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Role of the Endoplasmic Reticulum in Synaptic Transmission

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Abstract

Neurons possess a complex morphology spanning long distances and a large number of subcellular specializations such as presynaptic terminals and dendritic spines. This structural complexity is essential for maintenance of synaptic junctions and associated electrical as well as biochemical signaling events. Given the structural and functional complexity of neurons, neuronal endoplasmic reticulum is emerging as a key regulator of neuronal function, in particular synaptic signaling. Neuronal endoplasmic reticulum mediates calcium signaling, calcium and lipid homeostasis, vesicular trafficking and proteostasis events that underlie autonomous functions of numerous subcellular compartments. However, based on its geometric complexity spanning the whole neuron, endoplasmic reticulum also integrates the activity of these autonomous compartments across the neuron and coordinates their interactions with the soma. In this article, we review recent work regarding neuronal endoplasmic reticulum function and its relationship to neurotransmission and plasticity.

Introduction

Neurons are polarized cells of the nervous system that specialize in the transfer, processing and storage of information. They are the only nervous system cells with excitable membranes. Via synchronized opening of voltage gated ion channels, neurons can generate electrical signals, action potentials, that travel along the cell and its processes. When the action potential reaches the presynaptic boutons in the axon, it triggers calcium influx and subsequent release of small molecules called neurotransmitters, through regulated fusion of synaptic vesicles with the plasma membrane (Figure 1). Neurotransmitters then bind to specific receptors in the juxtaposed postsynaptic membrane at dendrites, and initiate electrical and/or biochemical signaling in the next neuron. Axon and dendrites can reach

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lengths that are several orders of magnitude longer than the size of the neuronal cell body or soma, and they can also present complex branching patterns, all of this makes neuronal plasma membrane (PM) 3–4 orders of magnitude larger than the membrane of most cells in peripheral organs. Neurons spend a considerable proportion of their ATP production in maintaining the molecular properties of this massive amount of membrane. Moreover, the endoplasmic reticulum (ER) in neurons is continuous and it spans the whole cell volume, from the soma to the most distal dendrites and the complete length of the axon [1–7] (Figure 1); although reversible fragmentation of the ER has been proposed to occur in response to neuronal activity [8, 9]. Thus, the neuronal ER constitutes one of the largest organelles in biology. Here, we review our current understanding of the roles the ER plays in regulating neurotransmission in mature neurons via two central mechanisms: synthesis and trafficking of membrane components and regulation of calcium signaling.

The neuronal ER and membrane trafficking for synaptic specifications

Proteins and lipids may travel distances that range from millimeters to centimeters or even up to a meter (e.g. in motor neurons) in order to reach the synapse from the cell body. Moreover, the molecular composition of the soma, the presynaptic axon terminals and postsynaptic dendrites is different [10]. Thus, the enormous distances together with the complex molecular, structural and functional compartmentalization of neurons poses a challenge for the secretory pathway. Neurons overcome this challenge using localized autonomous trafficking pathways at dendrites and axons, which are able to produce, sort, maintain and recycle proteins and lipids independently of the soma (see [11–13]) (Figure 1).

The dendritic secretory pathway and its role in neurotransmission and plasticity

The levels of electrical activity in neurons can shape not only the morphology and composition of the dendritic PM but also the dynamics of internal organelles. In mammalian central synapses, only a fraction of dendritic spines contain ER at any given time point (15–50%; [3, 14]) this dendritic ER however is highly dynamic and over time it will transiently enter and explore most of the spines [15]. The mobility of the ER is positively regulated by neuronal activity and vice versa, manipulating the mobility of the ER can strengthen synapses influencing their capacity to undergo long-term potentiation (LTP) and depression (LTD) in the rodent hippocampus [15]. The ER-mediated modulation of LTP involves a mechanism dependent on the small GTPase Ras and the phosphatidylinositol 3-kinase (PI3K [16]; also see calcium-dependent mechanisms in the next section). Lysosomes, in turn, may modulate LTD at spines via a different pathway [16]. Moreover, spine volume and synapse size become highly correlated after LTP specially at spines that contain ER [17], indicating that the presence of ER can determine the plastic properties of dendritic spines in response to neuronal activity.

The dendritic ER is an important local source of molecules for structural plasticity. The dendritic ER volume decreases after LTP in the rat hippocampus as a consequence of membrane trafficking to the surface to support the generation of new spines [18]. Synapses are enlarged preferentially at spines that contain ER and poli-ribosomes after LTP, which also correlates with the appearance of the spine apparatus [19]. The spine apparatus is an

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enlargement of the ER that takes the form of stacked sacs separated by dense plates and is enriched in large dendritic spines in mature neurons [6, 20] (Figure 1). Formation and stabilization of the spine apparatus is dependent on the protein synaptopodin, and thus synaptopodin influences spine stability, neuron excitability and memory-related processes [21–23]. The mechanism of spine apparatus remodeling via synaptopodin involves actin cytoskeleton and calcium [24]. However, the molecular mechanisms of spine apparatus remodeling and its role in synaptic plasticity and memory formation remain largely unclear.

Proteins diffuse rapidly along the dendritic ER and accumulate at ER exit sites present at branching points and near spines (Figure 1), due to the increased morphological complexity of the ER at those locations [25]. These local export sites positively regulate dendrite branching and local protein delivery, including surface levels of glutamate ionotropic receptors (specifically α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, AMPAR) [25] thus influencing dendritic morphology and synaptic strength. The ER also supports local translation of synaptic proteins (reviewed in [26–28]) allowing the dynamic modulation of the dendritic proteome in response to different forms of neuronal activity and pathological processes. After synthesis, synaptic proteins in dendrites may follow an atypical, Golgi-independent trafficking pathway. Proteins including AMPAR subunits and the cell-adhesion molecule neuroligin 1, accumulate at recycling endosomes after exiting the dendritic ER and these recycling endosomes mediate their delivery to the surface [12, 29]. Different subunits of the AMPAR, namely GluA1–4, are thought to follow different exit routes from the dendritic ER and also their removal from the PM via endocytosis may be independently modulated (reviewed in [20, 21]). AMPAR receptor assembly occurs in the ER [30, 31], however how receptors of different subunit composition traffic to the dendritic PM or whether assembly or reassembly can also happen at the dendritic PM remains elusive. The atypical secretory pathway at work in dendrites causes the surface N-glycosylation pattern of neuronal proteins to be different, more “immature” compared to other cells (e.g. lacking sialic acid) [10]. However, the Golgi apparatus can fragment and disperse into dendrites in response to neuronal excitation, generating small Golgi satellites that can locally modify glycoproteins and deliver them to the PM [32] and suggesting that the functional properties of surface neuronal glycoproteins can be modulated by changing their glycosylation pattern in response to neuronal activity [12] thus influencing plasticity-related processes.

Less is known about the role of dendritic ER in local lipid metabolism. In highly branched neurons from *Drosophila*, both the development and maintenance of dendritic morphology and complexity depend on lipid synthesis [33, 34]. Whether local lipid synthesis occurs at dendrites and if it has any impact on neurotransmission remains unknown.

The axonal ER and local synthesis and trafficking of membranes

Similar to dendrites, the lipidic and protein composition of axons differs from the cell body. In neurons from the dorsal root ganglia, axons show a higher protein to lipid ratio and an enrichment in cholesterol relative to other lipids [10]. Axons only contain tubular smooth-looking, anastomosed ER [3] (Figure 1). In peripheral neurons, phospholipids can be synthesized in the axonal ER but not cholesterol, which is mainly produced by

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glial cells [35, 36] and then incorporated from the extracellular space via lipoproteins [37]. Bioactive lipids such as the endocannabinoid anandamide have also been found to be synthesized and degraded at the ER membrane in hippocampal neurons [38, 39]. Little is known about the occurrence and role of local phospholipid synthesis in axons during neurotransmission, although several lines of work have shown this process to be key for axonal growth and regeneration [40, 41]. A recent study found that blockade of phospholipid biosynthesis, specifically phosphatidylethanolamine and phosphatidylcholine, leads to activity-dependent axonal degeneration and loss of synaptic vesicles in *Drosophila* photoreceptors [42], emphasizing the importance of lipid synthesis for maintenance of axonal integrity. Biosynthesis of cholesterol has been proposed to be more efficient in developing neurons and restricted to the somatic ER, while mature neurons may need supplementation from surrounding astrocytes [35, 36, 43, 44]. In central and peripheral axons, cholesterol is necessary for proper action potential propagation along the axonal membrane and for the consequent release of neurotransmitters at the synapse [45–48]. Cholesterol-dependent domains at the plasma membrane mediate the clustering of ion channels and receptors, and can modulate their opening probability and conductance [49, 50] (reviewed in [51]). Cholesterol levels modulate SNARE (Soluble N-Ethylmaleimide-Sensitive Factor Attachment Protein Receptor) mediated fusion [52] and the endocytosis of synaptic vesicle proteins [53]. Furthermore, while cholesterol depletion reduces action potential driven neurotransmitter release, it increases spontaneous neurotransmission in mammalian neurons [48, 54] as well as in other organisms [45, 47], indicating that axonal lipids play a central role in balancing different forms of neurotransmission.

Local protein synthesis at axons has been historically more controversial, mainly due to lack of rough ER at axons. However, a variety of mRNAs are present in axons in the peripheral and central nervous system [55–57]. Ribosomes and the ER molecular machinery for protein translocation, folding and modification have also been found in axons [55, 56], and the pattern of translation at axons can be dynamically modified by neuronal activity [55, 57] indicating that it may serve important roles in information transfer and storage in the brain. Moreover, retrograde axon to soma signaling of proteins locally synthesized at axons may contribute to neurodegeneration [58]. Not only the machinery for translation is present at axons, recent work has shown that newly synthesized proteins, specifically ion channels, can be assembled and trafficked to the plasma membrane in peripheral nerves [59, 60], suggesting that the secretory pathway is present and functional at axons. More research is still necessary to uncover the specific location and molecular mechanism underlying protein synthesis and delivery at axons, and its relevance for the maintenance of neurotransmission. Another open question is whether posttranslational modifications and processing of proteins can occur at axons, including glycosylation.

The neuronal ER and calcium signaling

Neurons have the largest and most complex ER, which can connect the whole cell and at the same time mediate highly localized signals that are segregated from the rest of the neuron [61]. The ER behaves as a calcium sink and a calcium source (see below), clearing or releasing calcium in different circumstances and maintaining homeostatic calcium levels. The ER has the capacity to modulate calcium signals that are involved in different aspects of

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presynaptic neurotransmitter release and postsynaptic function and thus, it is a key player in neuronal physiology.

Intracellular calcium stores and dendritic functional and morphological plasticity

At mammalian hippocampal glutamatergic synapses, activation of N-methyl-D-aspartate receptors (NMDARs) by glutamate leads to calcium influx into the dendritic spine which in turn triggers calcium-induced calcium release (CICR) from the ER [62, 63]. At rest, activation of this pathway by spontaneous glutamate release blocks the synthesis of AMPARs and thus maintains homeostatic levels of neurotransmission [62]. Spontaneous inhibitory neurotransmission can also modulate calcium signaling at rest at excitatory synapses, leading to changes in gene expression and tuning excitatory synaptic strength [64], indicating that calcium signals can propagate and convey information independently of action potentials. Opening of NMDARs and the consequent CICR during evoked, action potential-driven neurotransmission leads to a reduction in calcium levels in the ER [63]. Depletion of ER calcium activates the ER resident Stromal Interaction Molecule (STIM) which then aggregates at ER-PM junctions and triggers the clustering and opening of Orai calcium channels (also known as CRAC – calcium release-activated channel –) [65]. This mechanism is mediated by the store operated calcium entry (SOCE) pathway. NMDAR and STIM1-dependent SOCE activation at glutamatergic spines as a consequence of CICR leads to inhibition of postsynaptic voltage-gated calcium channels (VGCCs) and gene transcription, regulating the ER content of spines in a frequency-dependent manner [63]. STIM proteins actively modulate neurotransmission by directly activating AMPARs and inhibiting VGCCs and NMDARs [66], they also regulate AMPAR trafficking [67] and can increase the number and stability of mushroom spines via a calcium/calmodulin-dependent protein kinase II (CaMKII) and end-binding protein 3 (EB3)/microtubules dependent pathway [68]. These effects may be primarily driven by STIM2 and Orai1, influencing LTP, LTD and other memory-related processes in the hippocampus [67, 69–73], while STIM1 responds to calcium fluctuations during neuron development and regulates dendritic maturation [74]. Voltage-gated potassium channels and Ryanodine Receptors (RyRs) also colocalize at somatic ER-PM junctions of hippocampal neurons [75], suggesting that multiple calcium and neuronal signaling pathways might interact and crosstalk at these locations.

While RyRs have been implicated in fast calcium sparks in dendrites, CICR via the coincidence detectors IP3Rs can lead to longer lasting calcium signals that can propagate in waves [76]. These dendritic calcium waves can reach very high concentrations (higher than AP-driven calcium) and travel long distances, although they rarely reach the nucleus [76]. Interestingly, calcium waves have mainly been observed in cortical and hippocampal pyramidal neurons, and it remains unknown what role they play in neuronal physiology (for a review see [77]). For example, a recent report showed that propagating calcium signals from dendrites to the cell body are necessary for gene expression in cultured neurons, but calcium waves and CICR were not involved [78].

The dendritic ER is both a source of calcium and a calcium sink that can remove cytoplasmic calcium resulting from neuronal activity via the sarcoendoplasmic reticulum

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calcium transport ATPase (SERCA) [79].Recent mathematical modeling has suggested that the spine apparatus acts as an important calcium sink at spines [80]. Calcium release from the dendritic ER via inositol 1,4,5-trisphosphate receptors (IP3Rs) enhances postsynaptic responses and it can unsilence synapses via a protein kinase C (PKC) and CaMKII mediated mechanism in hippocampal neurons [81]. In Purkinje cells, CICR via IP3Rs leads to LTD [82]. Interestingly, RyRs and STIM1 also participate in this process [83, 84]. A recent model predicts that SERCA-dependent calcium sequestration determines the type of plasticity that glutamatergic spines will undergo [85], suggesting that the combination of stimulation frequency and duration, probability of neurotransmitter release, opening of inositol 1,4,5-trisphosphate receptors (IP3Rs) and RyRs, together with the level of saturation of SERCA determine if a particular synapse will undergo postsynaptic LTP or LTD (also see [86]). All these findings point to the existence of a dynamic network connecting postsynaptic glutamate receptors, CICR, SOCE and calcium buffers allowing multiple outcomes depending on the type, intensity and duration of neurotransmission.

Little information is available about the role of the dendritic ER in calcium signaling at other, in particular non-glutamatergic, types of synapses. Activation of neurons in the paraventricular nucleus of the hypothalamus by norepinephrine and adrenergic receptors requires CICR [87]. Calcium release from internal stores and SOCE do not seem to modulate spontaneous inhibitory neurotransmission [88–90], although it can potentiate action potential-driven presynaptic GABA and dopamine release in different neuron types and organisms (see next section).

The axonal ER and calcium modulation of neurotransmitter release

Early work proposed that calcium released from internal stores, including the ER and lysosomes, can potentiate neurotransmitter release at hippocampal synapses [91, 92]. Since then, numerous studies have shown that CICR and SOCE amplify calcium signals at axons augmenting spontaneous, synchronous and asynchronous evoked release of glutamate, GABA, dopamine and other neurotransmitters in different regions of the nervous system and model organisms [90, 93–100] (Figure 2). Specific forms of neurotransmission appear to be coupled to different calcium sources and use different calcium sensors (also see [101] and [102]). For example, the glycoprotein reelin activates presynaptic ApoER2 receptors leading to calcium efflux from the ER via IP3Rs and selectively mobilizing a VAMP7-containing pool of synaptic vesicles [103]. This pathway only augments spontaneous neurotransmission but not evoked release. At the zebrafish neuromuscular junction, while synchronous evoked neurotransmission depends on opening of VGCC, asynchronous release is maintained by a “propagating intracellular calcium source” along the axon [100], which appears similar to the IP3R-dependent calcium waves observed in multiple cellular systems (see [77]). Activation of nicotinic acetylcholine receptors in hippocampal neurons triggers CICR via RyRs and leads to synchronized glutamate release and firing of the postsynaptic neuron even in the absence of action potentials [104]. CICR also modulates synaptic vesicle trafficking to maintain tonic activity of auditory hair cells [105]. STIM2-dependent SOCE augments spontaneous release of glutamate but not GABA via the selective activation of the calcium sensor synaptotagmin-7 [90], while STIM1B-mediated SOCE mobilizes the reserve pool of synaptic vesicles to maintain evoked neurotransmission during sustained

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activity [99]. Spontaneous release of GABA from Purkinje cells is enhanced by calcium release through RyRs [106], while both RyRs and IP3Rs trigger dopamine release from nigrostriatal neurons, independently of influx of extracellular calcium [94] (also see [93] for IP3R-mediated dopamine release in *Drosophila*). Similarly, calcium release from internal stores also increases the size of the readily releasable pool of synaptic vesicles at glycinergic interneurons of the retina [95]. Accordingly, by regulating the content of tubular ER at axons, autophagy can modulate calcium signaling and glutamate release from neurons [107]. The ER in turn is crucial to provide the components for autophagosome formation (see [108]) suggesting that autophagosomes and ER work together to set axonal properties. Additionally, endogenous mobile calcium buffers differ among glutamatergic and GABAergic presynaptic boutons and may account for differences in the probability of release and levels of asynchronous fusion of synaptic vesicles [109]. Besides the direct boost in calcium caused by opening of ER ionic channels, there are other contributing factors to the potentiation of neurotransmission. SOCE activation, for example, can enhance the membrane depolarization increasing neuron excitability [110, 111] and modulating the synchrony of neuron networks and interictal spikes during seizures [112]. In conclusion, accumulating evidence points to the coupling of different axonal ER-related calcium sources (Figure 2) to segregated forms of neurotransmitter release, and this may vary among different types of synapses. More research is needed to understand the molecular basis and the relevance of these pathways in information processing at the circuit level.

Conclusion

Physiological studies to date have been largely focused on neuronal functional events associated with cellular excitability and synaptic transmission. However, as the emerging and increasingly rich phenomenology of neuronal ER indicates, neurons also harbor an extensive network of intracellular membranous organelles that maintains and integrates signaling events across their complex morphology. Nevertheless, mechanistic details of these ER-associated intracellular neuronal signaling events remain poorly understood. Recent advances in development of super-resolution imaging approaches, novel molecular probes and identification of molecular components that maintain neuronal ER will bring the study of neuronal ER-mediated signaling on par with classical neurophysiology and uncover its essential role in nervous system health and disease.

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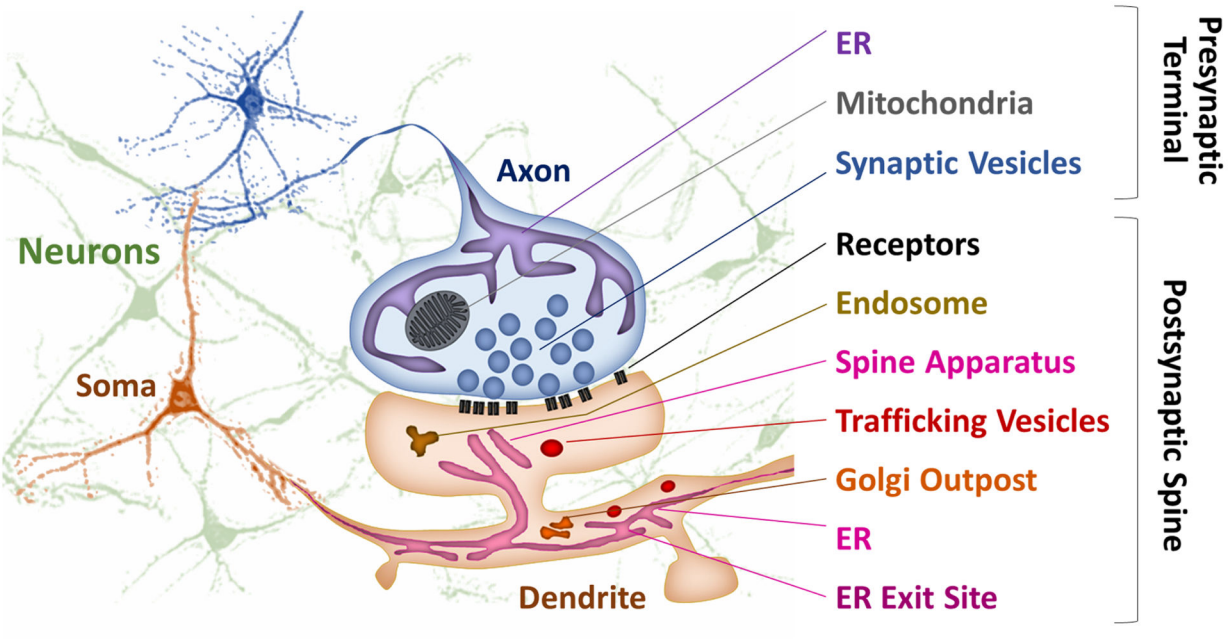

Figure 1. Endoplasmic reticulum and trafficking organelles at a model excitatory synapse.
Presynaptic terminals in the axon (in blue) contain tubular ER and are filled with synaptic vesicles, small trafficking organelles that are filled with neurotransmitters. Dendrites (in orange) contain ER, ER exit sites that mediate the delivery of proteins and lipids to the plasma membrane, spine apparatus, endosomes and Golgi satellites and outposts.

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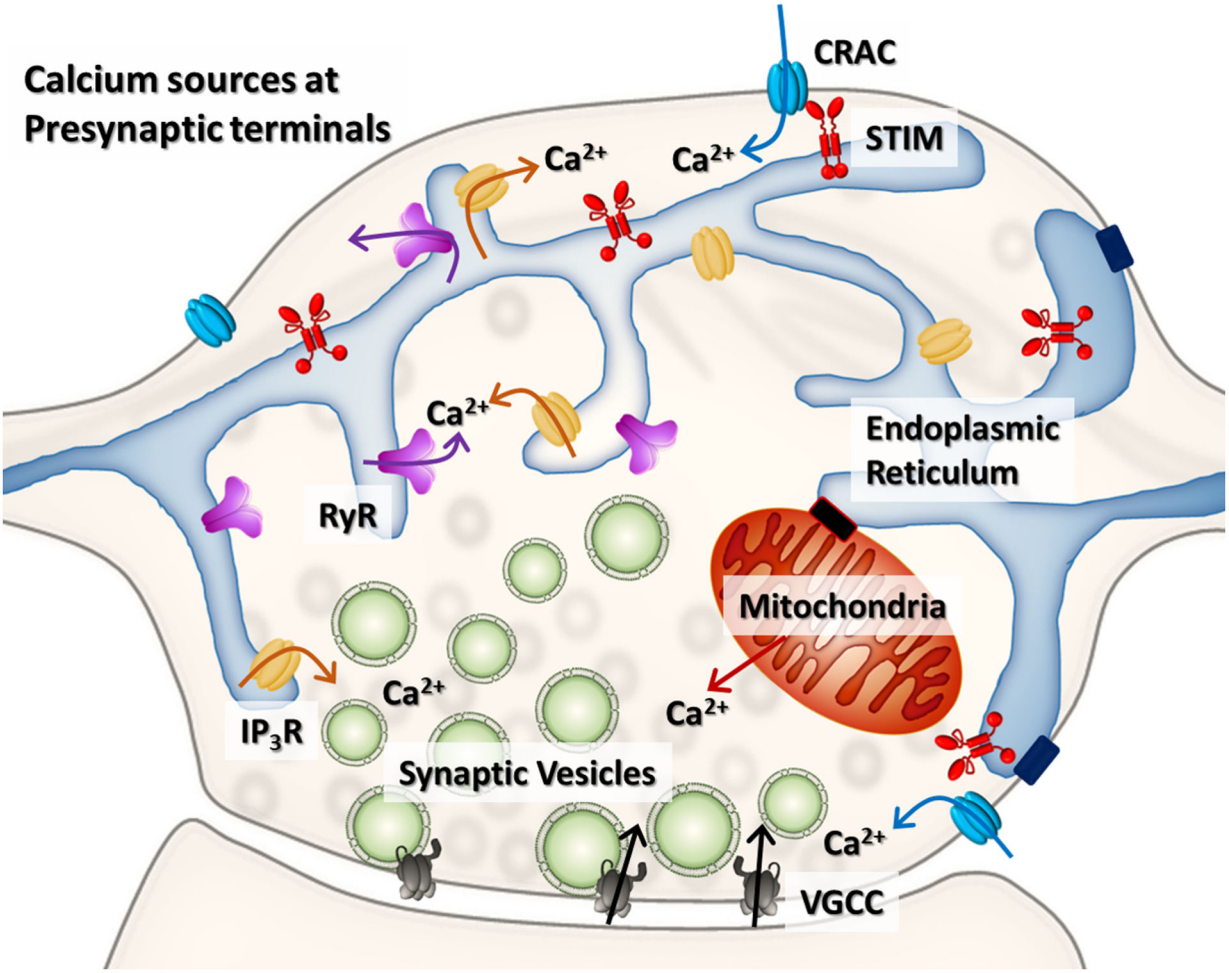

Figure 2. Calcium stores in an excitatory presynaptic terminal.

Action potentials gate the opening of VGCC with the consequent influx of extracellular calcium and the synchronized exocytosis of synaptic vesicles. The ER is the main intracellular source of calcium in axons. Calcium can be released via IP3Rs and RyRs during CICR, amplifying action potential-driven signals and neurotransmitter release. The SERCA sequesters calcium into the ER modulating calcium levels in the bouton. When calcium is depleted in the lumen of the ER, SOCE is triggered via STIM-CRAC interaction resulting in calcium influx into the terminal, which augments neurotransmitter release. Mitochondria can also work as a calcium source and a calcium sink (not discussed in this article).