“Role of Calcium Ions in Synaptic Plasticity & Neurophysiology”

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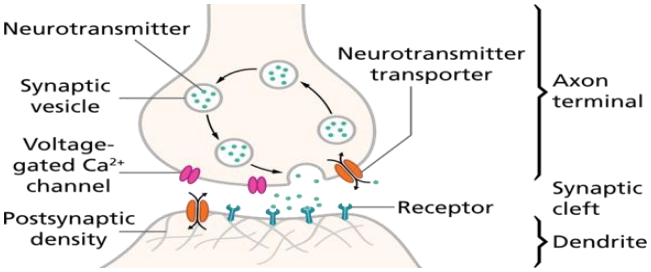
Abstract

Ca^{2+} is a second messenger and is well established in the nerve terminal and serves as a universal intracellular mediator. The Ca^{2+} enters the neuron through voltage-gated channels after the depolarization of the presynaptic neuron that causes an influx of calcium ions, which helps synaptic vesicles filled with neurotransmitter face the synaptic cleft. High Ca^{2+} concentrations are necessary, but they only last for a brief period of time (during APs) and are only present in the area around open Ca^{2+} channels. Voltage-gated Ca^{2+} channels initiate the release of neurotransmitters from presynaptic nerve axons in response to depolarization by action potentials when Ca^{2+} enters the presynaptic neuronal cell. Synaptic or neurotransmission is dependent on the power of Ca^{2+} entry. Short-term synaptic plasticity helps in encoding information in the nervous system by regulating the strength of neurotransmission through facilitation and depression of the synapse. Related neurotransmission is tightly regulated by Ca^{2+} binding proteins, calmodulin, and related Ca^{2+} sensor proteins. CaV2.1 is the major contributor of short-term synaptic plasticity, which can cause bidirectional variations in synaptic strength.

Keywords: Neurotransmission, Exocytosis, SV, Action Potentials, STP, LTP, Voltage gated Ca2+ channels, SNARE Proteins, Synaptotagmin, Ca^{2+} Buffers.

Introduction

[Ca^{2+}] plays an essential role in synaptic plasticity from presynaptic neurons to postsynaptic cells by releasing certain chemicals (neurotransmitters), which function as chemical messengers by carrying messages between neurons and can accumulate in presynaptic structures (exocytosis). This process, coupled with nerve impulse propagation along nerve fibers, turns isolated individual neurons into an integrated or functional structure in the brain and is the main function of nervous system [1]. Synapses are the connectors between neurons (nerve cells) that enable them to communicate through synaptic transmission. We learned that synaptic plasticity refers to a change that occurs at synapses. This alteration alters the activity of synapses, making them stronger or weaker over time. Synaptic or neuronal plasticity, a process in which the neuronal activity change (activity-dependent modification) in the strength of connection between neurons at synapses, plays a significant role in the brain's capacity to encode fleeting experiences into long-term memory (declarative memory) traces. Memory, the growth of motor or cognitive abilities, and damage adaptation are all built on it. In particular, Ca^{2+} voltage-gated channels are in charge of depolarizing the cell membrane of neuronal cells to let calcium in result contraction, secretion, neurotransmission, gene expression and other physiological processes. These channels, which are classified into the three Ca^{2+} voltage-gated channels subfamilies CaV1, CaV2, and CaV3, are each encoded by ten genes. However, there are slight differences when it comes to build complexes. The release of neurotransmitters and short-term presynaptic plasticity is triggered by the entry of calcium ions, which is made possible by the large signaling complexes that CaV2 channels create in the presynaptic nerve terminal at synapses (STP). Long-term potentiation, or LTP, is induced by the entry of calcium ions into signaling complexes of postsynaptic dendritic cells and dendritic spines by CaV1 channels (LTP). These calcium ion channels are primarily responsible for the majority of mutations & polymorphisms that affect the functions or regulation of these calcium ion channels and cause neuropsychiatric disorders like seizures, migraine headaches, cerebellar ataxia, autism, attention deficit disorders & cognitive deficit-disorders, palsies, addictions, uncontrolled anger, schizophrenia, bipolar disorder, depression and mood disturbance [2]. The review looks at and skims over theories about how different ion channel types, mitochondria, and endoplasmic reticulum participate in synaptic neuronal mechanisms and neuronal effector transmission as well as, in the function of calcium ions and associated voltage-gated channels [1].



Fiure 1. A typical central nervous system with synapse [3].

1. Complexes of Ca^{2+} channel signaling in synapse:

1.1 Complex of presynaptic calcium channel signaling

There are two types of calcium currents, one is P/Q-type calcium currents performed by CaV2.1 channel as well as another is N-type calcium currents carried out by CaV2.2 channel at synapses in central nervous system and peripheral nervous system are the mainsources of calcium-ions entry that have been discussed previously and that cause rapid neurotransmission [4]. Through calcium ion entrance, which has molecular dimensions roughly ten times larger than the calcium channel's own diameter, these channels produce a local micro-domain of high calcium concentration. In conclusion,the process that creates these complexes through signaling has a natural tendency to do so. And several proteins known as presynaptic calcium channel proteins are combined to create vast signaling complexes at active zones of presynaptic end terminal, which encirclepresynaptic calcium channels' intracellular mouth [5].

The first signs of the formation of the pre-synaptic calcium channel signaling complex are interactions between the CaV2.1 and CaV2.2 channel-proteins and proteins known as SNAREs (Soluble N-ethylmaleimide-sensitive Factor Attachment Protein Receptors) that play an important role in mediating exocytosis (the process by which neurotransmitters can be released from synaptic sacs). In addition to regulating calcium ions in channel activities, these protein interactions boost the effectiveness of neurotransmission in G-protein of the Beta and Gamma subunits, which are created by activating G-protein-coupled auto- receptors for a variety of neurotransmitters, regulate presynaptic calcium channels. During the time of intense synaptic activity, calcium channels are feedback-inhibited. Additionally, the activity of numerous protein kinases regulates the protein phosphorylation process that controls these channels [6].

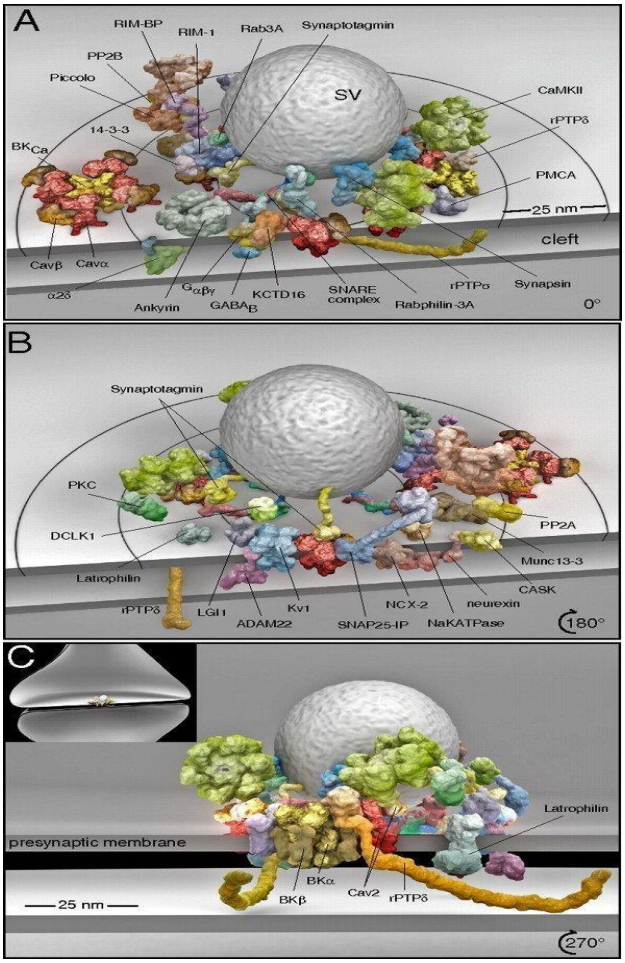


Figure 2. A presynaptic calcium channel is surrounded by a protein complexin three dimensions (3D) [6].

1.2 Postsynaptic compartment [calcium channel signaling complexes]

On membrane's postsynaptic side, calcium ion channels from CaV1 family typically can form signaling complexes. The CaV1 family has two subfamilies, CaV1.2 and CaV1. Three subfamilies are found in the neuronal cell bodies, dendritic shafts, and synaptic spines [7]. A crucial component of the control of β-adrenergic activity and long-term postsynaptic plasticity is the interaction of β-adrenergic receptors with a location in the CaV1.2 channel's C-terminal domain. Protein kinases and protein phosphatase enzymes are crucialin controlling the activity of CaV1.2 channels because they bind to them as well. As a result, whilst the presynaptic complexes created by CaV2 channels are more considerable than the postsynaptic signaling complex linked with CaV1 channels. Synaptic plasticity also requires local modulation of channel function by this form in the post synaptic compartment.

2. Presynaptic [Ca2+] current and synaptic transmission

The process of synaptic transmission is dynamic. Neurotransmitter release and short-term plasticity are significantly influenced by the intracellular calcium concentration [Ca^{2+}] (STP). While short-term facilitation is controlled by the global build-up of "residual calcium," also known as local calcium, which prompts release, this release is initiated by extremely high concentrations inside micro-domains. You should be aware that [Ca^{2+}] plays two distinct roles in vesicle recruitment: one is to promote "molecular priming" involving vesicle docking or orientation and the development of a [Ca^{2+}] release machinery, and the other is to increase the tight coupling between releasable vesicles and Ca^{2+} channels. Such connection is necessary to supply the action potentials (APs), which signify a rapid series of changes in the voltage across a membrane during depolarization. Given that the intracellular [Ca^{2+}] signal is thought to have a myriad of mysterious regulatory functions, skeptics may wonder how a second messenger could play so many varied roles. The specific response is that it is well-established in the nerve terminal, serves as a universal intracellular mediator, and accomplishes its special features by activating a Ca^{2+}sensor or receptor with a low degree of affinity. High Ca^{2+} concentrations are necessary, but they only last for a brief period of time (during action potentials) and are only presentin the area around open Ca^{2+} channels. Contrarily, other functions of this mediator are mediated by slow variations of [Ca^{2+}] in the cell with much smaller oscillation, which can be made up throughout the nerve terminal during the period of high synaptic activity that converts electrical activity into the release of a chemical called-neurotransmitter and decay that caused by a temporary depletion of synaptic vesicle during periods of rest. The recruitment of synaptic vesicles is accelerated by such gradual increases in [Ca^{2+}] [8] [9].

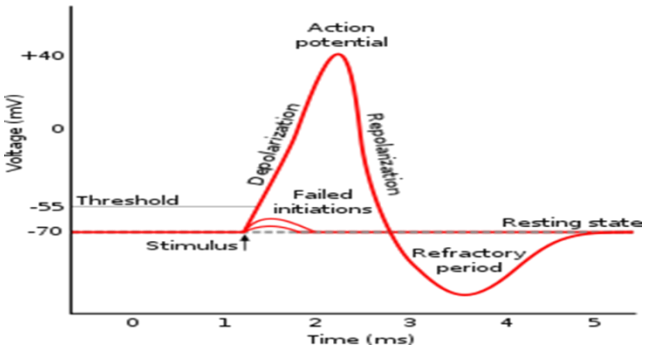


Figure 3. Action potential of synapses [8].

3. Role of calcium ions in different mechanisms and types of synaptic plasticity

3.1 Short-Term Presynaptic Plasticity (STP) and Calcium Channels

Instead of single spikes, the nervous system uses bursts of action potentials to encode information [10]. The neuromuscular junction (NMJ), a highly specialized synapses, originally showed rapid depression of synaptic transmission and short-term facilitation of synaptic transmission [the brief (milliseconds to seconds) increase and decrease in synaptic strength in response to repeated stimuli]. According to research, local calcium which build up in the nerve terminal as a result of rapid trains of action potentials (AP) plays a major role in facilitation. The

transmission of information encoded in frequency to the postsynaptic neurons has critical implications for this synaptic plasticity, which is an activity-reliant increase and decrease in synaptic strength and is crucial for brain computations [11]. However, despite their importance, it remains unclear what causes synaptic facilitation and rapid synaptic depression phase. Contrarily, other functions of this mediator are mediated by slow variations of [Ca^{2+}] in the cell with much smaller oscillation, which can be made up throughout the nerve terminal during the period of high synaptic activity that converts electrical activity into the release of a chemical called-neurotransmitter and decay that caused by a temporary depletion of synaptic vesicle during periods of rest. The recruitment of synaptic vesicles is accelerated by such gradual increases in [Ca^{2+}] [8].

3.2 Synaptic Facilitation and Regulation of Calcium Channels

The term "synaptic facilitation" refers to a widespread occurrence that is essential for information transfer and short-term enhancement of synaptic transmission. The enormous Calyx of Held synapses in the auditory brainstem are accessible for voltage clamp recording and can be used to measure and compute presynaptic calcium currents. It is frequently useful to keep in mind that CaV2.1 channels are required for synaptic activation. In Superior Cervical Ganglion (SCG) neurons in cell lines, CaV2.1 channels with endogenous calcium currents that are specifically inhibited by a neurotoxin cause synaptic facilitation to start. The IM-AA mutation prevents this mechanism, which predominantly depends on Calmodulin binding to the Calcium Sensor protein regulatory region [12]. Co-expressed CaS proteins regulate these transfected CaV2.1 channels, which can cause bi-directional variations in synaptic strength. From this, it is clear that CaBP1, a calcium-binding protein recognized as an inhibitor of facilitation, enhances depression, while NCS-1 and VILIP-2, two calcium-sensor proteins, promote facilitation and prevent rapid depression. Acoustic studies from a mouse line with the IM-AA mutation produced in the gene encoding CaV2.1 have provided crucial information on the activity of Calcium Sensor protein in control of CaV2.1 channels in vivo experimentalism. The neuromuscular junction (NMJ) and the synapses merged by Schaffer collaterals (parallel or similar axons) from CA3 neurons onto CA1 neurons and separated by CA3 pyramidal cells in the hippocampus experienced less synaptic stimulation when the induced IM-AA mutant genes were present [2].

Intriguingly, intracellular EGTA was shown in the hippocampus synapses, which prevented overall increases in calcium concentration. As a result, at these crucial synapses, calcium and Ca-Sensor protein control of CaV2.1 channels is required for majority of facilitation of synapses. In general, rapidly releasable pool is facilitated by local calcium entry (A) (RRP). We found in first step of the experimentation on the Calyx of Held that, the presynaptic terminal of a neuron was stimulated to produce a series of presynaptic Ca^{2+} currents (higher trace), which combined to elicit a series of excitatory postsynaptic currents (EPSCs) in the middle trace. Following the computation of the total amount of neurotransmitter released, the experiment resulted in a rise and fall release rate throughout the train (bottom trace).

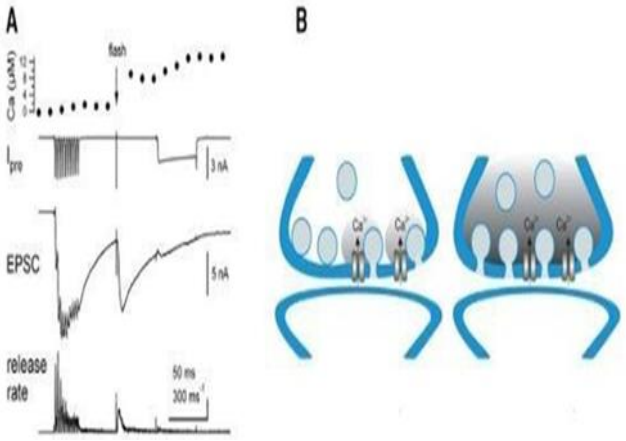


Figure 4. The experimentation on the Calyx of Held [2].

EPSC and subsequent neurotransmitter release were subsequently captured. A single light flash was then observed. According to the integration of annals, 34 percent of the whole pool of synaptic vesicles released from uncaging of Ca^{2+}, and 66 percent were extricated in period of APs of the train. (B) A representation of two synaptic sacs connected to CaV2 and four docked or reposed synaptic sacs. Two docked far away from one channeled Ca^{2+} influx via CaV2. The two synaptic sacs docked close to one channel begin exocytosis, whereas the two docked farther away do not (Left). All four docked synaptic vesicles discharged neurotransmitters as a result of a broad increase in Ca^{2+} brought on by photo-uncaging (Right) [3].

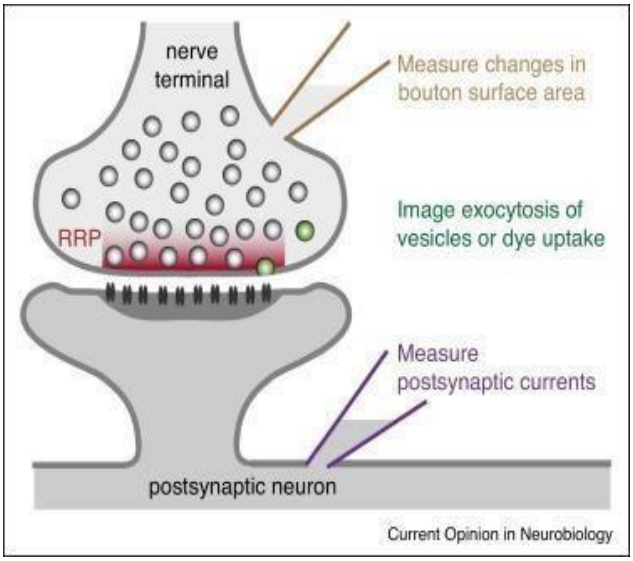


Figure 5. Calcium dependent readily releasable pool (RRP) at the Calyx of Held [3].

3.3 Rapid Synaptic Depression and Inactivation of Calcium Channels

Inactivation of Calcium ion channel and fast synaptic depression interact in a complex way. According to traditional research, the synaptic sacs are commonly physically depleted when the neuromuscular junction and SCG synapses are repeatedly stimulated for several minutes at a time. According to these studies, synaptic sacs' physical deterioration causes synaptic depression. The majority of synapses quickly depress in response to paired stimuli within ms (milliseconds) [13]. On this period, it is impossible to count the amount of synaptic vesicles that are physically attached. As a result, it is easy to measure the readily releaseable pool (RRP) of vesicles, which can be activated by a train of stimuli lasting one second. This strategy makes plausible given that the easily releasable pool (RRP) does really decline during a quick depressive episode. But is it accurate to say that the loss of physically docked synaptic vesicles can balance out the rapid lowering of synaptic vesicle RRP? Furthermore, it is hypothesized based on data that docked synaptic vesicles need to be situated close to active calcium channels in order to receive calcium influx that will cause them to release and create a pool that is easily releasable. Wadel et al. (2007) tested the notion that "For releasing readily releasable pool by synaptic sacs is highly dependent on the close proximity of calcium channel" using calcium uncaging, a particularly potent method of controlling the concentration of intracellular [Ca^{2+}], at presynaptic terminal of the Calyx of Held. He observed that when intracellular calcium ions were elevated rapidly as well as widely by photo-activated uncaging, even after exhaustive exhaustion of the RRP of synaptic vesicles by repeated stimulation, a large pool of residual synaptic vesicles could be released with the same kinetics (Figure 4A). The findings imply that presynaptic calcium channel shutdown would result in neighboring synaptic vesicles canceling out the functional RRP (Figure 4B)

From the information above, it may be concluded that calcium channel inactivation does, in fact, produce the fast phase of synaptic depression. At the Calyx Held, the fast synaptic depression phase and the calcium ion channel dependent inactivation of P/Q-type calcium- current, which is carried out by CaV2.1 channels, are temporally correlated [14]. In SCG neurons, rapid trains of stimuli or synaptic transmission induced by exogenously generated voltage gated CaV2.1 channels allow quick depression when paired pulses are available, a type of short-term, activity-dependent synaptic plasticity. This type of synaptic depression can be blocked by a mutation that disables the Ca-S protein, which controls the inactivation of voltage gated CaV2.1. Similar to this, rapid synaptic depression is delayed in Schaffer collateral-to-CA1 synapses in the hippocampus and neuromuscular nuclei of animals with IM-AA mutation in their calcium sensor protein regulatory region.

Here, it was postulated that rapid depression occurs at the synapse of rapid-spiking inter- neurons which are inhibitory that express parvalbumin (a calcium binding protein) onto CA1 pyramidal neuronal cells in the hippocampus without any prior facilitation. It may be inferred that the fundamental cause of early synaptic depression in these excitatory and inhibitory synapses with wide variety is called the inactivation of presynaptic calcium channels.

4. The relationship between the controls over the patter of synaptic facilitation and rapid depression

Numerous Calcium-ion sensor proteins, including NCS-1, VILIP-2, Calmodulin, Recoverin, Cameleon, and others, are often implicated in synaptic facilitation and depression. In neurotic situations, several synapses show branched-out patterns of fast depression and synaptic facilitation [13], [15]. Calmodulin (also known as calcium modulated protein or CaM) is expressed everywhere, so if facilitation and fast depression at all synapses are primarily caused by the regulation of voltage-gated CaV2.1 channels by Calmodulin, then these important functional characteristics can be considered constant at synapses where P/Q-type calcium currents drive neurotransmission. P/q-type calcium currents are produced and synaptic facilitation occurs as a result of the entrance of NCS-1 into the presynaptic nerve ending at the Calyx of Held [16]. The CaV2.1 calcium current is facilitated and resistant to inactivation by the proteins NCS- 1 (Neuronal Calcium Sensor) and VILIP-2, but the previously discussed Calcium binding protein-1 or CaBP-1, speeds up fast inactivation and prevents facilitation.

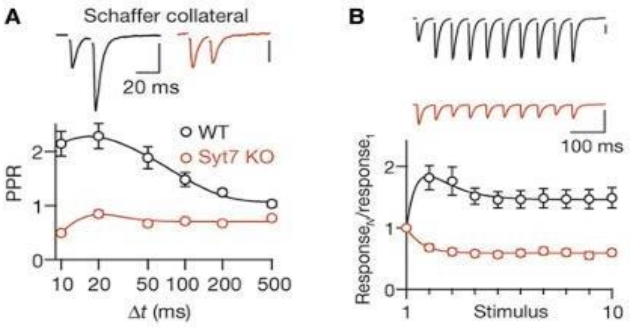


Figure-6. Short-Term Synaptic Facilitation & Synaptotagmin-7 [17].

We computed synaptic transmission from CA3 pyramidal cells to CA1 pyramidal using prepared hippocampal slices and whole-cell voltage clamp of the postsynaptic cell to CA1 pyramidal cells [17].

5. Regulation of the SNARE protein and short-term synaptic plasticity

SNAP stands for soluble NSF attachment protein, SNARE denotes SNAP receptor, and NSF (N-ethylmaleimide sensitive factor). From one action potential, residual calcium induces short-term synaptic facilitation at the end of nerve terminal. The effects of calcium entering in the subsequent closely spaced action potential on them are further enhanced by the remaining calcium. The second post-synaptic response, whether excitatory or inhibitory, has the same dynamics, rising and falling in just a few ms (milliseconds). The presynaptic calcium ion channel is hypothesized to function as a calcium sensor for this residual calcium by calcium-reliant facilitation or by inhibiting of second calcium current. It is widely proposed that calcium-reliant regulation, which includes short-time synaptic plasticity, may have as its target the SNARE complex, which functions as the effector of synaptic-sac exocytosis process. On the other hand, recent findings imply that short-term plasticity of synapses is mediated by synaptotagmin, a critical calcium-reliant regulator for SNARE protein function [17]. In all cell types and compartments, a total of thirteen different isoforms of synaptotagmin control calcium-dependent membrane fusion. The fastest support for neurotransmitter release during synaptic transmission is provided by Synaptotagmin-1, -2, & -9 at the synapses [18].

These synaptotagmin isoforms are completely eliminated by removing gene, which have no impact on basal synaptic transmission but completely counteracts the facilitation of paired-pulse facilitation (Figure 6A) and trains of stimuli (Figure 6B), with no alteration in predicted global calcium accumulation. Calcium binding to synaptotagmin-7 enhances release of neurotransmitter during the postsynaptic response by directly enhancing the action of the SNARE protein.However, in biochemical experiments, synaptotagmin-7 only slowly attaches calcium-ions to its C2A domain and can't participate in rapid synaptic transmission [16]. It is conceivable that synaptotagmin-7 interacts with the SNARE complex and binds to leftover calcium, boosting the function of a rapid synaptotagmin that initiates synaptic sac exocytosis. These recent findings on synaptotagmin-7 and calcium channels show that CaV2.1 channel facilitation is the primary prerequisite for synaptic facilitation which is affected by residual calcium transients, and indicating that all phases of synaptic facilitation require synaptotagmin-7.

6. Calcium buffering in the plasticity of short-term synapses

Calcium buffering is the process that helps maintain the amount of free calcium ions present inside the cell. The amount of calcium-ions that accumulate in neuronal terminals during trains of APs (nerve impulses) depends on the balance between calcium entry and calcium buffering through binding to calcium-binding proteins (CBP). In a wide range of cell types, parvalbumin, calbindin, and other CBPs are widely revealed. These proteins prevent calcium excess, function in several calcium signaling pathways, as well as regulate calcium transients [19]. Short-lived intracellular Ca^{2+} signals are modulated by Ca^{2+} buffers, a subclass of cytosolic Ca^{2+} binding proteins. They have an impact on the geographical and temporal components of these brief elevations in [Ca^{2+}]. The parvalbumins (and isoforms), calbindin-D9k, calbindin-D28k, and calretinin are a few examples of Ca^{2+} buffers.

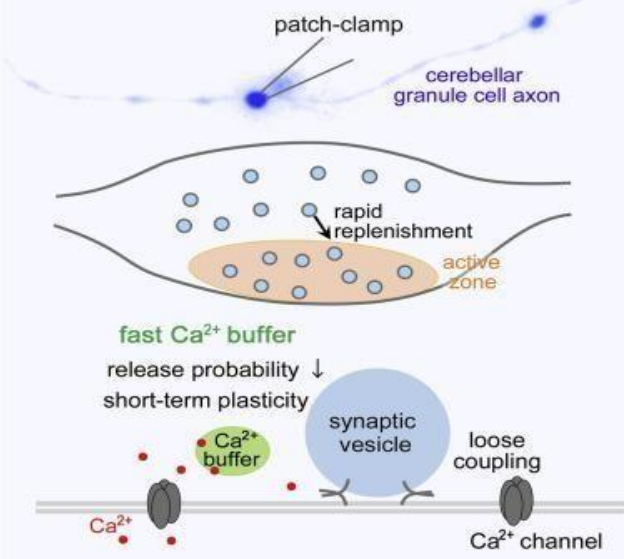


Figure 7. Calcium buffering in the plasticity of short-term synapses.

Studies on a variety of synapses demonstrate that the absence of these CBP alters synaptic plasticity and the control of synaptic strength by homeostasis. If calcium enters in response to the first action potential of a pair, residual calcium buffers will become saturated. However, calcium entry during a second action potential may result in a greater intracellular calcium transient due to the fact that it is less efficiently buffered and promotes both rapid synaptic stimulation and faster types of synaptic plasticity (ratio of fluorescence emitted). Parvalbumin, [20] a slow calcium buffer, is expressed at the Calyx of Held. Loss of parvalbumin in experiments with knockout mice did not influence the peak of short-term facilitation, but it did slow the rate of short-term facilitation and decline the global calcium transient in the nerve terminal. Parvalbumin decreases the global calcium transient's rate of decay, but it may also accelerate fast synaptic depression by increasing the calcium-dependent inactivation of CaV2.1 channels. By deleting calcium signaling, parvalbumin may cause compensatory alterations that subtly prevent facilitation. Rapid calcium buffer Calbindin D28K is another buffer that is expressed in a variety of neuronal cell types. Removal of intracellular buffers during extended whole-cell voltage clamp resulted in targeted removal of calbindin and deletion of paired-pulse facilitation (PPF) at inhibitory synapses of multipolar bursting neurons onto layer II/III

cortical pyramidal cells [21]. When the calbindin D28K protein is introduced into the presynaptic neuron using a whole- cell voltage clamp pipette, the intensity of the first excitatory postsynaptic current (EPSC) is reduced and paired-pulse facilitation is restored. While diminishing the maintenance of LTP, the full absence of calbindin D28K in knockout mice facilitated short-term synaptic facilitation at synapses in the brain on CA1 pyramidal neurons [22]. To make matters even clearer, it should be highlighted that calbindin-D28K is overexpressed at the synapses of Dentate granule cell mossy fibers onto CA3 pyramidal neuronal cells, which results in promoted excitatory postsynaptic potentials, reduced paired-pulse facilitation, and inadequate LTP. These studies also showed that short-term synaptic facilitation is altered by Calbindin-D28K calcium buffering in a variety of ways at various synapses, but they were unable to explain how these functional effects are transmitted.

7. Postsynaptic response in long-term potentiation

Long-term depletion (LTD) of synaptic efficiency & LTP tightly regulate synaptic strengthon the postsynaptic side of the synapse [23]. The long-term potentiation (LTP) and depression (LTD) of excitatory synaptic transmission are both pervasive processes that may be manifested at all excitatory synapse sites in the mammalian brain. The distinction between "LTP" and "LTD" cannot be argued anymore.Depending on the synapses and circuits in which they function, their mechanisms change. In standard experimental methods, 100 Heartz stimulation for 1 s is the most common high-frequency stimulation used to produce LTP [24]. A series of postsynaptic signaling events, including calcium entry, calcium/calmodulin- dependent protein kinase II (CaMKII), and activation of the NMDA subtype of glutamate receptors, can be brought on by repeatedly activating postsynaptic glutamate receptors [24]. When CaMKII phosphorylates AMPA receptors, glutamate activates them, and the phosphorylation of membrane targeting proteins promotes postsynaptic membrane insertion. Additionally, these receptors have a long-lasting positive impact on synapse strength. The size as well as protein composition of postsynaptic compartment change further as a result of ongoing synaptic stimulation, which also stabilizes an increase in synaptic strength by promoting gene expression and protein synthesis [25].

Ca^{2+} channel signaling in postsynaptic plasticity model showed that presynaptic terminals release glutamate during resting states, which stimulates AMPA-type glutamate receptors to cause the EPSC and lead to Na+ ion entry-dependent depolarization. In addition to directly expanding the EPSC by promoting PKA phosphorylation of the AMPA receptor and increasing Ca^{2+} influx by phosphorylating Ser1928 on CaV1.2, activation of β2-adrenergic receptors that are selectively coupled to both AMPA receptors as well as CaV1.2 channels in the postsynaptic compartment also induces LTP through CaMKII phosphorylation and subsequent signaling pathways [26].

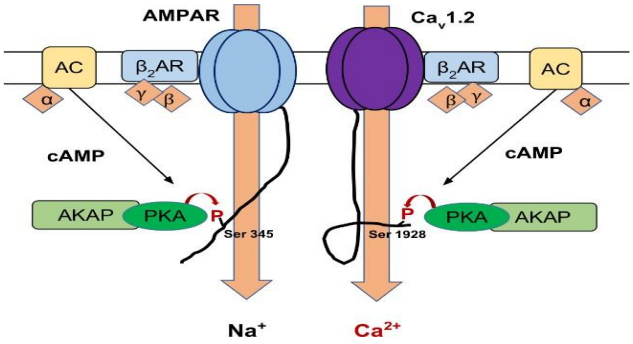


Figure 8. Long-term potentiation in postsynaptic neurons: Calcium ion channel function.

8. Conclusion

This review leads to the conclusion that Ca^{2+} is essential for synaptic signaling pathways, as well as for neural interactions. The significance of calcium ions in synaptic activities, such as nerve cells and neuron-effector transmission, as well as related to intracellular mechanism (participating in different types of ion channels, signaling complexes) is reviewed in this work. Changes in the intracellular level of free Ca^{2+} in association with activating excitable cells thus provide the framework for integrating individual neurons into the neuronal system and creating connections between neuronal and effector cells (calcium signaling). Due to their extremely precise binding to various cellular structures and ability to trigger conformational changes in these structures, Ca^{2+} ions play a special role in live cells that cannot be replaced by any other ions. As a result, one of the most important objectives of applied neuroscience is still to find substances that may change the calcium-signaling mechanism at multiple level (e.g., membrane ion channels, transporters, cytoplasmic Ca^{2+} accumulating organelles, and so on).

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Competing interest

The authors declare that they have no competing interests.

Data Availability

The authors confirm that the data supporting the findings of this review study are available within the article. Raw data that support the findings of this study are available from the corresponding author, upon reasonable request.

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