates the gene expression of transport proteins (such calbindin), which are involved in calcium absorption in the intestine.

Vitamin D deficiency

- Can result in lower bone mineral density and an increased risk of bone loss (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism in the body

- Vitamin D has been studied as a potential treatment for osteoporosis

Failures of Calcium Homeostasis

- **Hypercalcemia** – excessive mobilization (release) of calcium bone or increased calcium absorption from the intestine with inadequate renal excretion of the excess calcium..

➢ **Causes** include Primary hyperparathyroidism, malignancy or vitamin D excess

- **Hypocalcemia** – symptoms include neuromuscular irritability ; numbness & tingling occur around the mouth, fingertips and toes;

➢ **causes** include PTH deficiency (hypoparathyroidism)& vitamin D deficiency (Rickets, osteomalacia) , renal failure