



## Editorial

## Intracellular divalent ion oscillations: Is this the key phenomenon in rhythm generators?

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Segregation of various ions on the either side of the cell membrane is the key factor responsible for the resting membrane potential (RMP). Presence of transmembrane voltage-gated ion channels is the hallmark of excitable tissues which participates in generation of impulses — Action potentials (APs). Self generation of APs (Automaticity) is seen in pace maker cells / pace maker tissue distributed in various parts of the body and act as rhythm generators. These rhythm generators are either local/regional or central. The best examples for local rhythm generators being sino-atrial node (SAN) present in the heart and interstitial cells of Cajal in gastrointestinal tract where as central rhythm generators (also known as central pattern generators or central program generators) are a network of neurons located in central nervous system (CNS) which act as a driving force for the activity of different organs and systems.

The oscillations of the ionic calcium ( $\text{Ca}^{2+}$ ) in the cardiac pacemaker cell's microenvironment is a well established phenomenon which triggers the ionic changes across the cell membrane resulting in pacemaker potentials [1]. Not only the SAN, other parts of the conducting system of the heart including Purkinje fibers and working myocardial cells (atrial and ventricular myocytes) also possess this phenomenon [1,2,3]. Medullary centers which control the respiration have also been demonstrated to have cytosolic  $\text{Ca}^{2+}$  oscillations [4]. In the interstitial cells of Cajal, the trigger for pacemaker activity is due to localized drop in  $\text{Ca}^{2+}$

levels caused by the uptake of calcium by mitochondria [5,6]. Central pattern generators for locomotion are present in different segments of spinal cord and these neurons show NMDA (N-methyl-D-aspartate) receptor associated fluctuations in ionic calcium [7]. The neurons of the circadian rhythm generator — suprachiasmatic nucleus (SCN) — possess widespread AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor-evoked  $\text{Ca}^{2+}$  transients [8].

It is now proven beyond doubt that the oscillations in intracellular ionic calcium ( $\text{Ca}^{2+}$ ), having a valency of two, is playing a pivotal role in rhythm generation in consonance with other membrane and intracellular phenomena. Off late evidence is emerging about the actions of other divalent ions like magnesium ( $\text{Mg}^{2+}$ ) and zinc ( $\text{Zn}^{2+}$ ) in rhythmogenesis.

Intracellular magnesium ( $\text{Mg}^{2+}$ ) oscillations are deemed crucial to cellular circadian timekeeping and energy consumption [9,10]. Intracellular magnesium has been directly associated with pulsatile secretion of hormones like insulin and prolactin [11]. Since  $\text{Mg}^{2+}$  acts as a co-factor for many intracellular enzymes, changes in its concentration effect most of the cellular machinery.

Like  $\text{Mg}^{2+}$ , another divalent ion — zinc ( $\text{Zn}^{2+}$ ) acts as a co-factor for nearly 3000 metalloproteins thereby playing a substantial role in cell regulation [12]. Numerous pathways produce rapid zinc

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transients (Zinc Signals) whose magnitude is about a few nanomolar from the picomolar basal 'free'  $Zn^{2+}$  levels [12].

Physiological consequences of fluctuations in  $Ca^{2+}$ ,  $Mg^{2+}$  and  $Zn^{2+}$  may be independently manifested or may be interconnected as seen in redox reactions and phosphorylation signaling. These changes may be the beginning of pacemaker cell's activity to generate the periodic rhythm.

The technological advances have made the measurement of intracellular calcium much easy and with utmost accuracy which is not the case with the other intracellular ions. This is the reason for availability of considerable literature on the role of intracellular  $Ca^{2+}$  oscillations in pacemaker cells and scanty data on other intracellular divalent ions. The assessment and measurement of intracellular ions apart from calcium needs to be improvised so as to detect minute changes in their concentration during cellular activity.

It may be postulated that the divalent ions play a key role in rhythm initiation. It is now imperative on the part of scientific community to ponder and work on this postulate so that better understanding may emerge regarding the role of divalent ions as a key phenomenon in rhythm initiation.

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