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CALCIUM METABOLISM AND ITS REGULATION

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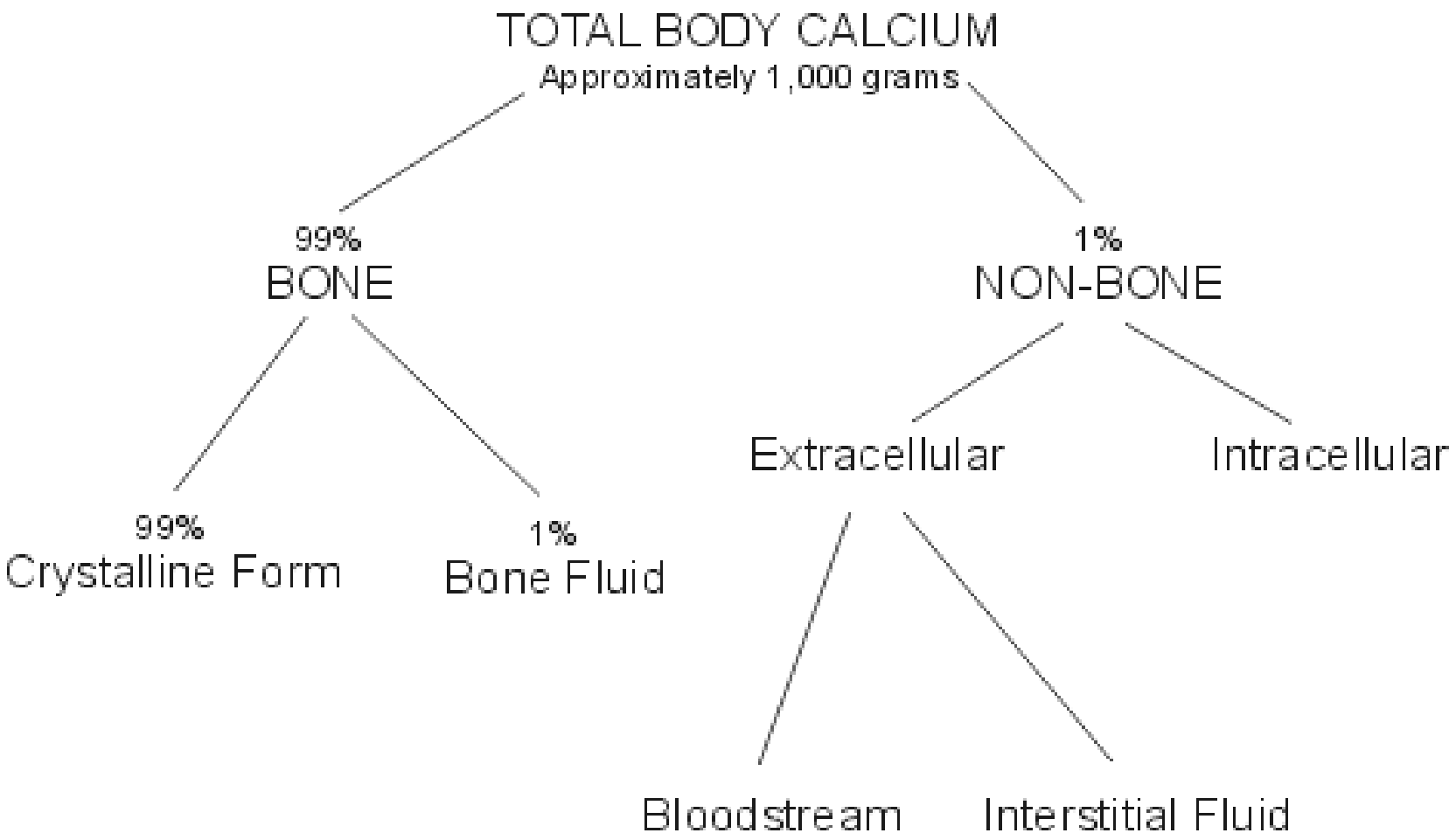

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Different Forms of Calcium

❖Most of the calcium in the body exists as the mineral hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$.

❑ Calcium in the plasma:

45% in ionized form (the physiologically active form)

45% bound to proteins (predominantly albumin)

10% complexed with anions (citrate, sulfate, phosphate)

➢ Both total calcium and ionized calcium measurements are available in many laboratories

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Body requirements

Age (in years)	Calcium Requirement
1 – 3	500mg
4 - 8	800mg
9 - 18	1300mg
19 - 50	1000mg
51+	1500mg

- ***Pregnant and lactating women are recommended a daily calcium intake of 1000mg.**

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source

- Calcium is found in milk and dairy products,
- Green leafy vegetables,
- seafood,
- almonds,
- blackstrap molasses,
- broccoli,
- enriched soy and rice milk products, figs,
- soybeans and tofu.

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Absorption of Ca

- **Absorption is taking place from the first and second part of duodenum against concentration gradients**
- **Absorption required a carrier protein , helped by Ca-dependent ATPase**
- **Increased absorption-**
  - **calcitriol , active form of Vit-D**
  - **PTH**
  - **acidic pH**
  - **Lys and Arg**

- **Inhibiting absorption -**
  - **phytic acid**
  - **oxalates**
  - **phosphate**
  - **Mg**
  - **caffeine**

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Biological functions of Calcium

- **Bone and teeth mineralization**
- **Regulate neuromuscular excitability**
- **Blood coagulation**
- **Secretory processes**
- **Membrane integrity**
- **Plasma membrane transport**
- **Enzyme reactions**
- **Release of hormones and neurotransmitters**
- **Intracellular second messenger**

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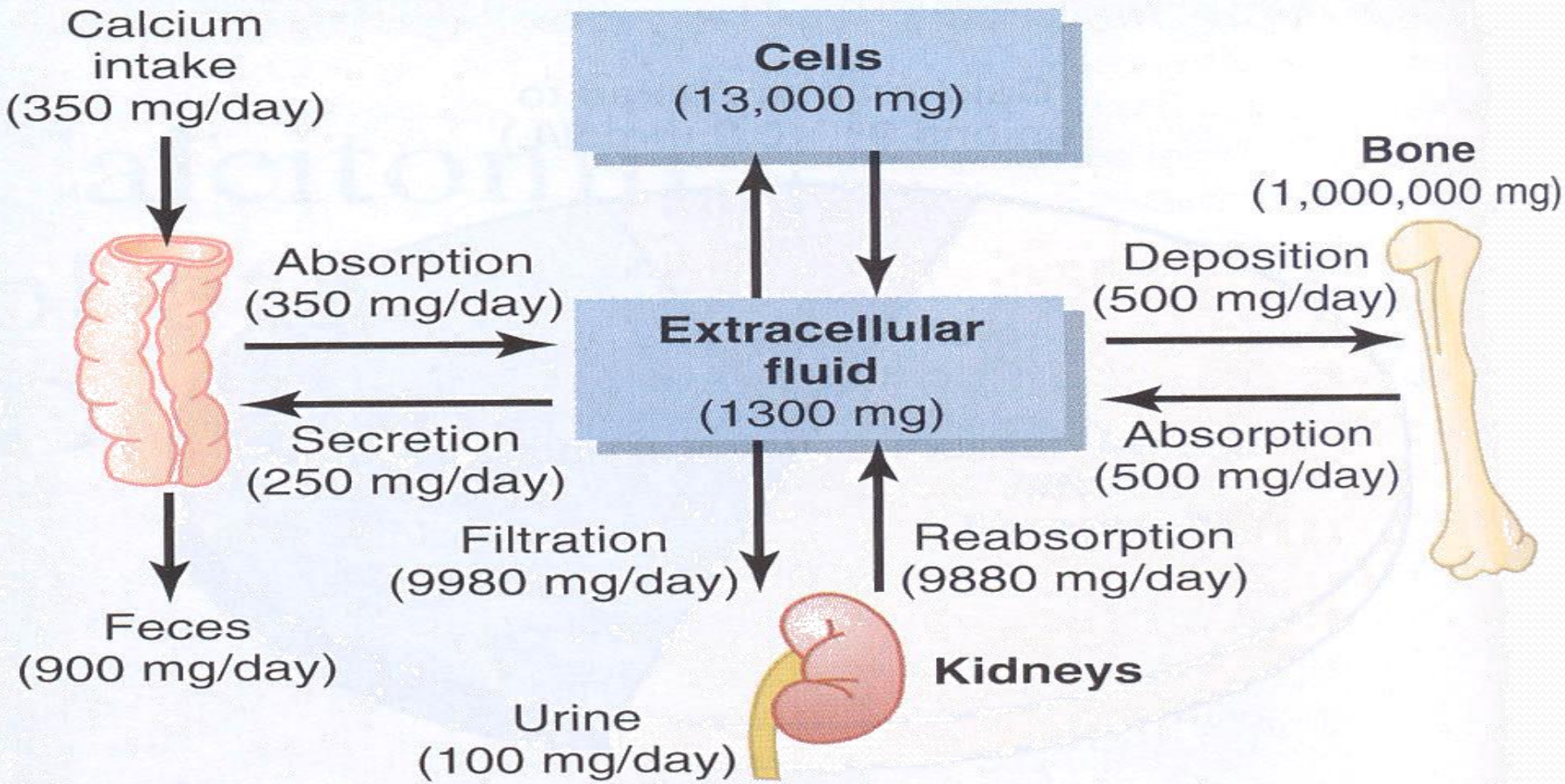
Calcium turnover



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Hormone regulation of calciummetabolism

Vitamin D

Parathyroid hormone (PTH)

Organ-target: bones, kidneys

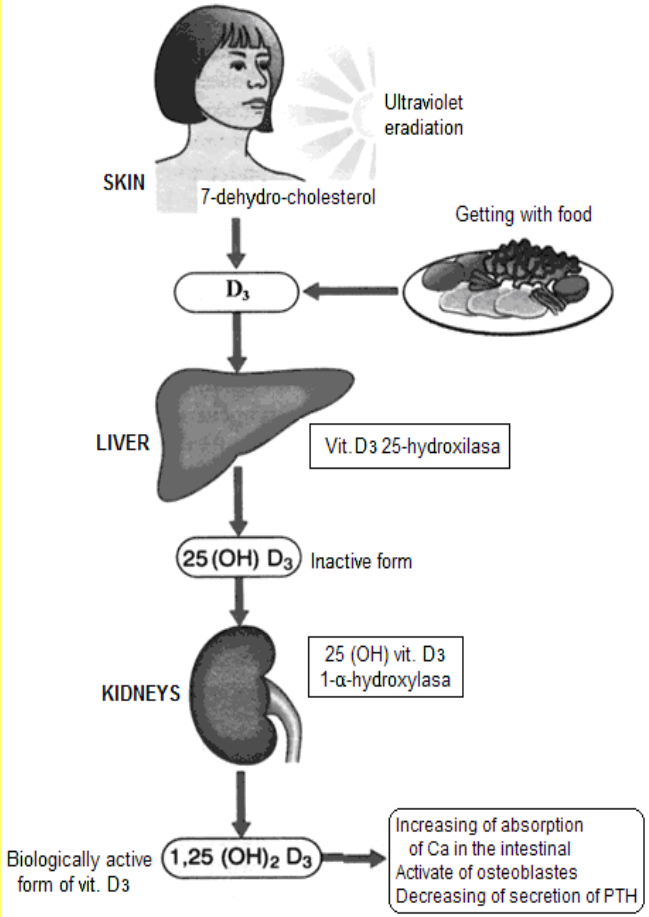
Function of PTH - increase of Ca concentration in plasma

Mechanisms:

1. Releasing of Ca by bones (activation of osteoclasts – resumption of bones)

2. Increase of Ca reabsorbing in kidneys

3. Activation of vit. D3 synthesis and increase of absorption in the intestine



Calcitonin

Organ-target - bones

Function - decrease of Ca concentration in plasma

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Vitamin D3

- Dietary cholesterol is converted into 7-dehydrocholesterol and transported to skin
- UV sunlight (290-320nm) penetrates the skin to break provitamine (7-dehydrocholesterol) to previtamine and it is then converted to Cholecalciferol by the process of isomerisation
- In the liver, cholecalciferol undergoes 25-hydroxylation to yield 25(OH) Vit-D (calcidiol)
- In the kidney , calcidiol undergoes further 1α-hydroxylation to produce 1,25 –dihydroxy Vit-D (Calcitriol). Its production in the kidney is catalyzed by 1α -hydroxylase .

❖ **1α -hydroxylase activity is increased by :**

- Decreased serum Ca^{2+}
- Increased PTH level
- Decreased serum phosphate

❑ **Action of 1,25-dihydroxycholecalcififerol(Calcitriol)**

- Increases intestinal Ca^{2+} absorption
- Increases intestinal phosphate absorption
- Increase renal reabsorption of Ca^{2+} and phosphate
- Increases osteoclast activity

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Vitamin D3 and Calcium Control

- **Vitamin D3 (Cholecalciferol)**
  - **Converted to precursor in liver**
    - **Initially stored**
    - **Converted to 25-Hydroxycholecalciferol**
    - **Feedback control limits concentration**
  - **Converted to active form in kidney**
    - **1,25-Dihydroxycholecalciferol**
    - **Under the feedback control of parathyroid hormone (PTH)**
- **The main action of 1,25-$(OH)_2$-D is to <u>stimulate absorption of Ca^{2+} from the intestine</u>.**
- **1,25-$(OH)_2$-D induces the production of calcium binding proteins which sequester Ca^{2+}, buffer high Ca^{2+} concentrations that arise during initial absorption and allow Ca^{2+} to be absorbed against a high Ca^{2+} gradient**

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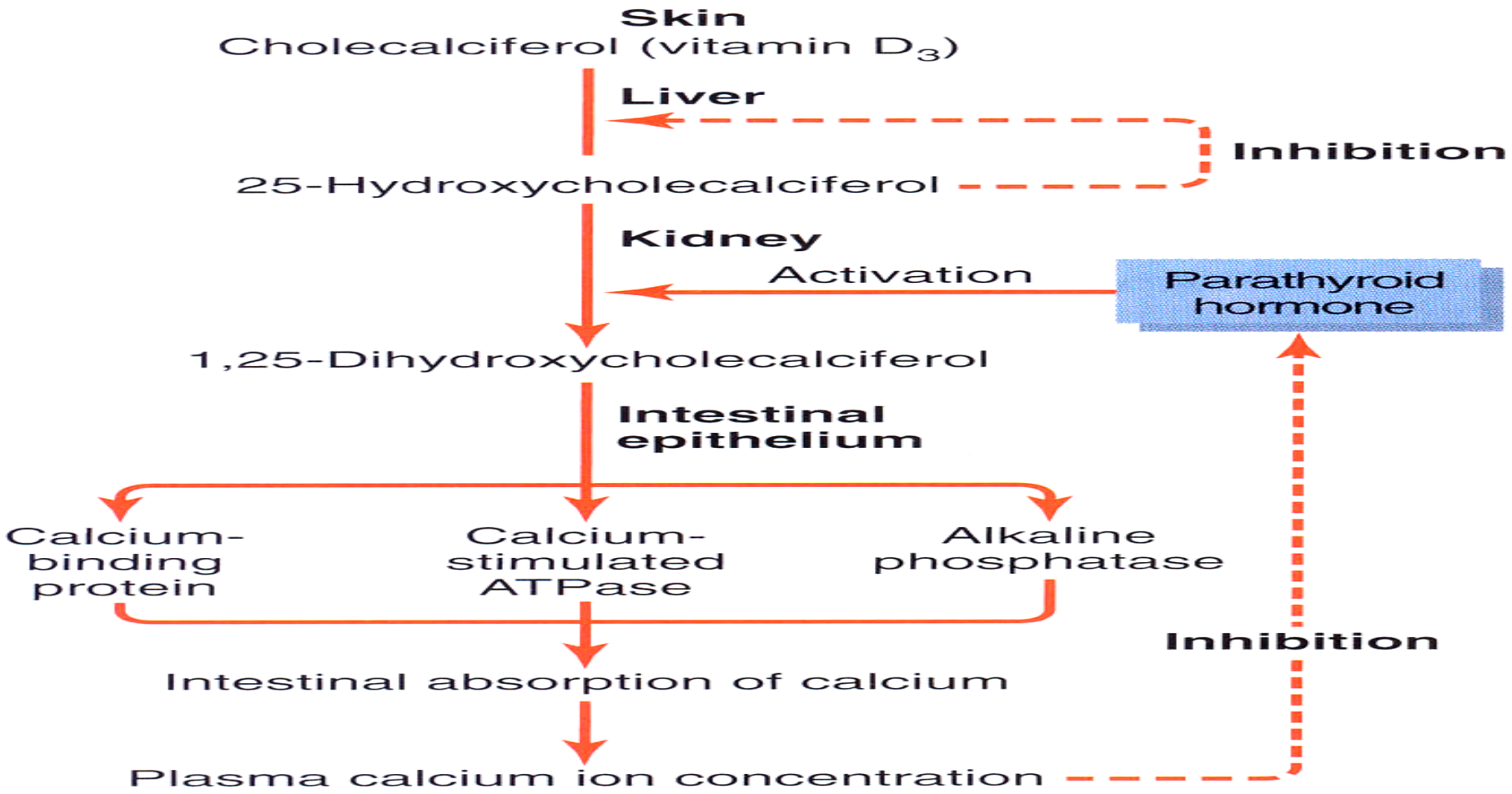
Vitamin D3 and Calcium Control



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Vitamin D_3 promotes intestinal calcium absorption

- Vitamin D3 acts via steroid hormone like receptor to increase transcriptional and translational activity
- One gene product is calcium-binding protein (CaBP)
- CaBP facilitates calcium uptake by intestinal cells
- Estrogen, prolactin and growth hormone also stimulate 1α -hydroxylase thus increasing Ca absorption during pregnancy, lactation and growth

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Vitamin D3 Actions on Bones

- Another important target for 1,25-$(OH)_2$-D3 is the bone.
- Osteoblasts, but not osteoclasts have vitamin D3 receptors.
- 1,25-$(OH)_2$-D3 acts on osteoblasts which produce a paracrine signal that activates osteoclasts to resorb Ca^{++} from the bone matrix.
- 1,25-$(OH)_2$-D3 also stimulates osteocytic osteolysis.
- In its absence, excess osteoid accumulates from lack of 1,25-$(OH)_2$-D3 repression of osteoblastic collagen synthesis.
- Inadequate supply of vitamin D3 results in **rickets**, a disease of bone deformation

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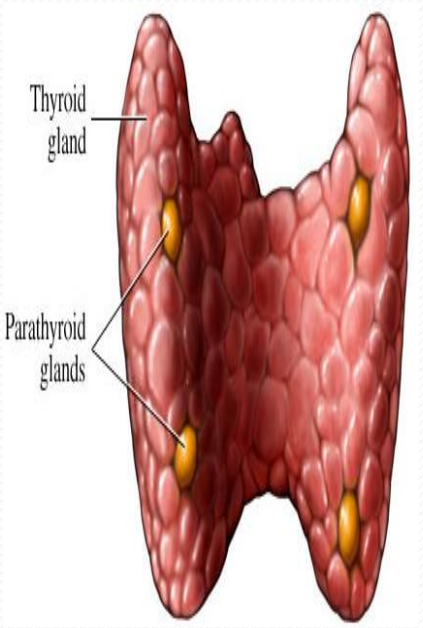
Parathyroid hormone (PTH



- It is synthesised as pre-pro-PTH(115aa) and is cleaved to pro-PTH(90aa) with cleavage before secretion of PTH(84aa).
- Intact PTH $T_{1/2}$ 3-4 mins
- Normal levels 1.3 – 6.8 pmol/L
- Secreted from the chief cells of the parathyroid glands.

- **Function:**

  Increase renal phosphate excretion , and increases plasma calcium by:

  - Increasing osteoclastic resorption of bone (occurring rapidly).
  - Increasing intestinal absorption of calcium (a slower response).
  - Increasing synthesis of 1,25-(OH)2D3 (stimulating GIT absorption).
  - Increasing renal tubular reabsorption of calcium

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PTH action

- The overall action of PTH is to increase plasma Ca^{++} levels and decrease plasma phosphate levels.
- PTH acts directly on the bones to stimulate Ca^{++} resorption and kidney to stimulate Ca++ reabsorption in the distal tubule of the kidney and to inhibit reabosorptioin of phosphate (thereby stimulating its excretion).
- PTH also acts indirectly on intestine by stimulating 1,25-$(OH)_2$-D synthesis.
- PTH indirectly increases Calcium absorption from GIT

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Regulation of PTH

- The dominant regulator of PTH is plasma Ca^{2+}.
- Secretion of PTH is inversely related to [Ca^{2+}].
- Maximum secretion of PTH occurs at plasma Ca^{2+} below 3.5 mg/dL.
- At Ca^{2+} above 5.5 mg/dL, PTH secretion is maximally inhibited.
- PTH secretion responds to small alterations in plasma Ca^{2+} within seconds.
- A unique calcium receptor within the parathyroid cell plasma membrane senses changes in the extracellular fluid concentration of Ca^{2+}.
- This is a typical G-protein coupled receptor that activates phospholipase C and adenylate cyclase—result is increase in intracellular Ca^{2+} via generation of inositol phosphates and decrease in cAMP which prevents exocytosis of PTH from secretory granules.
- When Ca^{2+} falls, cAMP rises and PTH is secreted.
- 1,25-$(OH)_2$-D inhibits PTH gene expression, providing another level of feedback control of PTH.
- Despite close connection between Ca^{2+} and PO_4, no direct control of PTH is exerted by phosphate levels.

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Calcitonin

- This is produced from the C-cells of the thyroid.
- Ploypeptide(32 aa) , MW 35KD , $T_{1/2}$ 10 mins
- The major stimulus of calcitonin secretion is a rise in plasma Ca^{++} levels
- Calcitonin is a physiological antagonist to PTH with regard to Ca^{++} homeostasis
- The target cell for calcitonin is the osteoclast.
- Calcitonin acts via increased cAMP concentrations to inhibit osteoclast motility and cell shape and inactivates them.
- The major effect of calcitonin administration is a rapid fall in Ca^{2+} caused by inhibition of bone resorption.

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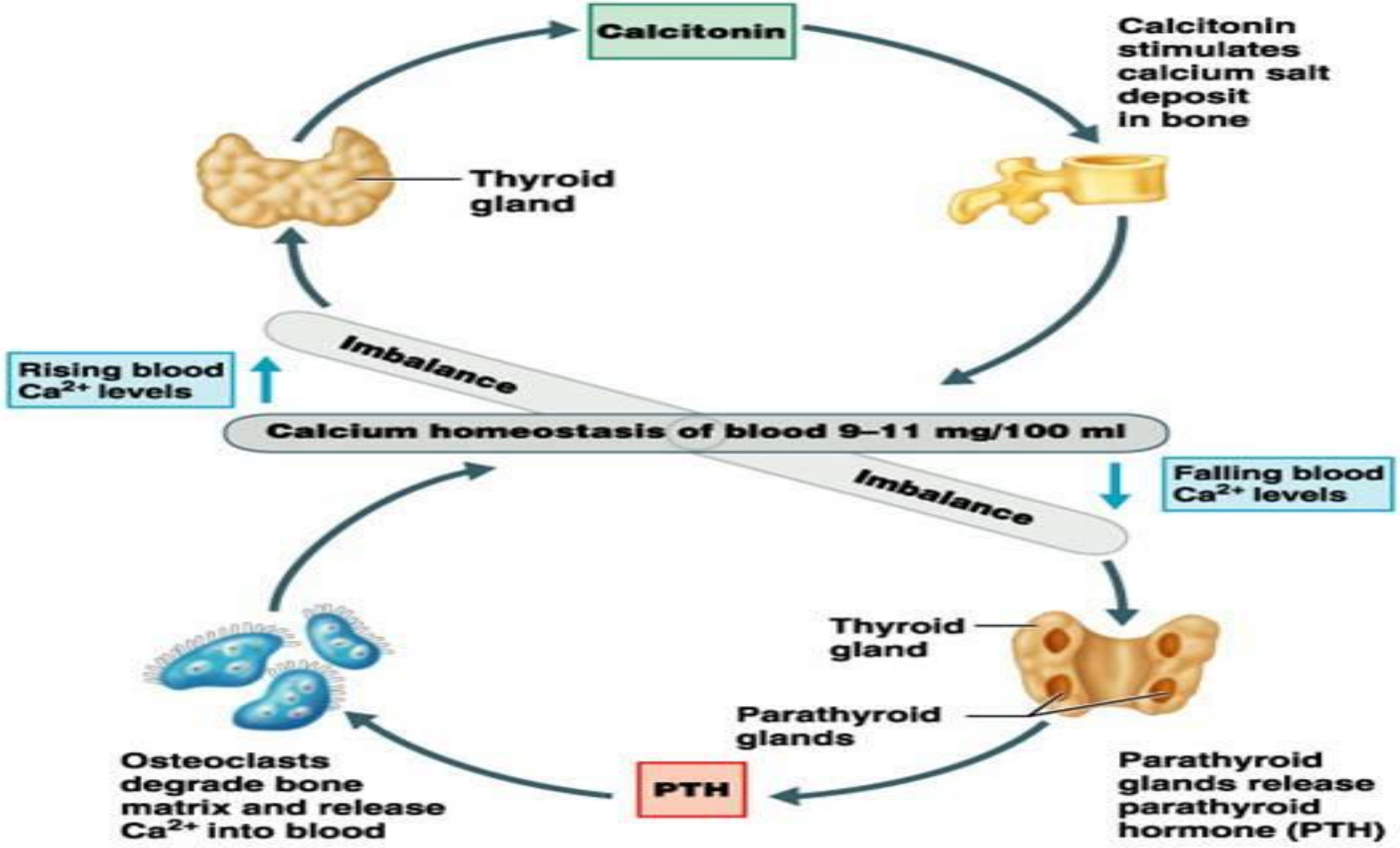

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