IOSR Journal of Environmental Science, Toxicology and Food Technology (IOSR-JESTFT)
e-ISSN: 2319-2402,p- ISSN: 2319-2399.Volume 9, Issue 10 Ver. II (Oct. 2015), PP 32-38
www.iosrjournals.org

Short review on the role of intracellular calcium in synaptic plasticity

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Abstract: *Calcium (Ca^{2+}) is ubiquitous second messenger in every living organism. Ca^{2+} is inevitable, as the neurone functions in information reception, integration, processing, interpretation and subsequent activation of the peripheral nervous system to produce effect in the target organ. Normal intracellular calcium concentration ($[Ca^{2+}]_i$) ranges between 70 nM -150 nM [1]. The above mentioned functions connote plasticity. Synaptic plasticity is activity dependent alteration in synaptic strength, which mediates memory storage mechanism [2-4]. Donald Hebb (1949) postulated that excitatory synapses that link two cells could be strengthened if both cells were simultaneously activated [5]. This can be divided into long and short term*
plasticity. The long term plasticity is subdivided into long term potentiation (LTP) and depression (LTD). The short term plasticity is also subdivided into short term potentiation (STP) and depression (STD). I took a look at the various forms of synaptic plasticity and later on x-rayed the role of Ca^{2+} in long-term, short-term plasticity and also the influence of neuronal Ca^{2+} stores on calcium dynamic. Ca^{2+} serves as a trigger for neurotransmitter release, sustains long term plasticity, which encodes long term memory and learning. The residual Ca^{2+} mediates short term plasticity which likewise encodes short term memory. Thus calcium is essential in all forms of synaptic plasticity
Key words: *Synaptic plasticity, intracellular calcium, neuronal stores, potentiation and depression*

I. Introduction

Synaptic plasticity is activity dependent alteration in synaptic strength, which mediates memory storage mechanism [2-4]. Donald Hebb (1949) postulated that excitatory synapses that link two cells could be strengthened if both cells were simultaneously activated. This can be divided into long and short term plasticity. The long term plasticity is subdivided into long term potentiation (LTP) and depression (LTD) while short term plasticity is also subdivided into short term potentiation (STP) and depression (STD).

Numerous forms of short- and long-term plasticity have been described within the

hippocampus with perhaps the most well known of these occurring at synapses formed by mossy fibres within the CA3 region [6-10], and between Schaffer collateral-associational commissural fibres and CA1 pyramidal cells in the CA1 region [11-13]. These authors reported an increase in Ca^{2+} amplitude following tetanic stimulation using electrophysiology and optical imaging [11-13]. The hippocampus has become a very widely studied region of the brain as it has a now well established role in the acquisition of memory, in particular spatial memory In this review we take a look at the different types of synaptic plasticity and elucidate the role of calcium in synaptic plasticity.

II. Long-term Plasticity

It has been reported that change in synaptic strength for long periods of time (hours to days) connotes long-term plasticity [14], which may be LTP or LTD. Studies showed that LTP, a strengthening of synaptic efficacy (Lomo 1966) fulfils many criteria for a neural correlate of memory (Bliss and Lomo, 1973). LTP was proposed as a mechanism responsible for storage of information (Bliss and Collingridge, 1993) while LTD mediates encoding of new information (Bear and Abraham, 1996; Manahan-Vaughan and Braunewell, 1999; Braunewell and Manahan-Vaughan 2001; Kemp and Manahan-Vaughan 2004).

LTP evoked by high-frequency stimulation, is mediated by two major glutamate receptor subtypes, α-amino-3-hydroxyl-5-methyl-4-isoxazole propionate receptors (AMPA) and N-methyl-d-aspartate receptors (NMDA) in the hippocampus [12, 13, 15] and the cerebellum [14, 16-18]. A study showed that receptor subunit composition and its interaction with cytoplasmic proteins constitute different pathways regulating synaptic plasticity [19]. It has been observed that high frequency stimulation (HFS) of the perforant pathway in anaesthetized rabbits led to a potentiation of synaptic responses which could last for several hours [20]. Many other pathways in the brain including the Schaffer collaterals in the hippocampus were also shown to express similar phenomena following HFS [21]. It is generally accepted that induction of LTP at CA1

synapses requires Ca^{2+} entry into the postsynaptic dendritic spine via the activation of the NMDA receptor [19, 22], however
increased Ca^{2+} concentration through NMDA-independent mechanisms may also lead to LTP in the cerebellum [16] and part of the hippocampus (Mossy fibres and CA3) [23-25]. The most recent mechanisms proposed to explain LTP at hippocampal synapses include; an incorporation of new AMPA receptors into the membrane [26, 27], activation of previously silent synapses [28], and HFS induced splitting of dendritic spines allowing a synaptic response to be amplified [29]. Although some studies demonstrated a strong correlation between a deficit in LTP and poor spatial memory [30, 31]), several reports described normal spatial orientation in spite of impaired LTP [32, 33]. These briefly unresolved arguments demonstrate some of the difficulties in accepting LTP as the molecular mechanism of memory formation.

III. Short-term plasticity

This is a change in synaptic strength that last from a few milliseconds to a few minutes [4, 34-36]. It may be short- term potentiation (STP) and depression (STD). Forms of synaptic enhancement such as facilitation, augmentation and post-tetanic potentiation (PTP) are usually attributed to effects of a residual elevation in pre-synaptic $[Ca^{2+}]_i$ acting on one of the molecular targets that appears to be distinct from the secretory trigger responsible for fast/phasic exocytosis [4, 37, 38]. Depression is usually attributed to depletion of some readily releasable pools of vesicles. It can also occur from feed-back activation of pre-synaptic receptors and from postsynaptic processes such as receptor desensitization [14, 17, 18, 39, 40]. Both STP and STD are well studied using pair pulse stimulation and are time dependent.

Zucker (1989) runs through a history of hypotheses that may account for synaptic short-term facilitation. Initially, increased spike (action potential) invasion of the synaptic terminal was thought to be a contributory factor. Spike broadening is another possibility due to inactivation of potassium currents. A broader spike suggests increasing calcium influx to successive stimuli although in some models, spike broadening is not accompanied by an increase in presynaptic calcium [41]. The most widely accepted hypothesis at the moment is the residual calcium hypothesis first proposed by Katz and Miledi (1968). In this model, facilitation arises from the non-linear dependence of transmitter release on intracellular calcium such that after a presynaptic action potential, a residual amount of calcium will persist within the

presynaptic terminal and this will enhance release triggered by subsequent stimuli whilst the residual calcium remains above baseline levels [2]. This is described in much more detail by Zucker and Regehr (2002) and a more up to date description can be found in a review by Kochubey et al (2011) but focusing on the Calyx of Held [42]. A relatively small increase in calcium can lead to a significant increase in transmitter release because of this. It is now thought that more than one presynaptic protein is calcium sensitive and so proteins other than synaptotagmin may influence release [37, 42].

The link between short-term plasticity and release probability is quite clear with low release probability synapses usually undergoing potentiation while high probability synapses undergoes depression. This is linked to the fact that high release probability synapses tend to release a significant proportion of vesicles within the readily releasable pool when stimulated leaving fewer vesicles available with subsequent stimuli. Not all synapses undergo paired pulse facilitation. Many synapses undergo paired pulse depression. Examples of synapses that do this include cerebellar climbing fibres. A paper that is one of the first to show the link between facilitatory and depressive behaviour of vesicles is by Xu-Friedman et al (2001) [43].

Role of calcium in synaptic plasticity Ca^{2+} is inevitable, as the neurone functions in information reception, integration, processing, interpretation and subsequent activation of the peripheral nervous system to produce effect in the target organ. Normal intracellular calcium concentration ($[Ca^{2+}]_i$) ranges between 70 nM - 150 nM [1]. I will x-ray the role of calcium in long term, short term plasticity and also the influence on of ER calcium store in synaptic transmission.

Figure 1 Involvement of calcium in pre-synaptic strength and post-synaptic modification during repetitive stimulation (synaptic plasticity)

Role of calcium in long term synaptic plasticity

Long-term plasticity may result from repetitive stimulation above basal frequency which may lead to either long term depression (LTD) or long term potentiation (LTP). Depolarisation of the cell membrane leads to opening of the Ca^{2+} channel and subsequent influx of Ca^{2+}. This influx of Ca^{2+} activates the NMDA and AMPA receptors. Increase in postsynaptic response to glutamate release leads to LTP while decrease in the postsynaptic response encodes LTD (Figure 1). In the cerebellum, the climbing fibre supplies the much-needed input - the high Ca^{2+} as it provides a strong AP but the parallel fibre releases glutamate. It has been shown that injection of Ca^{2+} chelators into the Purkinje cells block LTD in the cerebellum [14, 17, 44], the neo-cortex or the visual cortex [3]. Specifically phosphorylation of the GLUR2 subunit of the AMPA receptors results in less AMPA receptor sensitive to glutamate. Figure 2 gives a schematic description of this Ca^{2+} dependent activity. Bear (2007) indicates that learning occurs when $[Ca^{2+}]_i$ and $[Na^{+}]_i$ coincides with the activation of PKC, while memory occurs when AMPA receptors are internalized and postsynaptic currents are depressed. Thus Ca^{2+} plays a significant role in LTP and LTD, which are implicated in learning and long-term memory.

Figure.2 Schematic diagram of LTD processes in Purkinje cells
Following paired stimulation of the Climbing fibre and the Parallel fibre, subsequent activation of Parallel fibre alone results in less response in the Purkinje cells

Role of calcium in short-term plasticity

Modification of the postsynaptic responses that led to short-term synaptic plasticity are due to activities of the residual Ca^{2+} after repetitive stimulation [4] and influence of the Ca^{2+} channel [35]. Residual calcium may also encode short term-working memory [45]. Mongillo's group suggested that pre-synaptic calcium encodes working memory, since accumulation of the residual Ca^{2+} in the pre-synaptic terminals could store information about the recalled memory in working form; therefore this negates the need for metabolically costly action potentials. They also stated that memories are transformed into spiking activity either as a result of global reactivating input to the network or by virtue of the intrinsic network dynamic which is mediated by attention [45].

Numerous studies have been undertaken on AP and observation of the fast, phasic exocytosis (use of micro electrode and synthetic dyes) but little has been done on the aphasic exocytosis in terms of monitoring or measurement of the residual calcium. Hence this study, which characterises the synapse using our reporter gene (Ca^{2+} sensor) to evaluate the changes in synaptic strength (presynaptic Ca^{2+} kinetics) upon activation at various stimuli and varying frequency of stimulation in cultured cortical and hippocampal neurones, and also on transgenic mice tissues.

Neuronal calcium stores involvement in synaptic plasticity

Calcium (Ca^{2+}) is ubiquitous intracellular messenger, controlling a diverse range of cellular processes, such as gene transcription, muscle contraction, cell proliferation and neurotransmitter release to mention but a few. Intracellular calcium concentration ($[Ca^{2+}]_i$) increases, oscillates and decreases in response to adequate stimuli leading to the activation, modulation and termination of cell function [46]. Numerous channels and pumps allow Ca^{2+} to enter and exit cells, and move between the cytosolic and intracellular stores. The main supply of calcium is from the extracellular fluid (ECF). Entry into the cytoplasm is regulated by the plasma membrane channels, binding proteins and the release from stores. The major membrane channels are grouped into the voltage gated calcium channel (VOC/VGCC), store operated channel (SOC), second messenger operated channel (SMOC), receptor operated channel (ROC) and the sodium-calcium exchanger (NCX) see figure 3 for illustration. Ca^{2+} extrusion into the extra cellular fluid (ECF) is controlled generally by Plasma membrane calcium ATPase (PMCA) and the NCX.

Figure 3 Schematic diagram showing calcium regulators across the plasma membrane ECF is the major source of intracellular Ca^{2+}, the stores serves as reserve while the binding protein also modulates Ca^{2+} oscillations. Here VOC, SMOC, SOC, ROC, and NCX represent voltage-gated channels, second messenger operated channels, store-operated channels, receptor-operated channels and sodium-calcium exchanger respectively. SERCA, ER, RYR, IP3R, MCA and NHE stands for Sarco-endoplasmic reticulum Ca^{2+} ATPase, Endoplasmic reticulum, Ryanodine receptor, Inositol 1, 3, 5, triphosphate, Mitochondria Ca^{2+} ATPase and Calcium-hydrogen-sodium exchanger respectively.

The mitochondria and the endoplasmic reticulum (ER) are the prominent calcium stores in the cells. It has

been reported that in the ER stores, Ca^{2+} release is mediated by the Inositol 1, 4, 5 - triphosphate receptor (IP3R) and ryanodine receptor (RYR) while uptake is through the sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump [47]. The ER is a complex organelle carrying out numerous independent activities [48, 49]. It is a known agonist-
sensitive Ca^{2+} store and sink that partakes in protein folding and vesicle trafficking [50]. It is also involved in the release of stress signals [49, 51, 52], regulation of cholesterol metabolism [53] and in apoptosis [54].

As a major source of Ca^{2+}, it is reasonable to suggest that the ER Ca^{2+} content must fall after stimulation. In order to preserve the functional integrity of the ER, it is vital that the Ca^{2+} content does not fall too low. Replenishment of the ER with Ca^{2+} is therefore a central process to all eukaryotic cells. Reduction in ER Ca^{2+} content activates store-operated Ca^{2+} channels in the plasma membrane and this functions to maintain ER Ca^{2+} levels that are necessary for proper protein synthesis and folding [55]. Store-operated channels play a fundamental role in both the immediate and long-term regulation of cells. Unexpected perturbations in this process will have the potential for pathological outcomes, while planned pharmacological manipulations may find clinical utility in certain disease states [55]. Many studies have demonstrated that calcium from ER stores mediates miniature excitatory post synaptic current (mEPSCs) [56], underlies large-amplitude miniature IPSCs and spontaneous calcium transient [57, 58]. A number of chemical substances are able to modulate the ER calcium stores by affecting the SERCA pumps or through the activation or antagonism of RYR or IP3Rs

Cyclopiazonic acid (CPA; [59] and Thapsigargin (ThG; [60, 61] are known reversible and irreversible potent inhibitor of the SERCA pump respectively. Emptage (2001) reported a decrease in calcium transient amplitude on application of either CPA or ThG while Xue and colleagues (2000) reported that using ThG to deplete the stores in non-excitable cells is invariably accompanied by an increase in intracellular calcium. McPherson (1991) demonstrated that the brain RYRs are sensitive to caffeine and ryanodine. Several lines of evidence point to the idea that depletion of the ER store lead to processes which in turn lead to either opening of the store operated channel or activation of the Sodium-Hydrogen-Calcium exchanger (NCX) through a calcium induced calcium influx mechanism [55, 62, 63]. ER stores calcium also plays a role in synaptic plasticity [56, 57, 62, 63] although relatively little is known about stores influence on presynaptic calcium signalling. Ca^{2+} is ubiquitous second messenger in every living organism especially in neuronal synaptic transmission.

IV. Conclusion

Calcium ion (Ca^{2+}) plays a vital role in every living organism ranging from fertilization, development, differentiation, gene expression, motility, secretion, contraction, exocytosis, cell proliferation to apoptosis. Calcium thus is involved from the beginning of life to the end of life. Most cellular function will be affected by lower concentration of Ca^{2+} which may also lead to cell death in above normal concentration. Its involvement in synaptic plasticity cannot be overemphasized. Calcium is the major components of neurotransmitter release, progression of LTP and LTP. It also plays crucial role in all forms of short term synaptic plasticity. The neuronal calcium store helps shape synaptic transmission both presynaptic and postsynaptic dynamics.

Competing interest

The authors declare that they have no competing interests

Acknowledgment

Special thanks to ETF_EBSU staff development project for sponsoring my PhD overseas

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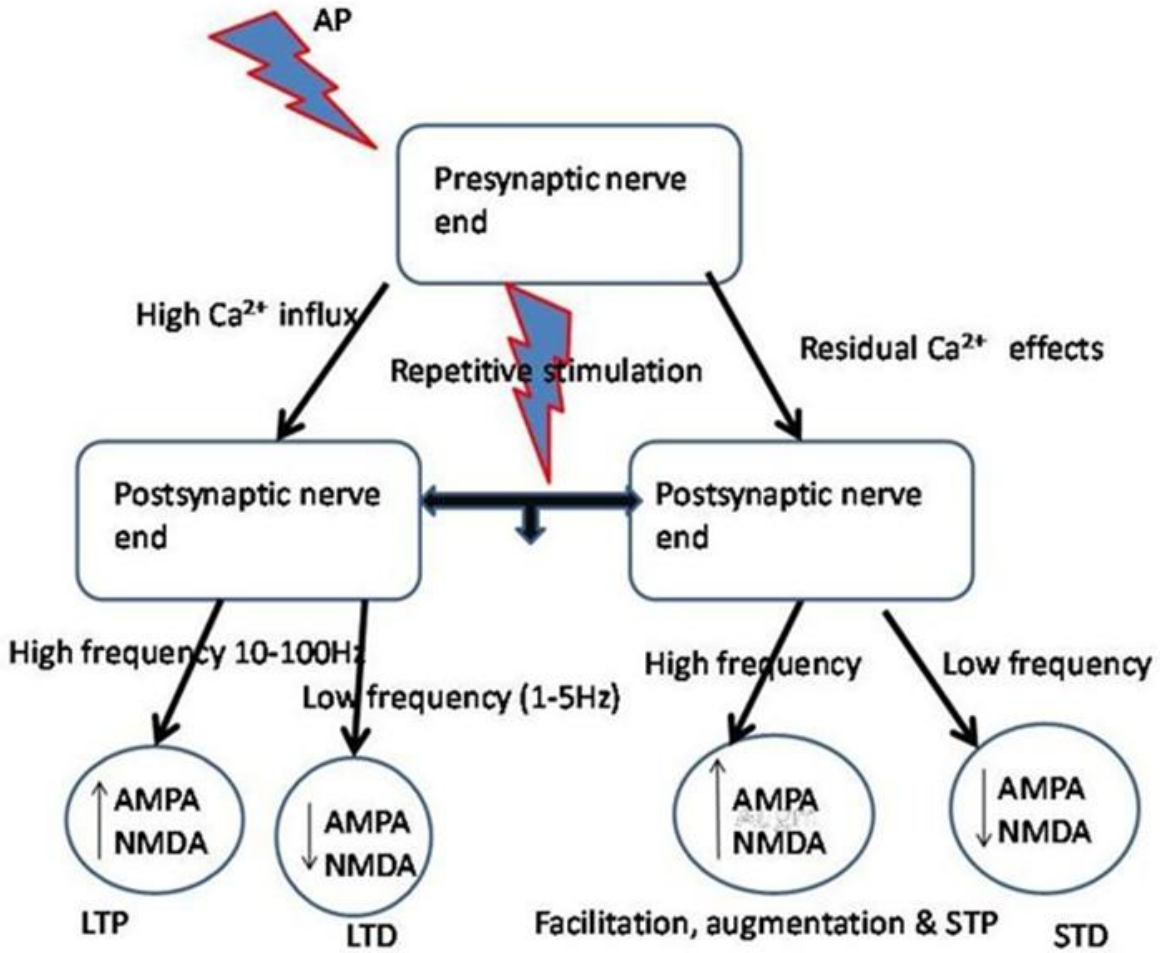

Figure 1

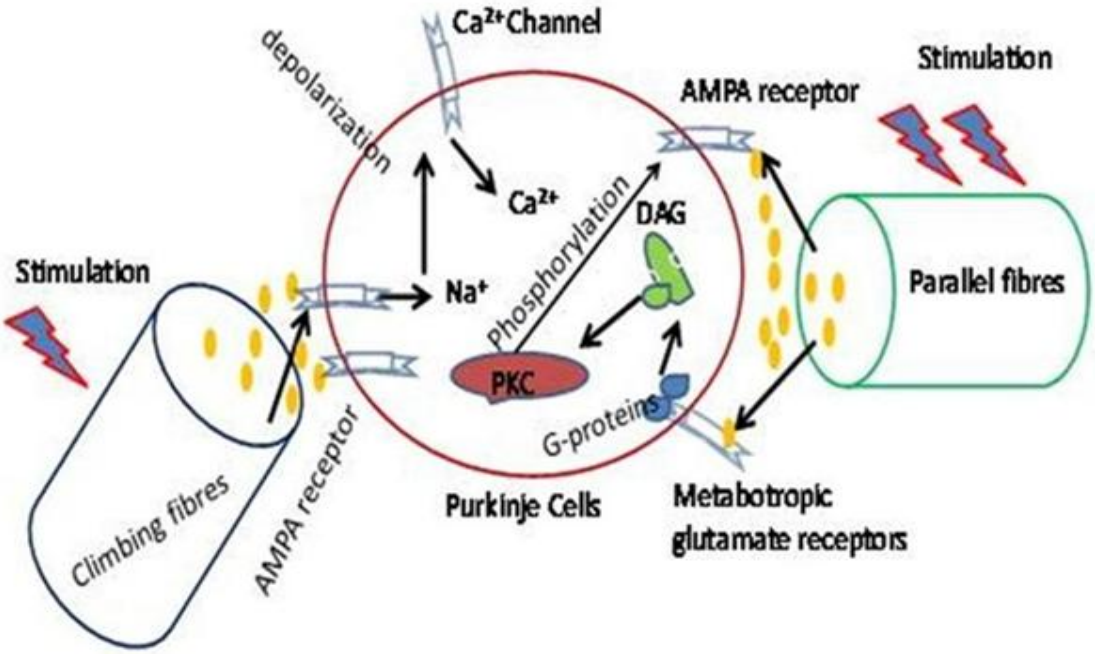

Figure 2

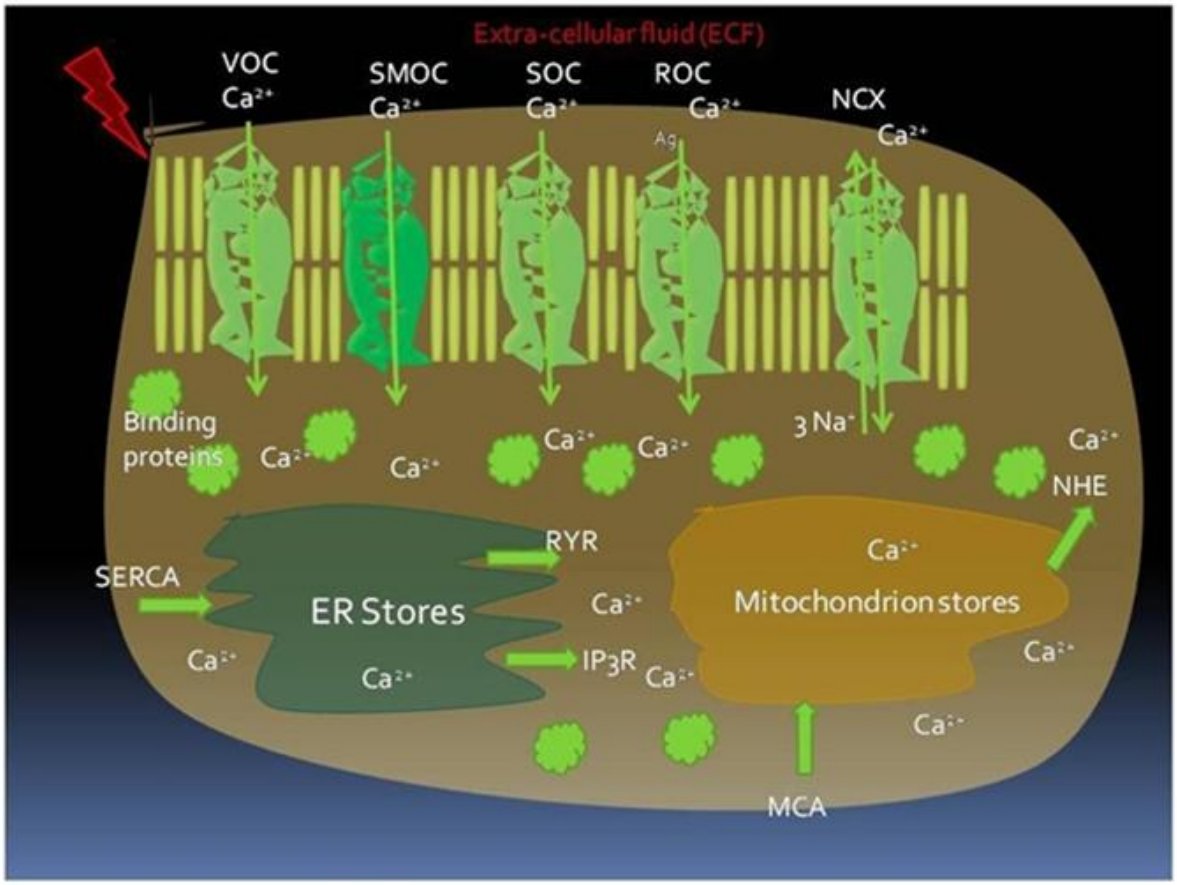

Figure 3