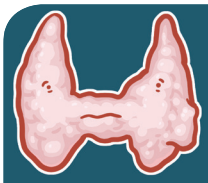

NOTES
CALCIUM & PHOSPHATE HORMONAL REGULATION

GENERALLY, WHAT IS IT?

CALCIUM & PHOSPHATE HOMEOSTASIS

Blood calcium level regulation

- *Normal total blood calcium*: 8.5–10mg/dl
- *Parathyroid hormone*: ↑ calcium level
- *Vitamin D*: ↑ calcium level
- *Calcitonin*: ↓ calcium level

Extracellular calcium

- *Diffusible*: can cross cell membranes
  - *Free-ionized calcium* (Ca^{2+}): involved in cellular processes → neuronal action potential, muscle contraction, hormone secretion, blood coagulation
  - *Complexed calcium*: Ca^{2+} ionically bound to other negatively-charged molecules (e.g. oxalate, phosphate → electrically-neutral molecules, do not partake in cellular processes)
- *Non-diffusible*: cannot cross cell membranes
  - Calcium bound to large negatively charged proteins (e.g. albumin → protein-albumin complex too large to cross cell membranes → not involved in cellular processes)

CALCITONIN

osms.it/calcitonin

CALCITONIN STRUCTURE

- Polypeptide hormone involved in blood calcium regulation
  - Not primary calcium regulator, even if thyroid gland removed, remaining regulatory mechanisms able to maintain calcium homeostasis
- Produced by thyroid gland's parafollicular cells (C cells)
- C cells synthesize preprocalcitonin (141 amino acid polypeptide) → successive enzymatic cleavage steps produces procalcitonin → immature calcitonin (33 amino acids) → mature calcitonin (32 amino acids) → stored/readied for release in secretory granules within C cells

CALCITONIN RELEASE

- Calcium-sensing receptors on C cells' surface monitor blood calcium levels → if calcium drifts above normal range → calcitonin released

CALCITONIN ACTION

- Lowers blood calcium level

Bone

- ↓ bone resorption → ↓ blood calcium concentration
  - When attaching to bone matrix osteoclast membranes form multiple arms (ruffled border) → aids attachment, increases surface area → arms secrete acid → assists bone breakdown

- Calcitonin binds to calcitonin receptor on basal osteoclast surface → G-protein coupled receptor activation → adenylate cyclase activation → adenosine triphosphate (ATP) converted to 3',5'-cyclic AMP (cAMP) → ↑ cAMP levels → ↓ number of osteocyte arms formed → ↓ bone resorption

Kidneys

- ↓ calcium, phosphate reabsorption by principal cells of distal convoluted tubules

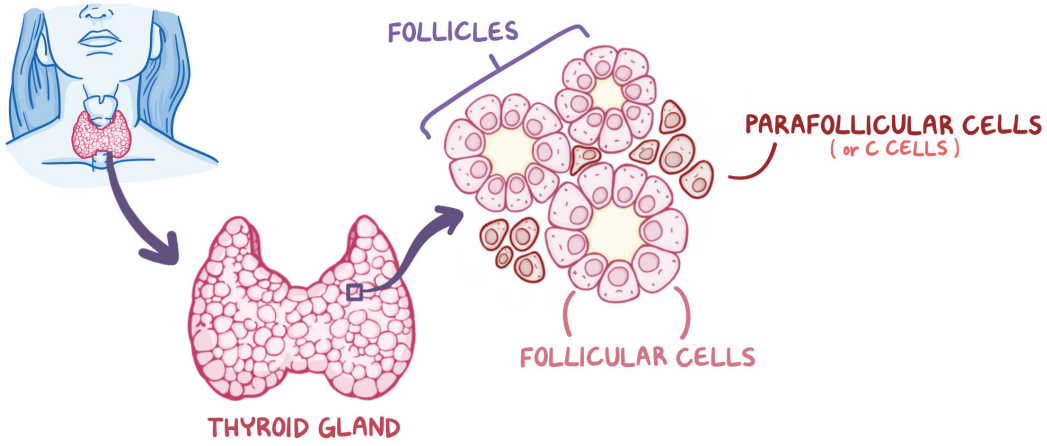

Figure 35.1 Calcitonin is made and stored in thyroid gland's C cells.

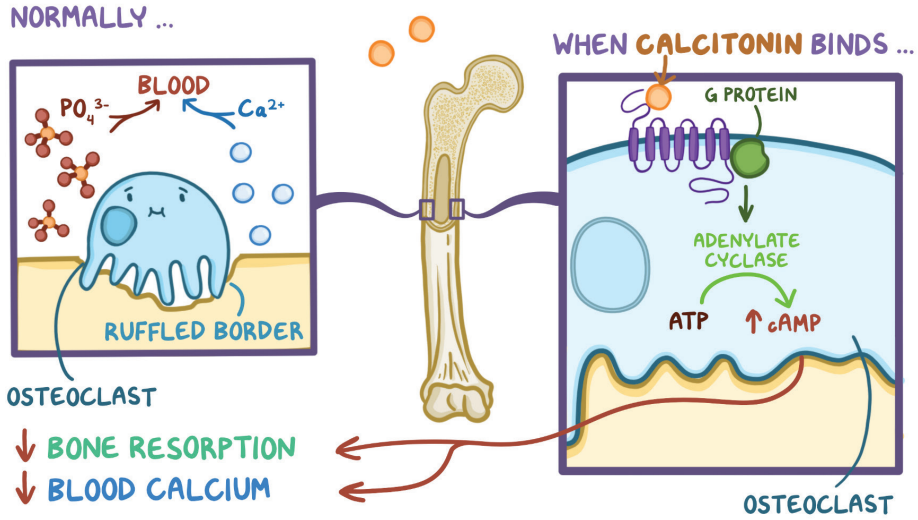

Figure 35.2 When calcitonin binds to its receptor on an osteoclast, it reduces number of osteoclast arms formed, decreasing bone resorption and blood calcium.

PARATHYROID HORMONE

osms.it/parathyroid-hormone

- Primary blood-calcium level regulator

PARATHYROID GLANDS

- Hormone produced by parathyroid glands, four pea-sized glands found posterior to thyroid
  - Parathyroid gland chief cells synthesize preproparathyroid hormone (preproPTH) (115 amino acid-long protein chain → contains biologically-active parathyroid hormone segment in N-terminal 34 amino acids)
  - Within chief cell endoplasmic reticulum, protein chain cleaved by enzyme peptidase (peptidase removes "pre" segment → proPTH → transported to Golgi apparatus)
  - Final processing in Golgi apparatus (trypsin-like enzyme cleaves off six amino acid "pro" segment → functional parathyroid hormone (single chain 84 amino acid polypeptide) → packaged into secretory vesicles → eventual release)

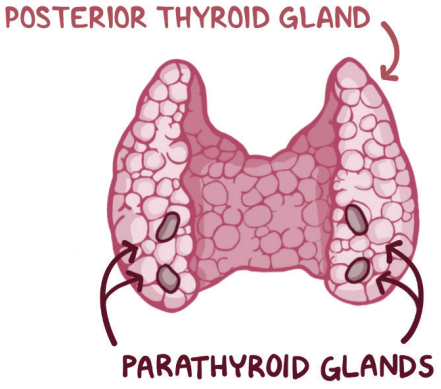

Figure 35.3 Location of the parathyroid glands which produce parathyroid hormone.

CA^{2+} CHANGES

- Ca^{2+} level changes detected by parathyroid cell surface receptor (calcium-sensing receptor)
- Calcium-sensing receptor is G-protein mediated receptor
- ↑ Ca^{2+} level → hormone release inhibition
  - Large Ca^{2+} amounts bind to receptor → phospholipase C activation → activated enzyme splits inositol bisphosphate (PIP_2) → diacylglycerol (DAG), inositol triphosphate (IP_3)
  - IP_3 diffuses through cytoplasm to endoplasmic reticulum → binds to Ins3PR receptor on ligand-gated Ca^{2+} channel → channel opens → calcium stored in endoplasmic reticulum released into cytoplasm → ↑ intracellular calcium → stops binding of PTH-holding granules to chief cell membrane → no PTH release
- ↓ extracellular Ca^{2+} levels → PTH release facilitation
  - Little/no calcium-sensing G-protein receptor activation → no inhibition of PTH granule binding → PTH release

PTH SECRETION

Stimuli

- ↓ serum Ca^{2+} concentration
- Mild ↓ in serum magnesium (Mg^{2+}) concentration
- ↑ in serum phosphate → calcium phosphate complex formation → calcium receptor stimulation ↓
- Adrenaline
- Histamine

Inhibitors

- ↑ serum Ca^{2+} concentration
- Severe ↓ serum Mg^{2+} concentration
- Calcitriol

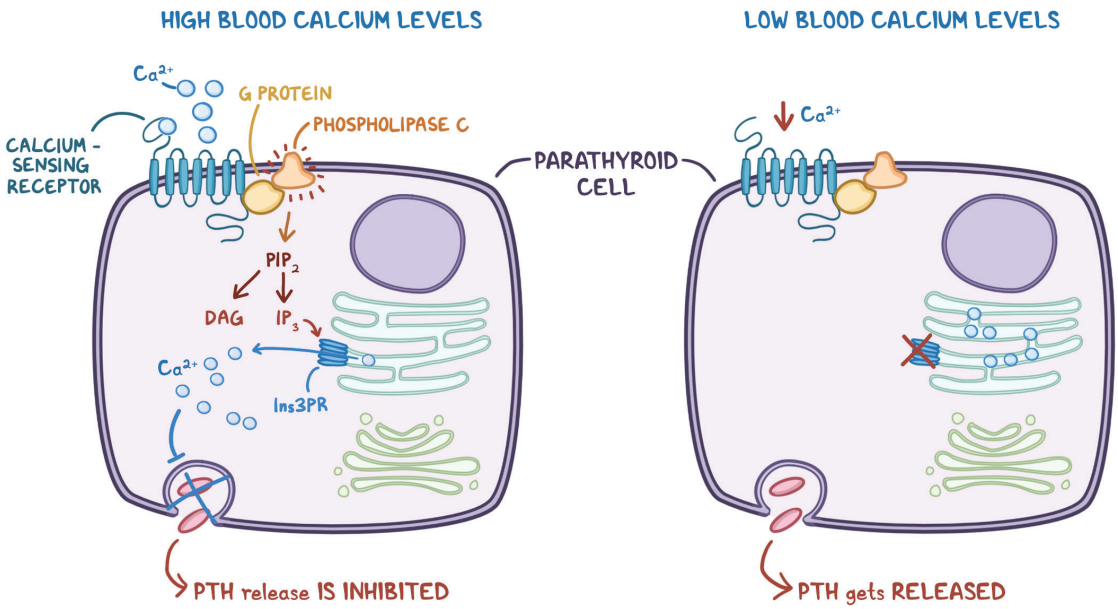

Figure 35.4 High calcium levels in blood inhibit PTH release from parathyroid cells, while low calcium levels in blood facilitate PTH release from parathyroid cells.

Magnesium

- Involved in stimulus-secretion coupling
- Moderate ↓ serum Mg^{2+} concentration promotes action of PTH on renal mineral resorption
- Severe hypomagnesemia (e.g. alcoholism) inhibits PTH secretion, causes PTH resistance

EXTRACELLULAR CALCIUM INCREASE

- PTH → ↑ extracellular calcium levels (three target organ systems)

Bones

- PTH receptors on osteoblasts
- PTH binding → ↑ cytokine release
  - Receptor activator of nuclear factor κB ligand (RANKL)
  - Macrophage colony-stimulating factor (M-CSF)
  - Inhibits osteoprotegerin (OPG) secretion (inhibition absence → free OPG binds to RANKL (decoy receptor) → prevents RANK-RANKL interaction
  - PTH-induced cytokine release permits RANK-RANKL interaction → multiple macrophage precursors fuse → osteoclast formation (bone breakdown)
- Bone breakdown → release of calcium, phosphate into blood (initially forms physiologically-inactive compound)

Kidneys

- PTH binds to receptors on cells of proximal convoluted tubules → inhibits sodium-phosphate co-transporters on apical surface → ↓ sodium, phosphate reabsorption → ↑ urinary phosphate excretion
- PTH binds to receptors on principal cells of distal convoluted tubules → sodium/calcium channel upregulation → ↑ calcium reabsorption from urine

Intestines

- PTH promotes vitamin D_3 (cholecalciferol) conversion → active form
  - Cholecalciferol synthesized by keratinocytes in skin epidermis when exposed to UV light (also found in foods) → cholecalciferol travels to liver, enzyme 25-hydroxylase catalyzes conversion to 25-hydroxycholecalciferol (calcidiol)
  - 25-hydroxycholecalciferol travels to kidney's proximal tubular cells → enzyme 1-alpha-hydroxylase (upregulated by PTH) converts it to

1,25-dihydroxycholecalciferol (calcitriol), AKA active vitamin D

- Active vitamin D travels to gastrointestinal (GI) tract → enterocytes of small intestine → upregulates calcium channels → ↑ dietary calcium absorption

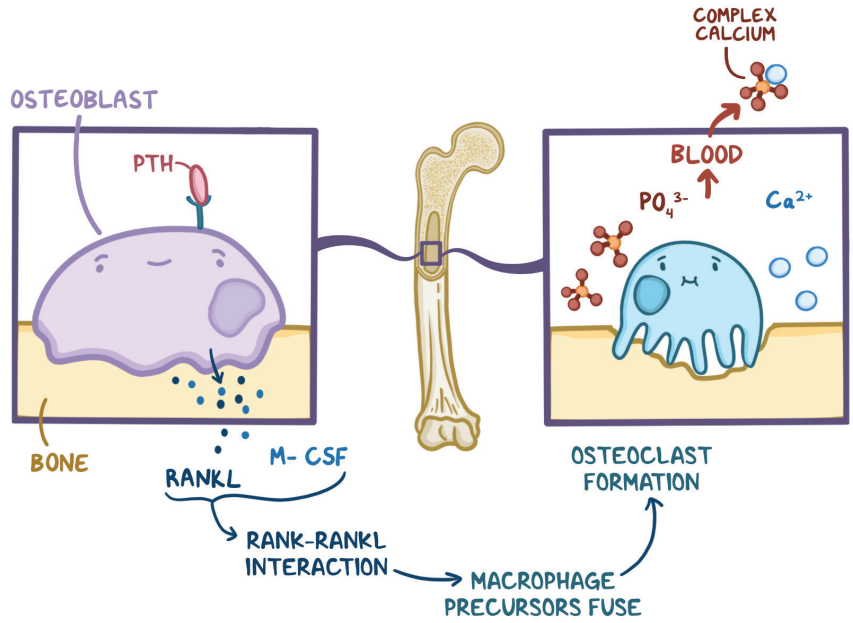

Figure 35.5 One way PTH increases extracellular calcium levels is by stimulating osteoclast formation in bone.

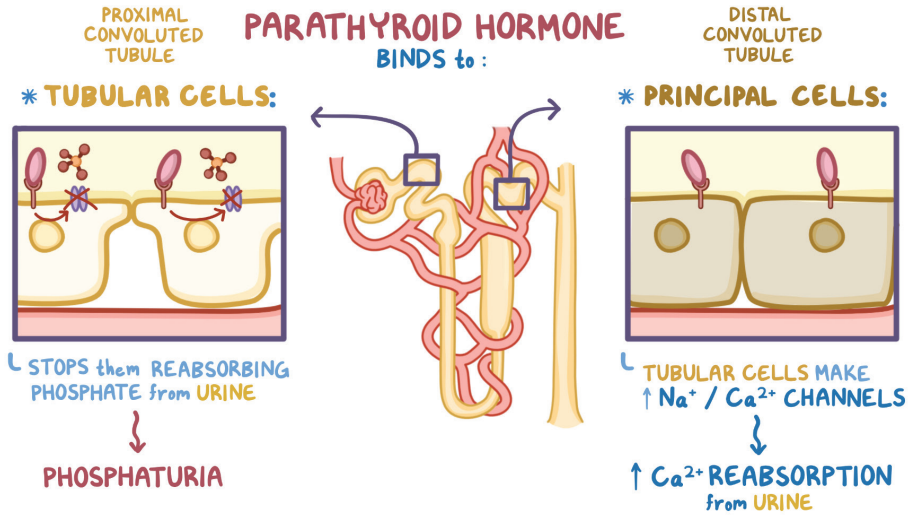

Figure 35.6 The second way PTH increases extracellular calcium levels is by ↑ urinary phosphate excretion and ↑ calcium reabsorption from urine.

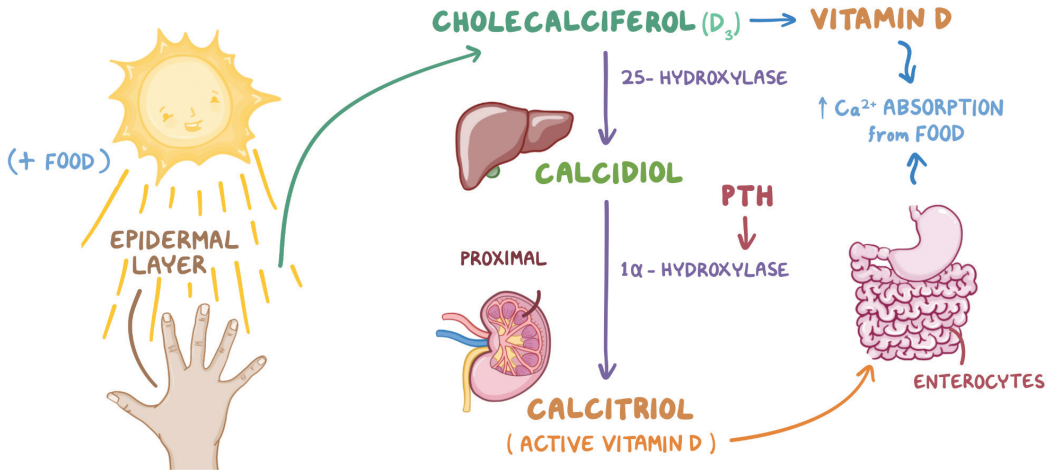

Figure 35.7 The third way PTH increases extracellular calcium levels is by helping convert cholecalciferol into vitamin D. It does so by upregulating enzyme 1α-hydroxylase.

VITAMIN D

osms.it/vitamin-D

- Steroid hormone (derived from cholesterol, fat soluble) → gene transcription stimulation
  - Promotes new bone mineralization
  - ↑ serum Ca^{2+}, phosphate concentration → ↑ available substrate concentration for bone mineralization

VITAMIN D SOURCES

Intestine

- Absorbs precursors (biologically inactive)
  - Vitamin D_2 (ergocalciferol) is derived from dietary plant sources
  - Vitamin D_3 (cholecalciferol) is derived from dietary animal sources

Skin

- Skin keratinocyte exposure (stratum basale, stratum spinosum) to UV light → vitamin D_3 production
  - 7-dehydrocholesterol reacts with UVB light (wavelengths between 270–300nm) → vitamin D_3

PRECURSOR ACTIVATION

- Ergocalciferol, cholecalciferol reach small intestine lumen → packaged in small fat-soluble sacs (micelles) with aid of bile salts → diffuse through apical membrane of absorptive intestinal cells (enterocytes)
- Within enterocytes inactive vitamin D precursors integrate into lipoproteins (chylomicrons) → exit into lymphatic system → drain into blood circulation (hepatic portal vein) → bind to carrier proteins (vitamin D-binding protein/ albumin) → transported to liver
- Hepatocytes contain 25-hydroxylase → hydroxyl group added to carbon 25 (C25) of ergocalciferol, cholecalciferol → 25-hydroxycholecalciferol (calcifediol) → calcifediol (primary vitamin D circulating form) reenters blood bound to carrier proteins
  - Hepatic hydroxylation requires NADPH, O_2, Mg^{2+} (not cytochrome P-450)
- Blood transports calcifediol to renal proximal tubules → proximal tubule cell mitochondria contain 1α-hydroxylase → hydroxyl added to C1 → 1,25 dihydroxycholecalciferol (calcitriol—active vitamin D form)

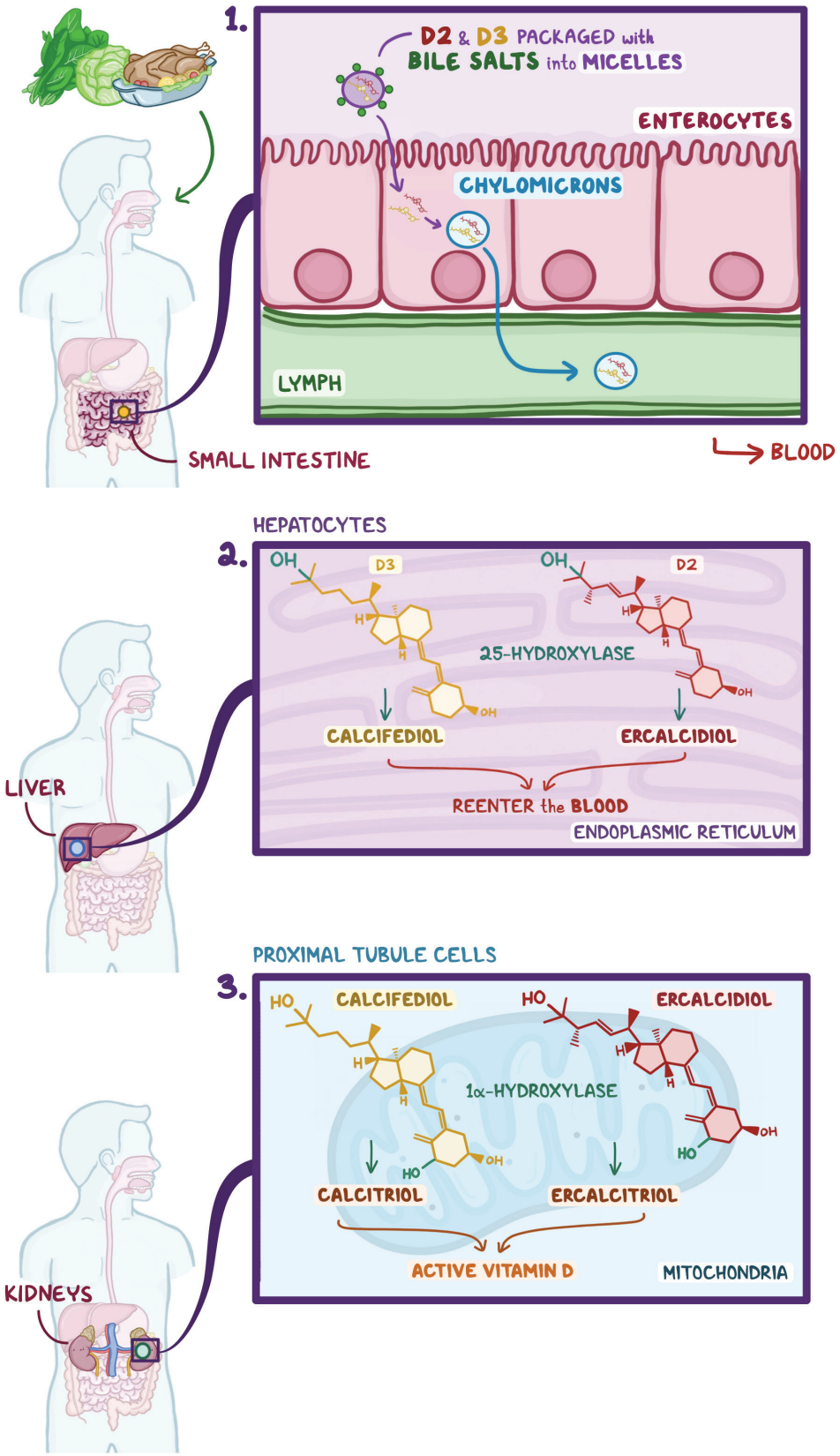

Figure 35.8 Conversion of vitamins D_2 and D_3 into active vitamin D.

Alternative pathway

- Hydroxylation at C24 → biologically inactive 24,25-dihydroxycholecalciferol
- Pathway choice regulated by blood calcium level, parathyroid hormone
  - C1 hydroxylation occurs as response to ↓ calcium/phosphate levels
  - 1α-hydroxylase activity ↑ through ↓ plasma Ca^{2+} concentration, ↑ circulating PTH levels, ↓ plasma phosphate concentration
  - C1 phosphorylation requires NADPH, O_2, Mg^{2+}, cytochrome P-450 pathway
  - If calcium levels sufficient, inactive metabolite preferentially produced

Kidney

- Stimulates Ca^{2+}, phosphate reabsorption

Intestine

- Increases Ca^{2+}, phosphate absorption
- Induces vitamin D-dependent Ca^{2+} binding-protein synthesis (calbindin D-28K)
  - Systolic protein → binds four Ca^{2+} ions
- Intestinal Ca^{2+} absorption mechanism
  - *Ca^{2+} diffusion:* intestinal lumen → cell (through electrochemical gradient)
  - *Inside cell:* calbindin D-28K binds Ca^{2+} → Ca^{2+} pumped across basolateral membrane by Ca^{2+}-ATPase

VITAMIN D ACTIONS

Bone

- Acts synergistically with PTH → osteoclast activity stimulation → bone resorption → old bone demineralization → ↑ Ca^{2+}, phosphate concentration for new bone mineralization

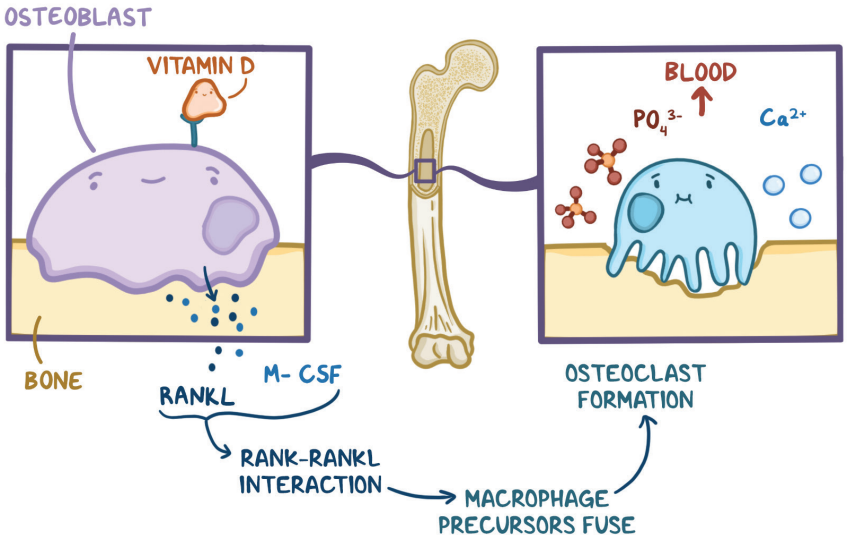

Figure 35.9 Vitamin D stimulates osteoclast formation, increasing blood calcium and phosphate concentrations.

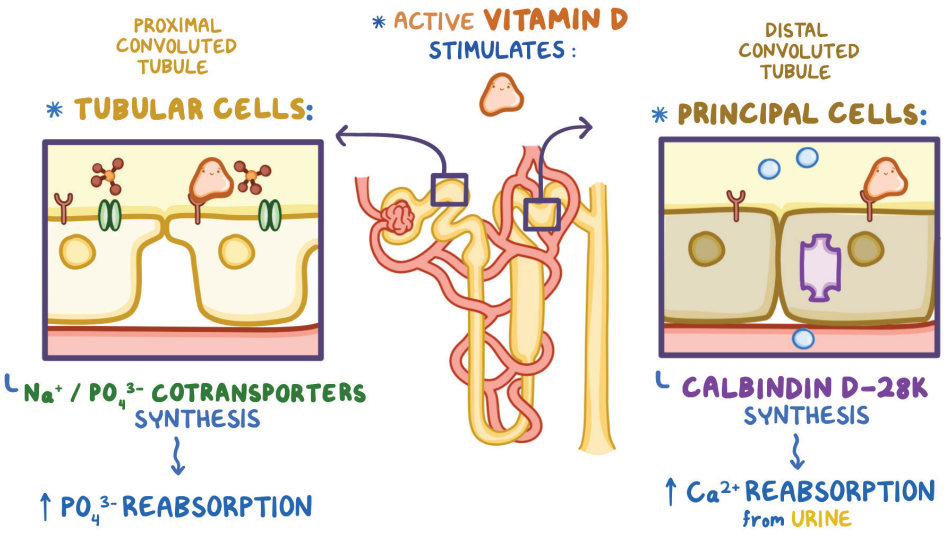

Figure 35.10 Vitamin D stimulates calcium and phosphate reabsorption in kidneys.

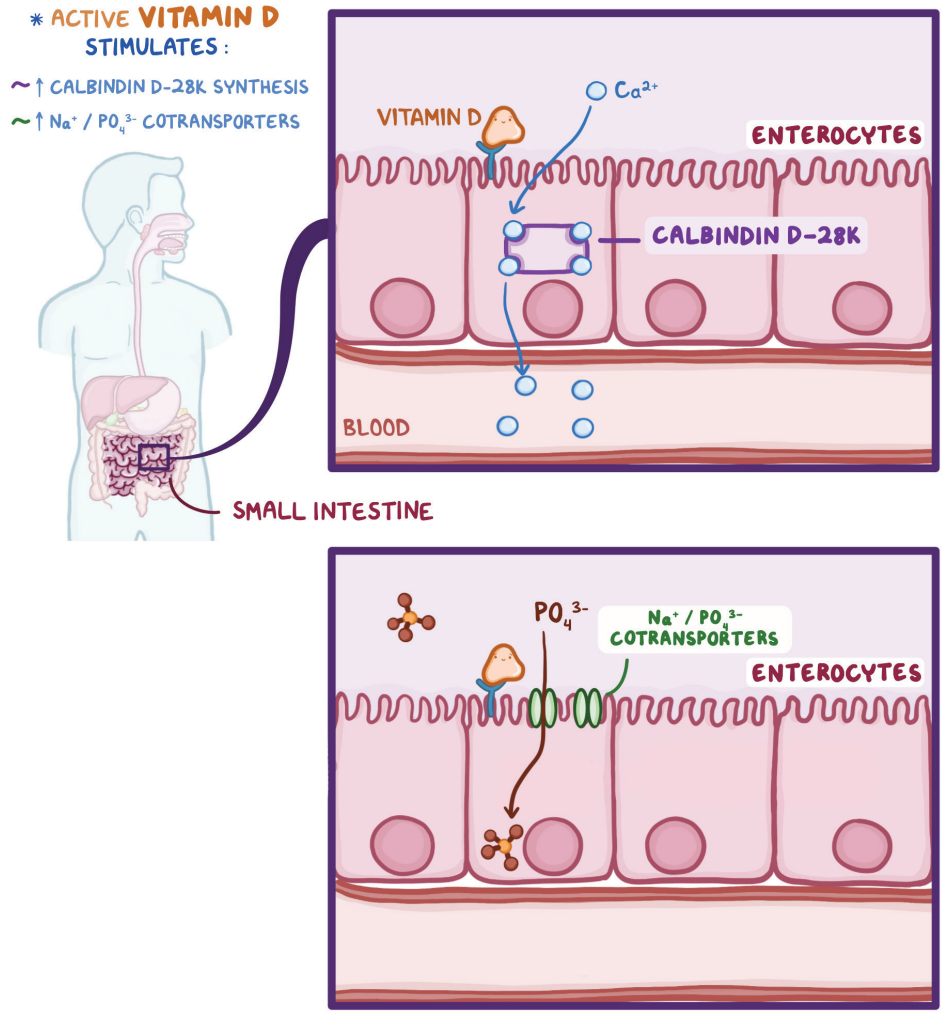

Figure 35.11 Vitamin D stimulates calcium and phosphate absorption in the small intestine by increasing synthesis of calbindin D-28K and sodium/phosphate cotransporters.