



## Review Article

### **INTRACELLULAR CALCIUM OSCILLATIONS IN EXCITABLE AND NONEXCITABLE CELLS: A REVIEW**

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Article Received on: 26/06/18 Approved for publication: 29/07/18

**DOI: 10.7897/2230-8407.097123**

#### **ABSTRACT**

Calcium level in a cell controls different activities of a cell. The role of free calcium ion in the cytosol of excitable and non-excitable cells is different. Excitable cells like a neuron, muscle cell, and astrocyte control different physiological activities including neurotransmitter, glia transmitter release, apoptosis and necrosis etc while in non-excitable cell calcium causes the release of important chemicals like histamine. In excitable cells, secretory functions are regulated by direct entry of calcium into the cytoplasm while in non-excitable cells release of calcium from intracellular storage that may modulate the second messenger and the secretion is via second messenger system. Molecular study on calcium oscillation pattern in the different living cell indicates frequency and amplitude characteristics. Intracellular communication between neighbouring cells also takes place through calcium. In brain and other nervous tissue, cellular communication between neuron and astrocyte take place through calcium oscillation signal.

**Keywords:** Calcium oscillation, excitable cell, non-excitable cell.

#### **INTRODUCTION**

Calcium is a regulating factor of different activities of the cell. Periodic protein kinase c activation is required for initiation of calcium oscillations<sup>1</sup>. Intracellular calcium is found in attached and free form. Free cytosolic calcium regulates different cellular functions including contraction, neurotransmitter, hormone release, metabolism, cell division, and differentiation. Changes in cytosolic calcium level alteration are observed in the cell under different stress<sup>2</sup>. Calcium ions are present inside the cell either free or binding with proteins. In the different compartment of a cell, calcium ions are stored, and upon stimulation the calcium ions are released to the cytoplasm. Most of the calcium ions inside the cells are present in the endoplasmic reticulum and mitochondria. Inside the endoplasmic reticulum, calcium ions are distributed heterogeneously due to unequal distribution of calcium binding protein<sup>3</sup>. Calcium is a divalent ion and can bind with different proteins. Calcium in free form is dangerous for a living cell and so chelating of calcium ion is very important. Chelation of calcium ions is performed by proteins present in the cytoplasm, mitochondria, and endoplasmic reticulum. Most of the cellular energies are utilized by the cell to lower the calcium level in cytosol<sup>3</sup>. The present analysis is focusing on the calcium oscillation pattern in different excitable and non-excitable cells and their importance in controlling different cellular functions.

#### **Baseline intracellular calcium and calcium oscillation**

Calcium oscillations following application of different toxic chemicals shows the elevation shortly and returns to baseline level and remains for prolonging. However, all the neurons do not respond excite-toxic effect but in case of responding cell the

calcium level elevated and return to normal level does not mean the cell will survive. The cell may struggle to maintain calcium homeostatic equilibrium and reported that cells are vulnerable for second time excitotoxic exposure<sup>4</sup>. Earlier work on calcium oscillation and baseline calcium study reports that after first exposure of toxic agents most of the responding neurons show higher basal calcium level and these cells will not respond for second time toxic insult. It is also believed that the non-responder neurons may be a very fast responder and calcium level returns to basal calcium level before measurement of calcium signal.

#### **Feedback control of intracellular calcium level**

Living cells have the capacities to control the calcium level and overload of intracellular calcium is regulated by negative feedback mechanism where calcium entry is blocked by calcium channel<sup>5</sup>. Interestingly it is observed that protein kinase c causes the elevation of intracellular calcium level in molluscan neuron while the same enzyme reduces the calcium level in dorsal root ganglion neuron in chick<sup>6</sup>.

#### **In hypoxic condition**

In hypoxia, there is an elevation of intracellular calcium level. In hypoxia, due to a lower level of oxygen, the cell initiates the glycolysis for production of ATP. For glycolysis, required glucose molecules are transported through sodium glucose co-transporter that activates the sodium-calcium exchanger finally calcium influx<sup>7</sup>. Depletion of oxygen level and increase in the intracellular calcium in the cell causes the synthesis of some intracellular intermediates that may cause the cellular inflammation.

## **COMPARISON BETWEEN CALCIUM OSCILLATION WAVES WITH A PHYSICAL WAVE**

### **The Calcium oscillations follow the characteristics of the physical wave**

Changes of free calcium ions in the cytoplasm occur continuously and these oscillations can be considered as a waveform. These calcium waves follow some of the characteristics of a physical wave characteristic like wavelength, frequency, phase shift and amplitude. The wave follows the energy equation of physical wave <sup>8</sup>.

### **Calcium oscillations can be analyzed with mathematical equations**

Mathematics is a tool for analysis of different scientific records. Calcium oscillations can be analyzed with fractional calculus and linear equations. Different mathematical models are proposed by the different workers to analyze calcium oscillations in excitable and non-excitable cells <sup>8</sup>.

Previously it was observed that depolarization evokes strong calcium rises in the axonal varicosities but not in the somatodendritic compartment in neurons <sup>9</sup>.

## **THE BIOLOGICAL IMPORTANCE OF INTRACELLULAR CALCIUM OSCILLATIONS**

### **Intracellular calcium oscillation regulates genetic function**

Gene transcription and translation in neurons are regulated by the influx of intracellular calcium <sup>10</sup>. Although calcium associated gene expression depends upon the calcium entry however the calcium influx through different route is not equivalent. Transcription of a brain-derived neurotrophic factor is strongly induced by calcium influx through L VSCCs on the other hand weekly stimulated by NMDA receptors <sup>11</sup>.

### **Mitochondrial membrane potential alteration can induce elevation of intracellular calcium level**

Decrease in mitochondrial membrane potential causes release of calcium ion from mitochondria via mitochondrial sodium-calcium exchanger

### **Calcium oscillation inside the cell is directly proportional to the Endoplasmic reticulum**

The amount of  $Ca^{2+}$  in the ER is directly related to the  $Ca^{2+}$  load, and one model predicts that  $Ca^{2+}$  oscillations will also be highly sensitive to ER  $Ca^{2+}$  concentration <sup>12</sup>.

### **Intracellular calcium oscillations regulate electrical activity of a neuron**

Earlier it has been reported that the intracellular calcium signal indicates the electrical activities neuronal signalling in neurons <sup>13, 14</sup>.

### **Calcium dynamics in Cell**

Study on calcium dynamics in a living cell under different stimulants have shown that the calcium level returns to the baseline level within a short period<sup>15</sup>. Static measurement of intracellular calcium is although helpful to study the condition of the cell but it will not indicate the proper physiological status of the cell so, calcium dynamics in the intracellular level is most

important to predict the status of the cell with calcium homeostasis mechanism.

The velocity of a calcium wave is measured 0.1 to 1 micrometer per second at slow state while at fast wave velocities goes up to 10 to 50 micrometer per second <sup>16</sup>.

### **Calcium oscillation may be monophasic or biphasic**

Researcher observed that calcium oscillation in some cells showed biphasically. The initial peak is the longer duration and is followed by a short duration second peak. The biphasic calcium transient of a non-excitable cell is maintained by internal storage and influx from extracellular media. The rate of calcium decay was shown to relate to the rate of calcium cycling across the plasma membrane. Calcium cycling across the plasma membrane and calcium decay depend upon the cell excitation and elevated level of cytoplasmic calcium <sup>17</sup>. Biphasic calcium oscillation peaks are also observed in cells stimulated by histamine. The initial peak is followed by a small peak of calcium oscillation in non-excitable cells treated with histamine.

## **BASELINE FLUORESCENCE INTENSITY IN CULTURED NEURON**

Calcium oscillation in a cell follows some basic nature. Intracellular calcium oscillation is not influenced by extracellular calcium influx <sup>18</sup>. It is observed that there is no intracellular calcium alteration after blocking voltage-gated calcium channel.

### **Physical factors can alter calcium oscillation**

The magnetic field can influence the elevation of intracellular calcium transient in non-excitable cells <sup>19</sup>. Calcium efflux from the cultured cells is observed when the cells are exposed to high-frequency radiation. In stem cell research calcium oscillation modulation is applied to differentiation of human mesenchymal stem cell to divide and differentiate to osteoblast cell <sup>20, 21</sup>.

### **Nano-particles can change the intracellular calcium level**

Different nano-particles can change the intracellular calcium level through activation of intracellular machinery. In cancer therapy, nano-particles are used to kill the malignant cells <sup>22</sup>. Mitochondrial calcium leakage and mitochondrial polarization are the causes of cellular death caused by nano-particles in neurons <sup>23</sup>. One of the mechanisms of the killing of the cancerous cell by nano-particle is through elevation of intracellular calcium level. One study reported that after 48 hours of nano-particle treatment, cytosolic calcium level increases 1.8 times in adenocarcinoma cells <sup>24</sup>.

### **Calcium oscillations in Astrocytes**

Calcium oscillations in astrocyte is a very complex mechanism and neuron astrocyte communication is regulated by calcium oscillation pattern <sup>25</sup>.

### **Calcium oscillations in other non-excitable Cells**

Calcium oscillations are also studied in hepatocytes and other non-excitable cells. In hepatocytes, calcium oscillations occur in a synchronized way and distributed among all the hepatocytes of a liver. The junctional complex is also important for synchronized calcium wave distribution. But in absence of junctional complex, the individual cell shows different calcium oscillations and synchronization is lost <sup>26</sup>. Calcium oscillations in hepatocytes are mainly induced by hormones. Different calcium sensor

molecules are present in the cell that regulates the intracellular calcium oscillations and calcium storage in the endoplasmic reticulum. Scientists have reported that stromal interacting molecule 1 is a calcium sensor that regulates calcium storage in the endoplasmic reticulum of hepatocytes<sup>27</sup>. Recent work on the importance of intracellular calcium on the regeneration of hepatocytes indicates that cytosolic calcium is a major regulator of regeneration of liver cell. Besides, nuclear calcium and mitochondrial calcium play a critical role in hepatocyte regeneration and cell cycle.<sup>28</sup>

Different stimulus able to generate calcium oscillations in astrocyte and activates calcium oscillations in neighbouring astrocyte via gap junctions<sup>29</sup>. In neurons, calcium oscillation is triggered by neighbouring astrocytes. The signal passes from astrocytes to neurons through gap junction communications<sup>30</sup> or calcium-dependent release<sup>31</sup>.

Calcium oscillations in excitable and non-excitable cells show the different pattern. In excitable cells the calcium oscillation pattern is nonlinear. In some cells, calcium oscillation regulates some cytoplasmic domain only while in some other cases calcium oscillations propagate to neighbouring cell<sup>32</sup>.

One type of calcium oscillation, baseline spiking, in which there is a discrepancy in calcium spikes with frequency but not amplitude. Calcium oscillation frequency is closely associated with the energy utilization.

#### **Calcium oscillation and calcium decay**

Exponential calcium decay is very important for the survival of a cell because prolong intracellular calcium at higher level leads initiation of death signal. It is observed that calcium oscillation depends upon the energy level of a cell. The healthy living cell can maintain a proper intracellular calcium level and after elevation can bring to sustain level using ATP. Glucose derived cell unable to maintain the calcium level due to lower ATP production. Different channel proteins are responsible for calcium transport requires ATP and maintain calcium at level baseline calcium. Calcium decay in a cell depends upon the sodium level of the extracellular media. Sodium-calcium exchanger system has an influence on cytosolic calcium decay process. Increase in calcium level in the active zone of a neuron clearly indicates the association between calcium level and secretion. After exocytosis calcium decay starts in the active zone area<sup>33</sup>.

#### **Neuron and Astrocyte communicate with each other through calcium signal**

Both excitable and non-excitable cells communicate with each other through calcium oscillations. The calcium spike which is generated in one cell transmits to another cell through gap junction. Stimulation of neural through glutamate receptor causes elevation of intracellular calcium in neuron and long lasting oscillation in Astrocytes in neuron and astrocyte co-culture. Intracellular calcium oscillation in astrocyte closely associates with the neuronal function. Stimulation of afferent point of a neuron activates the elevation of calcium level in the cytoplasm and releases glutamate that can activate the release of calcium level in astrocytes. The calcium oscillation pattern is not unidirectional, rather it is a bidirectional communication between astrocytes and neuron<sup>34</sup>.

#### **Cytoplasmic free energy and calcium oscillations**

Cytosolic calcium level has a close association with free energy. Decreasing free energy in a cell cytoplasm there is also a decrease in sodium level in the cytoplasm while the calcium level elevated and calcium peak is found after 30 seconds. It is also observed that decrease in extracellular sodium level and increase in intracellular potassium level following depolarization causes increase in intracellular calcium level. There is an acceleration of intracellular calcium decay in an exponential way was observed after restitution of extracellular sodium<sup>35</sup>.

#### **Extracellular chemicals and ions are the regulator of Intracellular calcium oscillation**

Synchronized intracellular calcium oscillations in a cell also observed under oscillation of extracellular insulin<sup>36</sup>. Excitable cells have the sodium leakage channels that cause the changes in intracellular ionic concentration including calcium oscillations<sup>37</sup>. Calcium enters into the cell after repetitive stimuli and calcium oscillates inside the cells and leads pathophysiological effect.

Intracellular calcium oscillation and communication between neighbouring cells are studied and observed a different pattern of calcium oscillation and extracellular physical factors can modify the calcium oscillation pattern<sup>38</sup>. Non-excitable cell-like mast cell release histamine in presence of immunoglobulin G (IgG). The release of histamine is calcium-dependent. Elevation of free intracellular calcium has a close association with the secretion of histamine. But the calcium elevation within physiological limit is unable to release histamine. Additional stimulatory pathways can trigger the histamine release<sup>39</sup>.

#### **Calcium Oscillation wave follow the wave equation**

Wavelength and frequency are inversely proportional as observed in electromagnetic wave and the same character also observed in calcium wave of a cell. Spatiotemporal characteristics of calcium oscillation wave also show the characteristic of a traveling wave.

Calcium oscillations in adipocytes are studied and reported that adipocyte stimulated by acetylcholine causes the elevation of intracellular calcium in absence of extracellular calcium indicated the possibility of release of calcium from intracellular storage<sup>40</sup>.

#### **CONCLUSION**

Fine tuning of intracellular calcium oscillation is very important for proper functioning of a cell as the most of the intracellular mechanism is regulated by intracellular calcium level of a cell. It is observed that elevation of intracellular calcium is the primary response in excitable and non-excitable cells to initiate a function. Even death signals also are initiated by elevation of intracellular calcium. Intracellular calcium sensor also plays a major role in calcium homeostasis in the cytoplasm. Studies on calcium oscillation pattern in different cells reveal the information that the wave characteristics of calcium oscillation wave follow the same basic wave characteristics of the radio wave. Though different extracellular chemicals can change the calcium oscillations through activation of different receptors high-frequency radiation and magnetic field can change the calcium oscillation pattern. After discussing the different mechanism of calcium oscillations in the excitable and non-excitable cell it is clear that calcium oscillation is dose and time-dependent phenomenon and can be modulated by different receptor blockers and extracellular ionic concentration. So, modulation of calcium oscillation pattern is possible with the help of different mechanisms to treat the cell. Mathematical model can be developed to predict calcium

oscillation patten to apply different therapeutic agents for disease treatment.

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**Cite this article as:**

Manash Barthakur and Jitendra Goswami. Intracellular calcium oscillations in excitable and nonexcitable cells: A review. *Int. Res. J. Pharm.* 2018;9(7):42-46 <http://dx.doi.org/10.7897/2230-8407.097123>

Source of support: Nil, Conflict of interest: None Declared

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