Biochemistry of Calcium

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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
Calcium turnover

- Calcium intake: 350 mg/day
- Absorption: 350 mg/day
- Secretion: 250 mg/day
- Filtration: 9980 mg/day
- Reabsorption: 9880 mg/day
- Urine: 100 mg/day
- Feces: 900 mg/day
- Bone: 1,000,000 mg
- Extracellular fluid: 1300 mg
- Cells: 13,000 mg
- Deposition: 500 mg/day
- Absorption: 500 mg/day
Hormone regulation of calcium metabolism

**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

**Vitamin D**

**Calcitonin**

*Organ-target - bones*

*Function - decrease of Ca concentration in plasma*
Calcium Metabolism

- Dr. Chintan
Calcium as Hormonal Messenger
Normally, cytosolic calcium $[\text{Ca}^{2+}]$ ions is kept very low ($10^{-7}$ M) by the action of $\text{Ca}^{2+}$ pumps in the ER, mitochondria and plasma membrane.

Hormonal, neural, or other stimuli cause either an influx of $\text{Ca}^{2+}$ into the cell through specific $\text{Ca}^{2+}$ channels in the plasma membrane or the release of sequestered $\text{Ca}^{2+}$ from the ER or mitochondria, in either case raising the cytosolic $[\text{Ca}^{2+}]$ and triggering a cellular response.

This phenomenon is called Calcium ion flux.
Calcium ions are also important intracellular messengers.

In fact, calcium ions are probably the most widely used intracellular messengers.

Calcium (Ca\(^{2+}\)) plays an essential role in the physiology and biochemistry of organisms and the cell.

It plays role in common signalling mechanism because once it enters the cytoplasm it exerts allosteric regulatory affects on many enzymes and proteins.
Calcium is a second messenger produced by indirect signal transduction pathways such as G-protein coupled receptors.

Calcium ions (Ca\(^{2+}\)) impact nearly every aspect of cellular life. The principles of Ca\(^{2+}\) signaling, from changes in protein conformations driven by Ca\(^{2+}\) to the mechanisms that control Ca\(^{2+}\) levels in the cytoplasm and organelles.

The highly localized nature of Ca\(^{2+}\) -mediated signal transduction and its specific roles in excitability, exocytosis, motility, apoptosis, and transcription.
Calcium as second messenger
Calcium as second messenger

Calcium ions—once they enter the cytoplasm exert allastERIC regulatory effects on many enzymes and proteins.

Calcium acts as a second messenger by indirect signal transduction pathways such as via G protein-coupled receptors.
Calcium-Calmodulin as 2nd Messenger

1. Hormone (first messenger) binds to receptor, causing calcium channel to open.
2. Calcium (Ca++) enters the cell, activating calmodulin.
3. Calmodulin-calcium complex activates or inactivates enzymes.
4. Substrate is converted to product.

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Calcium as a 2nd Messenger

- Calmodulin
- $\text{Ca}^{2+}$/Calmodulin
- $\text{Ca}^{2+}$/Calmodulin-dependent protein kinase
Calcium-Calmodulin Second Messenger System

This second messenger system operates in response to the entry of calcium into the cells.

Normally, the level of calcium in the cell is very low (~100 nM). There are two main depots of Ca^{2+} for the cell:

- The extracellular fluid (ECF — made from blood), where the concentration is ~ 2 mM or 20,000 times higher than in the cytosol;
- the endoplasmic reticulum ("sarcoplasmic" reticulum in skeletal muscle).
In response to many different signals, a rise in the concentration of Ca$^{2+}$ in the cytosol triggers many types of events such as

- muscle contraction;
- exocytosis, e.g.,
  - release of neurotransmitters at synapses.
  - secretion of hormones like insulin
- activation of T cells and B cells when they bind antigen with their antigen receptors (TCRs and BCRs respectively)
- adhesion of cells to the extracellular matrix (ECM)
- apoptosis
- a variety of biochemical changes mediated by Protein Kinase C (PKC).
However, its level in the cell can rise dramatically when:

- channels in the plasma membrane open to allow it in from the extracellular fluid or
- from depots within the cell such as the endoplasmic reticulum and mitochondria.
Role of Calcium in muscle contraction
Biochemical events that occur during one cycle of muscle contraction & list the determinants that lead to relaxation

Muscle contraction subject to fine regulation via the nervous system
(1) Discharge of motor neuron
(2) Release of transmitter (acetylcholine) at motor endplate then binding receptors
(3) Increased Na+ and K+ conductance in endplate membrane
Steps in Muscle Contraction (Resting sarcomere)

Step 1:
Head of myosin hydrolyzes ATP to ADP and Pi to result ADP-Pi- myosin complex (high-energy conformation.)

Step 2: (in response to nerve/Ca\(^{2+}\) stimulation)

Ca\(^{+}\) binds to troponin exposing active site on actin forming actinomycin complex

Then binding to ADP-Pi- myosin complex

Step 3:

Promotes the release of Pi, which initiates the power stroke (conformational change in myosin heads), then release of ADP

Pulling of crossbridge actin towards center of sarcomere (shortening)
Step 4:

Myosin head binds another ATP

Forming an actin-myosin-ATP complex.

Step 5: (key component of relaxation)

Myosin-ATP has a low affinity for actin, and actin is thus released.

In step 4: If intracellular levels of ATP drop (eg, after death),

ATP does not bind myosin head (step 4 above), and
actin does not dissociate, and relaxation (step 5) does not occur.
Steps in relaxation

Step 1: Ca\textsuperscript{2+} pumped back into sarcoplasmic reticulum by Ca\textsuperscript{2+} ATPase

Step 2: Release of Ca\textsuperscript{2+} from troponinC

Step 3: Troponin, via interaction with tropomyosin, inhibits further myosin head and F-actin interaction.

Step 4: Presence of ATP, myosin head lead to release of F-actin.

Step 5: The end of interaction between actin and myosin
The role of calcium ions in muscle contraction & relaxation

During contraction

1) Sarcolemma depolarization: Spreads to internal T tubule system
2) Ca2+ is released from the SR and from the extracellular space
3) Ca2+ interacts with calmodulin (Tpc) and myosin light chain kinase to activate myosin (uncovering of myosin binding sites).
4) Activated calmodulin activates the Myosin/ATPase (kinase)
5) Activated kinase transfers phosphate from ATP to myosin cross bridges
6) Phosphorylated cross bridges interact with actin to produce shortening (contraction)
During relaxation:

1) Sarcoplasmic Ca ++ reduced and pumped into the SR by ATP-driven Ca ++ pump

2) Troponin and tropomyosin, inhibits myosin head and F-actin interaction (covering of myosin binding sites), and in the presence of ATP the myosin head detaches from the F-actin.
Role of Calcium in Neurotransmission
Role Of Ca In Release Of Neurotransmitter

FIGURE 2.30 Release of Neurotransmitter
ROLE OF CALCIUM

• Your nerves rely on calcium to properly regulate the release of neurotransmitters.
• When a nerve cell becomes activated, it transmits an electrical pulse that moves down the length of the cell toward the synapse.
• This electrical signal triggers the flow of calcium into the nerve cell close to the synapse.
• This influx of calcium promotes the fusion of neurotransmitter vesicles to the cell membrane, triggering neurotransmitter release.
How Can Low Calcium Levels Affect the Release of Neurotransmitters?

- Neurotransmitters -- signalling molecules produced in your nervous system -- allow for communication between nerve cells, facilitating brain functioning, nerve signalling to muscle tissue and a number of other neurological processes.

- Calcium from your diet plays an important role in neurotransmitter signalling, with low calcium potentially inhibiting neurotransmitter release.