Mathematical Modeling of Blood Ionized Calcium Concentration

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The blood ionized calcium concentration (Ca^{2+}, iCa) is tightly regulated in animals ranging from the most primitive fishes and nonvertebrates to humans. This is because iCa is utilized by diverse cell types as a transcellular and intracellular signaling molecule, such as in the nervous system, cardiac and skeletal muscle, epithelial cells, endocrine cells, blood cells, among others. The blood ionized calcium concentration is approximately 1.5 mM in all animals. If the concentration changes by as little as 10-20% dysregulation of body systems (such as the neuromuscular system) will result and can be fatal. Therefore, there are multiple, redundant regulatory systems that exist to maintain blood calcium in a narrow biological range.

Terrestrial animals live in a calcium poor environment and are dependent upon calcium absorption from the gastrointestinal tract to provide calcium as a regulatory ion and component of bones. In contrast, sea animals live in a calcium rich environment (since seawater has 10 mM calcium) and excretion of calcium is important.

Blood calcium exists in three forms:

- 50% Free ionized calcium (biologically active form)
- 40% Bound to serum proteins
- 10% Bound to serum anions (such as citrate)

Organs that are responsible for the systemic regulation of blood iCa:

- Parathyroid gland (produces parathyroid hormone, PTH)
- C-cells of the thyroid gland (produces calcitonin)
- Kidney (excretion and reabsorption of Ca)
- Gastrointestinal tract (absorption of Ca)
- Bones (accretion and release of Ca)

Calcium-sensing membrane receptor (CaR):

The cells of organs that regulate blood iCa have unique G-protein-linked cell membrane receptors for the calcium ion. This is the only known biological receptor for an ion, which enables the regulator cells to monitor blood iCa concentrations and respond appropriately. The levels and activity and CaR can be altered by drugs, disease, or different physiological states.

Parathyroid gland:

The parathyroid gland secretes the hormone, parathyroid hormone or PTH, which is important in the minute-to-minute regulation of blood iCa. PTH has a sigmoidal response curve to blood iCa that enables it to respond rapidly to a decrease in blood iCa. If blood iCa increases its production is suppressed.
PTH has the following actions:

- Increases release of Ca from bones rapidly from a labile pool of Ca and chronically by stimulating osteoclastic bone resorption.

- Increases Ca absorption from the gastrointestinal (GI) tract via calcitriol (active form of vitamin D synthesized by the kidneys).
- Increases Ca reabsorption by the kidney tubules.
- Increases calcitriol production in the kidneys.

PTH is suppressed by calcitriol (negative feedback loop)

C-cells of the Thyroid gland:

The C-cells of the thyroid gland produce calcitonin. Calcitonin is an emergency hormone that is secreted when blood iCa increases, such as after eating a high calcium meal.

Calcitonin has the following (temporary) actions:

- Inhibits loss of calcium from bone
- Reduces calcium reabsorption from the kidneys

Kidneys and Blood iCa Regulation:

The kidneys are important for regulation of blood iCa. They respond to parathyroid hormone and calcitonin and produce the active form of vitamin D, calcitriol. Kidneys can preserve or excrete iCa. In general, the kidneys preserve about 98% of the filtered iCa. This enables them to excrete large quantities if necessary. The renal tubule cells also have the calcium receptor (CaR) that enables them to directly respond to changes in blood iCa independent of hormonal regulation by PTH and calcitonin.

Calcitriol, the active form of Vitamin D:

Calcitriol is produced by the kidneys from precursor molecules and is controlled by PTH. Calcitriol regulates the absorption of iCa from the GI tract and renal excretion of Ca. Absorption of dietary Ca ranges from 20-70% depending on the amount of calcitriol.

Gastrointestinal Tract:

The intestines are responsible for absorption of Ca from the diet. Some Ca is absorbed in an unregulated manner. However, most Ca is absorbed under the control of calcitriol.

Bones:

The bones of the body represent a massive store of Ca. In addition, during growth and late pregnancy, there is a tremendous demand for Ca in the diet for the growing bones of the fetus or neonate. Bones have a small, relatively mobile pool of Ca (available in minutes). The abundance of Ca in the bones can be released by the process of osteoclastic bone resorption (available in days). This is controlled by PTH and calcitonin. Excessive bone resorption leads to weak bones (osteoporosis), such as occurs in older people and astronauts.

Disease:

There are many diseases that can disrupt calcium balance in the body or blood iCa. These include metabolic disorders, kidney disease, bone disease, and cancer.

Cancer can induce hypercalcemia (increased blood iCa) by stimulating bone resorption by endocrine mechanisms or bone metastases.

Comparative Calcium Regulation:

Calcium regulation is important for biological processes in diverse animals. This includes moulting of exoskeletons in crustaceans, egg laying in birds and reptiles, differentiation of epithelial cells, and bone development. Fish have specialized glands and hormones for calcium regulation, such as the Corpuscles of Stannius that produce stanniocalcin. In addition, the gills of fish play an important role in Ca absorption.

Mathematical Modeling:

Mathematical modeling of blood iCa would be a useful tool to model potential effects of different diseases, drugs, or environmental chemicals on the adaptive and counterregulatory mechanisms involved in calcium balance at the organismal level. There is an abundance of empirical data in the literature on regulation of blood calcium in normal or diseased animals and humans.