Calcium and Phosphorus Homeostatis

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Physiological Importance of Calcium

- the most abundant mineral in the body
- provide structural integrity of the skeleton
- Ca2+ ions in extracellular and cellular fluids are essential to normal function
  - Neuoromuscular excitability and signal transduction
  - Blood coagulation
  - Hormonal secretion
  - Enzymatic regulation
  - Neuron excitation

Calcium Homeostasis

- The amount of Ca^{2+} is balanced among:
  - Intake
  - Storage
  - Excretion
- Controlled by :
  - Intestine
  - Bone
  - Kidneys

Intake of Calcium

- 1000 mg of Ca is ingested per day
  - 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 bones (about 1000 grams)
  - Some calcium is stored within cells.
- There is constant exchange of calcium between bone and blood.

Bone Deposition and Resorption

- Bone is produced by osteoblast cells which produce collagen, which is then mineralized by calcium and phosphate (hydroxyapatite)

- Bone is remineralized (broken down) by osteoclasts, which secrete acid, causing the release of calcium and phosphate into the bloodstream

Excretion of Calcium

- The major site of Ca excretion is the kidneys

- The rate of Ca is regulated
  - Paratyhtoid hormone and calcitonin

Calcium Homeostasis

- Ca concentration is maintained within a very narrow range both extracellularly and intracellularly
- Intracellular Ca^{2+}
  - in cytoplasm approximately $1/1000^{th}$ of extracellular concentration
  - stored in mitochondria and ER
  - “pump-leak” transport systems control $[Ca^{2+}]$
    - Calcium leaks into cytosolic compartment and is actively pumped into storage sites in organelles to shift it away from cytosolic pools

Plasma Calcium

- Plasma calcium totals 2.4 mM (9.4 mg/dl)
  - Ionized calcium is 1.2 mM (50% of total calcium), it is the physiologically active form.
  - 41% protein-bound, 9% complexed to anions

Calcium Homeostasis

Extracellular Ca^{2+}

- When extracellular calcium falls below normal, the nervous system becomes progressively more excitable because of increase permeability of neuronal membranes to sodium.
  - Hyperexcitability causes tetanic contractions

- Binding of calcium to albumin is pH dependent.
  - Acute alkalosis increases calcium binding to protein and decreases ionized calcium
  - Only free, ionized Ca2+ is biologically active

Phosphate

- P is an essential mineral necessary for ATP, cAMP 2nd messenger systems, and other roles.

- Ca is tightly regulated with P in the body

- 85 % of the body's phosphate is stored in bones
- 14-15 % is in the cells
- Less than 1% is in the extracellular fluid

Hormonal Control of Ca

- **Vitamin D3**
  - Diet and sun
- **Parathyroid hormone**
  - Parathyroid gland
- **Calcitonin**
  - Thyroid gland

Vitamin D_3

- Vitamin D is a prohormone that must undergo two successive hydroxylation reactions to become the active form known as **1,25-dihydroxyvitamin D** or **calcitriol**
- Formed in the skin from (7-dehydrocholesterol) by Ultraviolet B light
- Stored in the liver
- Converted in the liver to 25-Hydroxycholecalciferol
- Feedback control limits concentration
- Converted to the active form in the kidney: (parathyroid hormone (PTH) stimulates 1α hydroxylase which makes 1,25-Dihydroxycholecalciferol (calcitriol)
  - Under the feedback control of (PTH)

Effects of Active Form of Vitamin D3

- Promotes intestinal absorption of calcium and phosphates
- Causes synthesis of calcium-binding protein and related facilitated transport
- Has slight effect to increase calcium re-absorption in kidneys
- Works with PTH to cause calcium absorption from bone

Vitamin D Actions

- Intestine
  - ↑ Ca^{2+} absorption
  - ↑ phosphate absorption
- Bone
  - ↑ mineralization
  - ↑ bone resorption
- Kidney
  - ↑ Ca^{2+} reabsorption (weak effect)
  - ↑ phosphate reabsorption (weak effect)

Parathyroid Hormone

- Secreted by Chief (principal) cells of the parathyroid glands
  - Rapid response to reduced calcium (minutes)
- Polypeptide
  - 84 amino acid
  - 9,500 daltons M.W.
- Operates in tissues via GPCRs, cAMP second messenger
- The primary targets of PTH are bone and the kidneys.

Parathyroid Hormone

- Increases Calcium and Phosphate Absorption from the Bone
  - osteocytes stimulated (minutes to hours) to transport calcium – calcium pumps
  - osteoclasts activated and new osteoclasts formed (days to weeks) to digest bone and release calcium and phosphate.
    - Stimulated indirectly by osteoblasts: osteoblasts express RANKL which binds to RANK on osteoclasts leading to its activation.

Parathyroid Hormone

- Decreases excretion of calcium by kidneys
  - Important to prevent bone deterioration
- Increases phosphate excretion by the kidney
- Increases calcium absorption by the intestines
  - Effect manifested via Vitamin D3
    - Produces most active form of Vitamin D3 in the kidney (1,25-dihydroxy-cholecalciferol)
- Increases phosphate absorption

Calcitonin

- A peptide hormone (32 amino acids)
- produced by the C cells of the thyroid gland

- Attenuates absorptive ability of osteoclasts
- Inhibits formation of new osteoclasts
  - Effect to decrease calcium is transitory
  - Causes reduced bone turnover
- Has weak effect in kidney and intestines

- Probably more important during first years of development