Chapter

Mitochondria-Endoplasmic Reticulum Interaction in Central Neurons

Liliya Kushnireva and Eduard Korkotian

Abstract

The proteins presenilin-1/2 play a key role in the interactions between mitochondria and the endoplasmic reticulum at synaptic contacts of central neurons. Several novel observations suggest that mutations in presenilin-1 lead to an abnormal energy state, an early sign of neurodegeneration and Alzheimer's disease. Recent studies suggest that in the postsynaptic region, calcium stores are widely represented in the spine apparatus, which is located in a strategically important compartment - the neck of mature mushroom-shaped dendritic spines. Moreover, in the dendritic shaft area, at the base of the spines, one finds oblong mitochondrial clusters supplying the postsynaptic area and the local protein synthesis with ATP. Calcium signals, generated by the postsynaptic membranes, affect both calcium release from local stores through ryanodine channels and the uptake based on store-operated calcium entry. The entire complex of nanoscale signaling most likely determines the production of ATP. Violation of the functional relationship between mitochondria and reticular calcium depots can lead to disruption of signaling pathways that stimulate ATP production at the stages of increased activity of individual synapses. In this chapter, we will present the signaling mechanisms of interaction between mitochondria, spine clusters, and calcium nano-stores in postsynaptic area.

Keywords: calcium, ATP, neurodegeneration, presenilin, mitochondria, calcium store, spine apparatus

1. Introduction

The endoplasmic reticulum (ER) is the largest intracellular organelle in neurons. It ranges from the nuclear membrane through the axon to presynaptic terminals, and through all dendritic arbors, penetrating into some dendritic spines in the form of thin smooth tubules or their extensions such as spine apparatus [1]. Internally differentiated into smooth (sER) and rough (ribosomal, rER), the ER performs many cellular functions, including the synthesis and transport of essential intracellular molecules. However, the most enigmatic and least explored function of the ER is the storage and transmission of Ca^{2+} signals from a small compartment called the spine apparatus (SA), which is located mainly in mature, mushroom-type dendritic

spines [2]. This is a small multilayer lamellar structure, sometimes connected to the sER in the dendritic shaft by a thin tube passing through the neck of the spine [3]. Localization of the spine apparatus depends on synaptic activity [2]. About 80% of the large dendritic spines have a spacious SA, while only 20% of the small thin (immature) spines contain it [3] since more often the sER network can reach only the neck of the spine or be completely absent [4]. The cytoplasm of the spine has been shown to be composed of actin and actin-regulating proteins that are longitudinally located in the neck of the spine and organized into a dense lattice surrounding the sER, or SA in the head of the spine [5], whose marker is the actin-modulating protein synaptopodin (SP) [6, 7]. There are contradictions in studies involving electron microscopy (EM), which do not allow unequivocal answers to the question of whether the SA is an autonomous structure derived from the ER, indicating the final stage of the "maturity" of the spine, and all other inclusions of the ER in the spine are only transitional stages, or SA formation occurs independently of inclusion of a continuous ER compartment into the spine, and in such a case, they may sometimes coexist [3, 4, 8–12]. Nonetheless, there is a growing number of studies in which the spine apparatus is mentioned as one of the main players in the regulation of synaptic plasticity and learning and memory mechanisms. [7, 11, 13–17].

2. Spine apparatus functions

Calcium deposition in the postsynaptic terminal underlies synaptic transmission, driving a wide range of synaptic plasticity mechanisms for efficient learning and memory processing. Excitatory or inhibitory inputs lead to a differentiated local increase of calcium in dendritic spines, which functions as units of biophysical and biochemical computations in the neuron, regulating their duration and distribution [18]. The volume of the SA, also considered an ER store, affects the temporal dynamics of Ca^{2+}, its distribution to neighboring dendrite sites, and binding to numerous Ca^{2+} – gated signaling pathways [2]. The volume of the spine apparatus positively correlates with the total volume of the spine [6], with the size of the spine head (which is indirectly confirmed in experiments with SP) [19] and may increase due to the activity of N-methyl-d-aspartate receptors (NMDAR) [2]. Activation of postsynaptic NMDARs by glutamate in CA1 hippocampal neurons triggers the activation of ryanodine receptors (RyR) and Ca^{2+} – induced release of Ca^{2+} (CICR) from the store. This release of Ca^{2+} occurs and is often limited to the head of the spine [2], however, it is able to spread further along the dendrite, penetrating into adjacent spines, especially in young neurons [20]. In young (P8-P17) tissues, hippocampal postsynaptic RyRs CA3-CA1 mediate a propagating Ca2+ signal from active synapses, triggered by NMDAR-mediated Ca^{2+} influx into the dendrite and adjacent coactive synapses, lowering their induction threshold for plasticity [21]. Immunological experiments show colocalization of SP and RyR in calcium stores [19]. Modeling indicates that RyRs are likely located on the SA at the base of the spine neck and their activation is triggered by the binding of two calcium ions, which move from the head to the neck inside the spine cytoplasm and generate calcium flow from the SA down into the dendritic shaft, which also is verified experimentally [22]. RyR – mediated calcium-induced calcium release (CICR) from stores can lead to either long-term potentiation (LTP) or long-term depression (LTD), depending on the pattern of synaptic activity. The mechanisms of LTP and LTD are the basis of synaptic plasticity and require an increase in postsynaptic Ca^{2+} concentration ($[Ca^{2+}]i$). Caffeine, which releases

Ca^{2+} from stores, increases the number of active α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) in hippocampal cultures, thus enhancing the function of synapses [19] and increasing LTP induction in hippocampal slices [23, 24]. Pharmacological blockade of CICR by RyR impairs LTP induction at hippocampal synapses [2, 11, 25]. In addition to LTP, RyRs also promote LTD, and their genetic ablation inhibits low-frequency stimulation-induced LTD in the same area of the brain [19]. In addition, it has been shown that glutamate-induced growth of new spines in the cortex is also mediated by the release of Ca^{2+} from calcium stores [26].

SP-positive spines demonstrate stronger responses to glutamate uncaging than SP-negative ones. In addition, SP mediates the accumulation of the GluR1 subunit of the AMPA receptor in the heads of spines [19]. Adult mice have more mature spines containing SA and a larger area of SP inclusions than the young. Hippocampal neurons in SP knockout (SPKO) young mice lack SA and decrease LTP, do not solve cognitive tasks, and lose spatial memory. However, with age, SPKO mice develop compensatory mechanisms for LTP recovery. They demonstrate increased excitability and expression of an activity-regulated cytoskeleton-associated protein (Arc), encoded by a member of the immediate-early gene (IEG) family *ARC*, in hippocampal dentate gyrus (DG) granule cells after exposure to a novel environment. Arc mRNA and protein are known to accumulate in dendritic regions that receive high-frequency synaptic inputs [27]. Learning or stress-induced Arc accumulation in dendrites is critical for plasticity and memory consolidation [28]. DG is an area required for spatial learning processes, which in SPKO mice activates more cells than in mice with a normal genotype. Since the intracellular concentration of Ca^{2+} regulates excitability through the activation of calcium-gated K^+ – currents, a decrease in calcium availability as a result of the absence of SP and calcium stores can cause increased excitability in the SPKO brain. Therefore, it is important to compensate for the decrease in $[Ca^{2+}]i$ in postsynaptic sites for synaptic plasticity [29].

In addition to RyR, the release of calcium from ER stores is enhanced by activation of inositol triphosphate receptors (IP3R), which are enriched in dendritic branches [19]. Activation of type I metabotropic glutamate receptors (mGluR) on the plasma membrane (PM) causes an increase in the concentration of inositol triphosphate via phospholipase C (PLC). This, in turn, enhances the release of Ca^{2+} from the stores into the cytoplasm by stimulating the IP3R on the ER membrane. IP3R activation can propagate the calcium wave along the dendritic segment or be limited to postsynaptic microdomains, depending on the ambient level of inositol triphosphate in the cytoplasm. IP3R is able to be co-activated by intracellular Ca^{2+} and these two mechanisms, RyR-mediated CICR and IP3R-induced release of calcium from the stores, are capable of mutual reinforcement [30]. Thus, the SP -associated Ca^{2+} – stores in the form of a SA play an important role in the storage and regulation of Ca^{2+} secretions needed for neuronal plasticity.

In ER stores, Ca^{2+} is bound to calcium-binding proteins (CBPs), such as calnexin and calreticulin. Each CBP binds to many Ca2+ ions in a low affinity and high-capacity manner. When the Ca^{2+} store is open, exporters can easily separate Ca^{2+} from the CBP. The store also maintains the concentration of free Ca^{2+}, which determines the driving force for the release of Ca^{2+}. To compensate for the depletion of the Ca^{2+} pool, its accumulation in the ER is carried out through the use of Ca^{2+} pumps of the Ca^{2+}-ATPase family (SERCA) together with a store-operated calcium entry (SOCE) via store-operated calcium channels (SOCs). The functioning of SOCs depends on the Ca^{2+} concentration inside the store and calreticulin, which accounts for nearly half of total ER Ca^{2+} binding, acts not only as a Ca^{2+} buffer but also as an important

chaperone and regulator of SERCA pumps. Calcium depletion from ER stores is determined by stromal interaction molecules (STIMs), which are diffusely distributed throughout the resting ER. When the storage is empty, STIM transmembrane calcium sensors accumulate on the membrane of the depleted ER store, closest to PM, where they activate the voltage-independent calcium release-activated protein (Orai), providing an influx of Ca^{2+} into the store so as to replenish it (**Figure 1**) [30]. Two homologs of STIM, STIM1 and STIM2, are found in neural tissue but appear to be associated with different functions in developing and mature neurons, although both are associated with the Orai channel. STIM1 clusters predominate in young cells, they are more mobile, and their movement along dendrites triggers local Ca^{2+} transitions, while STIM2 clusters are active in mature neurons, are more dispersed, and much less mobile. STIM1 plays an important role in the formation and functional maturation of filopodia and growth cones in young cells, and STIM2 binds to SOC under conditions of Ca^{2+} deficiency, restoring local $[Ca^{2+}]i$ levels and moving into active dendritic spines [31]. Inhibition of SERCA pumps by thapsigargin results in slow Ca^{2+} leak from the ER, stimulating STIM1 oligomerization and formation of STIM1/Orai1 complexes, and antagonists of STIM/Orai dependent SOCE reduce LTP in hippocampal neurons. Synaptic activity is critical for maintaining the morphology of mature dendritic spines, as blockade of synaptic activity by tetrodotoxin (TTX) causes STIM-associated increases in spontaneous calcium transients and a decrease in the proportion of mature spines versus the proportion of immature filopodium [31, 32].

The STIM/Orai complex is also studied in the context of the development of neurodegenerative diseases, in particular Alzheimer's disease (AD). STIM1 and STIM2 are involved in maintaining Ca^{2+} homeostasis in neurons and are involved in the production of beta-amyloid peptide (Aβ), which accumulates in AD. Overexpression of these proteins can initiate pathological activation or deactivation of SOCE-dependent mechanisms, disrupting synaptic transmission and thus stimulating neurodegenerative mechanisms [31, 33].

3. Structural plasticity of spines

LTP and LTD are associated with an increase and decrease in spine volume, respectively. Similar to functional plasticity, structural plasticity also requires Ca2+ influx through postsynaptic NMDARs, activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) for recruiting GluR subunits, small guanosine triphosphatases (GTPase) and actin polymerization [34]. What specific interactions are required in local targeting of mRNA and protein synthesis to increase the morphology of active spines? To answer this question, the synaptic tagging and capture (STC) hypothesis was proposed: LTP induction creates a "tag" in potentiated synapses that can capture plasticity-related proteins (PRPs), including Homer protein homolog 1a (Homer1a) and Arc. Homer1a, a postsynaptic scaffold protein, is recruited from the soma into the stimulated spine. A synaptic tag can be a temporary morpho-functional state of the synapse, which is represented by a complex of proteins in interaction with the structures of the actin cytoskeleton. For example, LTP is known to induce the formation of a stable pool of F-actin that can act as a synaptic tag. However, this tag is also found in unstimulated spines. So, after LTP, Arc accumulates in unstimulated spines and is excluded from potentiated ones. The amount of synaptic Arc is negatively correlated with the amount of surface GluA1 at the synapses and promotes AMPAR endocytosis. It is likely that this reverse synaptic labeling helps maintain the synaptic

weight contrast between active and inactive spines in areas of high synaptic plasticity such as the hippocampus [27, 34]. This mechanism is especially attractive when the spines are close to each other and are part of the same functional synaptic cluster. It is known that morpho-functional changes correlate among neighboring spines. Decrease in the LTP induction threshold decays along ~10 μm of the dendritic branch, and in young neurons, the repeated release of glutamate from individual spikes reduces the induction threshold in the surrounding area to several minutes [34]. We hypothesize that intra-cluster differentiation of synapses is essential for structural plasticity. For example, after LTP induction, the activity of GTPases Ras and Rho extends to ~5–10 μm along the dendrite with the ability to penetrate into neighboring spines. In addition, single spike activity can also trigger molecular signaling involving calcineurin, IP3R, and metabotropic glutamate receptor 1 (mGluR1), which act on adjacent spines [35]. It is possible that Arc-dependent depotentiation of non-target spines helps de-tag neighboring spines for accurate PRP capture.

The mechanism linking local synaptic events in individual spines and signals entering the nucleus includes such transcriptional regulators as cAMP response element-binding protein (CREB) and synapto-nuclear protein messenger *Jacob*, which are translocated into the nucleus in response to synaptic activity. Upon NMDAR activation, *Jacob* is phosphorylated and dissociated from the spines, translocating to the nucleus in an importin-dependent manner. The presence of phosphorylated *Jacob* in the nucleus increases CREB phosphorylation, inducing the expression of CRE-dependent genes that are involved in the generation of the protein tag only in potentiated synapses [34]. However, such a tag is likely not so much a complex of protein molecules as a short-term reconfiguration of the spine cytoskeleton due to CaMKII activity, including restructuring of postsynaptic density (PSD) and the number of AMPAR. During LTP, the autophosphorylated form of CaMKII remains active in the PSD even after the Ca^{2+} concentration returns to baseline levels and such a tagged synapse is able to capture PRP. Such synapse stabilizes its new structural conformation before the tagging state disappears, and thus will retain a change in its synaptic efficiency. Inhibition of CaMKII autophosphorylation disrupts the tag, interfering with structural, but not early functional plasticity [36].

If we also turn to SA as a potential tag of functionally improved synapses, like Ostroff et al., who have shown that the presence of SA in large spines correlates with the presence of polyribosomes in their heads after learning. This may be an indicator of a high degree of spatial specificity of translation in dendrites. Accumulation of polyribosomes in the heads of large spines reflects the enhancement of translation during learning, suggesting a link between structural plasticity and memory consolidation [37].

4. The role of mitochondria

The development, maturation, and maintenance of functioning synapses require the maintenance of ionic balance, proteostasis, and modification of synaptic proteomes at the expense of a significant amount of energy [38]. Of great importance is the local specificity of these processes for plasticity, which has an advantage in comparison with the generalized delivery of proteins from the soma. To meet global and local energy needs, cells regulate mitochondrial movement, fission, fusion, and "parking" mitochondria in every area of the cell. Neuronal mitochondria play a crucial role in maintaining synaptic functions, in particular, by providing local

translation both under basic conditions and during plasticity processes [38–40]. Rangaraju et.al from Schuman's laboratory used adenosine triphosphate (ATP) inhibitors, local inhibition of mitochondrial compartments, and visualization of newly synthesized proteins, to show that local translation is provided by local mitochondrial clusters. Translation of proteins necessary for morphological plasticity, going on from mRNAs, localized near synapses. Glutamate-inducted LTP was not established in areas containing nonfunctioning mitochondria, preventing the morphological changes characteristic of this mechanism. Also, in mitochondria-free regions, there was a significant decrease in protein synthesis compared to stimulated regions with functional mitochondria, although at basal levels of neuronal activity, the energy needs of local translation are adequately met by global levels of ATP available in the dendrite or ATP produced by neighboring functioning mitochondria [38].

Fluctuations in cytosolic calcium, glucose and ATP levels, synaptic activity, neurotransmitters, and growth factors are able to regulate positioning, mitochondrial transport, and dynamics. Moving these organelles to energy-demanding sites, such as synapses, dendritic spines and axons [41], is essential for their functioning. Mitochondrial morphology differentiates not only depending on cell type but also on localization in a particular cellular compartment and can change with age [42]. *In vitro* and *in vivo* imaging of axonal mitochondria often shows them to be short, while dendritic mitochondria have a more elongated morphology and often show greater complexity than axonal [43]. This complexity can be expressed at least in terms of length or volume and tendency to form clusters of mitochondria in the form of tubes, often overlapping with each other in dendritic shafts. For example, in the experiments of Faitg and others, the average volume of individual mitochondria in hippocampal neurons varied between 0.11 and 1 μm^3, while axonal mitochondria had an average volume of 0.12–0.27 μm^3 and did not reach values >1 μm^3; somatic mitochondria occupied intermediate values (0.14–0.16 μm^3) [42]. In another study with cortical neurons, the length of dendritic mitochondria varied from 0.52 to 13.28 μm, while the length of axonal mitochondria was much smaller from 0.3 to 1.13 μm [43]. More than 50% of dendritic extensions are filled with mitochondria, but less than in axons 1% are filled [38, 43]. Another study compared mitochondria in the presynaptic bouton and in the postsynaptic dendrites of the hippocampus. The area of presynaptic mitochondria was almost half, on average, 0.077 μm^2 versus postsynaptic 0.146 μm^2. In addition, presynaptic mitochondria were significantly darker, i.e., had a higher electron density than postsynaptic [44]. It is possible that the elongated morphology of mitochondria in dendrites provides them with a bioenergetic advantage [45], while an increase in density indicates their greatest activity. Tubular mitochondrial stretches in dendrites are observed in hippocampal neurons, the average length of which sometimes even exceeds 10 – 30um in length [38, 46]. These may be called a mitochondrial cluster, since such a structure more likely represents individual mitochondria undergoing longitudinal outer (OMM) and inner mitochondrial membranes (IMM) fusion [47, 48], because normal elliptical mitochondria are smaller under normal conditions (see numbers above). Such clusters can be cleaved by mitochondrial uncouplers such as FCCP or CCCP [49]. Clustering of mitochondria increases their functional stability, optimizing the use of the local mitochondrial pool in cell compartments under basic conditions and during activity. Fusion and fission, the direction of movement and parking of mitochondria in certain areas of neuronal processes are of great importance for meeting the changing energy needs of various areas of the cell.

5. Mitochondrial movement and parking

In neurons, the movement of mitochondria is realized by their attachment to microtubules and it depends on their polarity [50]. In axons, microtubules have a distinct polarity, so that anterograde transport of mitochondria along (+)-terminal microtubules move them toward the growth cone or presynaptic end of the axon using kinesin family proteins (KIFs), while retrograde transport along (−)-terminal microtubules use motor protein complex of dynein, directing mitochondria toward the soma. In dendrites, microtubules can show mixed polarity so that KIFs and dynein motors can drive cargo transport in dendrites either anterograde or retrograde depending on microtubule polarity [50]. There are also reports that the movement of mitochondria over short distances in areas rich in actin cytoskeletons, such as the axon growth cone, presynaptic terminal, and sometimes in large dendritic spines observed in the cortex and hippocampus, is carried out with the help of myosin motors [46, 50]. The share of movement mitochondria varies from 5 to 20 to 35–45% of the mitochondrial pool in a culture of hippocampal neurons, and mitochondrial movement occurs more intensely in axons than in dendrites, where mitochondria can often be relatively immobile both in synaptic and non-synaptic areas. Movement increases during blocking of activity by TTX in all outgrowths, while induced glutamate excitotoxicity induces a persistent increase in $[Ca^{2+}]i$, slowing down movement and promoting mitochondrial rounding in all neuronal outgrowths [45]. Under physiological conditions, Ca^{2+} influx occurs in areas of high metabolic demand, such as axon terminals and complexes of postsynaptic structures, where mitochondria tend to accumulate. According to various data, from 36% to ~50% of presynaptic axon terminals of hippocampal neurons contain mitochondria [38, 45]. Sustained elevation of $[Ca^{2+}]$ i levels in some areas of the cell may be a marker of local activity or ATP deficiency, which will recruit and retain mitochondria to stop in these areas, thus balancing ATP production with local needs [51]. Numerous signaling pathways have been elucidated that are regulated by Ca^{2+}, modulating mobility or inducing arrest of mitochondrial pools. Mitochondrial microtubule-based mobility is mediated by KIF Ca^{2+}-dependent manner, and the OMM-anchored mitochondrial Rho GTPase 1 (Miro1) is a Ca^{2+} sensor (because it contains two helix-loop-helix EF-hand Ca^{2+}-binding motifs) for mitochondrial localization in synapses, and its association with PTEN-induced kinase 1 (PINK1) and recruitment of the Parkin protein is necessary for mitochondrial motility stops [50, 52, 53]. Mitochondrial arrest during neuronal activity is produced by synapse-released glutamate, which activates NMDA receptors and induces Ca^{2+} − influx, which binds to Miro1. The miro1-mediated mitochondrial arrest may recruit passing mitochondria to active synapses where ATP and calcium buffering requirements would be higher [53]. In a culture of rat hippocampal neurons, perfusion of 30 μM glutamate (with 1 μM glycine to activate NMDA receptors) for 10 min reduced the number of moving mitochondria by 95% in the presence of extracellular calcium ($[Ca^{2+}]o$), but only a 28% decrease in movement was observed with absence of $[Ca^{2+}]o$. In the same study, it was demonstrated that moving mitochondria were stopped in areas that were positive for the synaptic marker synaptophysin and synaptic vesicle protein 2 (SV2), and the distribution of mitochondria in dendrites to the nearest synapse was reduced after the application of glutamate. All of this indicates that mitochondria are recruited to synaptic zones during activity [53]. In addition to these mechanisms, a positive correlation is also found between anterograde mitochondrial transport in axons and electrical potential through IMM (MtMP, Ψm), increasing ATP production. Thus, the

maximum rate of ATP production in isolated mitochondria approximately doubles with an increase in Ψm for every 10 mV [54]. Mitochondria with high membrane potential also tend to accumulate at synapses [55]. It can be concluded that the motility and spatial distribution of mitochondria for ATP production can be dynamically regulated by local $[Ca^{2+}]i$.

6. The role of mitochondria in Ca^{2+} buffering and signaling

Mitochondria play an important role in Ca^{2+} signaling in neurons. They have a buffering capacity for Ca2+ binding that arises from their highly hyperpolarized membrane. Membrane potential values of functioning mitochondria in a culture of rat cortical neurons vary within ≃100 – ≃160 mV [54]. MtMP allows rapid transfer of cytosolic Ca^{2+} across the IMM along its electrochemical gradient into the organelle by the mitochondrial calcium uniporter (MCU), despite the last low affinity for Ca^{2+} ions. The mitochondrial matrix accumulates high levels of Ca^{2+} both during global Ca^{2+} signals and in response to a moderate local increase in $[Ca^{2+}]i$ [56]. This uptake is balanced by Ca^{2+} efflux through the Na^{+}/Ca^{2+} antiporter or, more rarely, through the mitochondrial permeability transition pore (mPTP), these pathways are also sensitive to mitochondrial membrane depolarization [56, 57]. Small transient mitochondrial depolarizations reflect mitochondrial buffering activity in high $[Ca^{2+}]$ i micro-domains. From studies in isolated mitochondria, uptake of 17 μM Ca^{2+} caused a 2–3 mV mitochondrial depolarization [58], while a much greater loss of MtMP accompanies opening of mPTP, nonselective pores in the inner mitochondrial membrane. Through these any molecule weighing less than 1500 da can penetrate, which can lead to an increase in osmotic pressure, swelling of mitochondria and subsequent rupture of the OMM, or cause depletion of matrix substances, incl. and Ca^{2+} [55]. Temporary opening of the pore can be caused by Ca^{2+} overload and is characterized by uncoupling of the oxidative phosphorylation chain, resulting in a decrease in ATP production, but is reversible upon restoration of cellular homeostasis. In contrast, the permanent opening of mPTP triggers mitochondria-mediated apoptosis due to the release of cytochrome C [30, 57]. Mitochondria are able to buffer about 75 μM of Ca^{2+} before it is released, and this point of maximum buffering seems to depend on the rate of Ca^{2+} uptake. Rapid mitochondrial depolarization also leads to subsequent calcium release, as shown in experiments with CCCP [59]. Interestingly, the content of Ca^{2+} in mitochondria is inversely proportional to the rate of mitochondrial movement. Motile mitochondria tend to have a lower intra-mitochondrial Ca^{2+} signal ($[Ca^{2+}]m$), however, the $[Ca^{2+}]m$ levels do not affect the direction of movement, and no difference was shown in $[Ca^{2+}]m$ between anterograde and retrograde mitochondrial movement. We have previously said that microtubule-based mitochondrial motility is driven by $[Ca^{2+}]i$ levels, however direct Ca^{2+} influx into the mitochondrial matrix via the Miro1 mediated MCU is also capable of altering mitochondrial motility. In experiments with mutations in the EF-hand domains of Miro1, mitochondrial movement did not stop, despite an increase in $[Ca^{2+}]i$ levels. Blocking the MCU also allowed mitochondrial movement to be preserved even in the presence of high levels of cytoplasmic $[Ca^{2+}]$ i, but only partially, indicating that $[Ca^{2+}]i$ also makes a significant contribution to mitochondrial mobility. Miro1 can change the level of Ca^{2+} influx into mitochondria, acting as a $[Ca^{2+}]i$ sensor, similar to STIM ER, influencing the amount of Ca^{2+} influx into mitochondria and their rate, which can be regulated by the amount of Miro1 protein associated with kinesin motors at a given time, while as soon as the concentration

of $[Ca^{2+}]$m reaches a critical level, the interaction of Miro1 with kinesin complexes is disintegrated and mitochondria stop. The influx of Ca^{2+} into mitochondria increases ATP production by activating the tricarboxylic acid cycle, as well as increasing the activity of electron transport chain enzymes and the ATP synthase complex, so that ultimately mitochondrial arrest is beneficial near synaptic areas [60].

7. ER-mitochondria interactions

Mitochondrial clusters occupy most of the dendritic branches and are closely associated with the ER, especially at the base of the spines (**Figure 1**) [18]. However, such a distribution of ER and mitochondria is not constant. Contacts between mitochondria and the ER along the dendrites enable functional inter-organellar communication and play a central role in the regulation of postsynaptic calcium-signaling, and dysregulation of its communication has been demonstrated in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases [18]. Contact sites between OMM mitochondria and ERs (Mitochondria-ER Contact Sites, or MERCs), constituting about 2–20% of the mitochondrial surface area, were detected using EM studies, then demonstrated in experiments using dimerization-dependent fluorescent proteins. Membrane constituents from a specific set of protein and lipid complexes that form MERC are called mitochondria-associated ER membranes (MAMs). The term MAM is used to describe the results of experiments on the biochemical/functional characterization of isolated contacts between mitochondria and the ER, while the term MERC is used during morpho-functional visualization [61].

MERCs provide a direct route for calcium transfer from the ER to the mitochondria and are required for mitochondrial functions, including ATP production. An increase in MERC surface area increases mitochondrial calcium influx and hence stimulates ATP production [18]. The MERC width is not constitutive and can change depending on the metabolic status of the cell. Excessive expansion, or vice versa, constriction of MERC disrupts the efficient transfer of calcium from the ER to the mitochondria. Ca^{2+} uptake by the MCU is most effective when the ER membrane faces the OMM at a distance of ≈15 nm, but not more than 30 nm, when calcium will leak and diffuse into the cytoplasm and not less than 10 nm, which is determined by the length of the protruding part of IP3R or RyR [61]. The Ca^{2+} release from the ER is able to control mitochondrial mobility by locally increasing $[Ca^{2+}]$i. Inhibition of movement of mitochondria at an optimal distance from active Ca^{2+} receptor channels from the ER is necessary for mitochondrial calcium buffering, which also serves as a means of stimulating mitochondrial ATP production. Although mitochondria store less Ca^{2+} than ER, they are important buffers of $[Ca^{2+}]$i. Voltage-gated anion channels (VDACs) located on the OMM are responsible for the rapid transfer of Ca^{2+} from the ER to mitochondria, and their function results in the formation of Ca^{2+}-rich microdomains in the mitochondrial intermembrane space [62]. Balance of $[Ca^{2+}]$m is maintained by influx through the MCU and outflow through the mitochondrial sodium-calcium exchanger (NCLX), but at elevated levels of activity, mitochondria are also able to buffer excess $[Ca^{2+}]$i due to precipitation inside the matrix in the form of Ca^{2+} – phosphate [30]. Sigma-1 receptors (σ-1R) found on MAM may influence mitochondrial Ca^{2+} – signaling. σ-1Rs are able to exhibit chaperone activity, stabilizing IP3R to MAM under conditions when Ca^{2+} reserves in the ER are depleted, preventing degradation of Ca^{2+} entry into mitochondria, restoring Ψm and subsequent ATP production (**Figure 1**) [62].

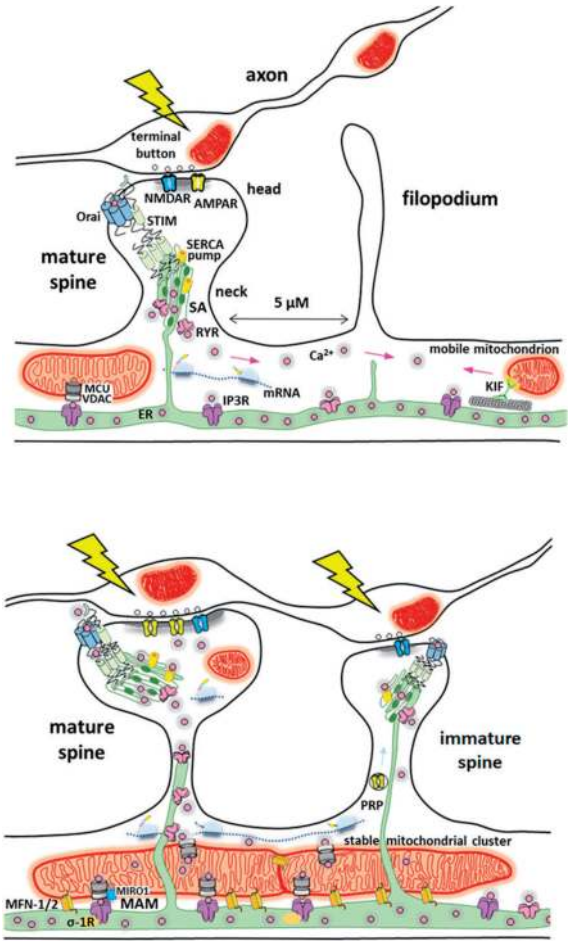

Figure 1.
Top. Mature mushroom-shaped dendritic spine contains spine apparatus (SA), which is required for synaptic transmission and plasticity. SERCA pump mediates Ca^{2+} uptake into SA due to synaptic activity or STIM/Orai-dependent store-operated calcium entry mechanism. Excitatory input (lightning) activates calcium influx through postsynaptic NMDAR, which triggers calcium-induced calcium release from SA through RyR. This Ca^{2+} transient spreads along the spine neck toward the dendrite. In turn, this initial transient trigger molecular signaling leads to the release of Ca^{2+} from IP_3Rs, which are localized on the dendrite-running ER. Calcium released from RyR and IP_3R may attract Mobile extrasynaptic mitochondria located within 5–10 µm to the base of the spine. Mobile mitochondria move along microtubules driven by a protein of the kinesin family (KIF). Continuous Ca^{2+} transients at the base of mature spine dock the mitochondrion by dissociating it from microtubule. Retention and accumulation of mitochondria take place in the area of locally elevated calcium around ER. Calcium originated from IP_3R covers an area around voltage-gated anion channels (VDAC), the intermembrane space of mitochondria, and then through the mitochondrial calcium uniporter (MCU) moves to the mitochondrial matrix. Stable postsynaptic mitochondria provide ATP-dependent mechanisms of plasticity, the local ribosome-dependent translation of proteins on the base of mRNAs possibly attracted by local Ca^{2+} gradients. The nearby filopodium does not receive presynaptic inputs and is therefore unable to take part in synaptic plasticity. Bottom. Mature and immature dendritic spines both receive excitatory presynaptic inputs. A more intense postsynaptic response occurs in a mature spine containing both NMDA and AMPA receptors. Synaptic input initiates calcium release from the SA and ER, inducing local translation of plasticity-related proteins (PRPs). PRPs can also penetrate into the adjacent, co-activated but yet immature spine, causing the incorporation of AMPA receptors. A stable postsynaptic mitochondrial cluster sequesters $[Ca^{2+}]i$, which has been released during activity. This mechanism highly limits calcium distribution along the dendrite, maintaining individual spine autonomy. New mitochondria fuse into a cluster. Their contacts with the ER are maintained by mitofusins (Mfn) 1/2. Sigma-1 receptor (σ-1R) helps to stabilize and attach IP_3R to VDAC in mitochondria-associated ER membranes (MAM). Ca^{2+} influx through MCU is also mediated by mitochondrial rho GTPase 1 (Miro1), which is able to function as a $[Ca^{2+}]m$ sensor. Miro1 modulates the level of Ca^{2+} influx into the mitochondrial matrix. It is also involved in MAM - mitochondria stabilization mechanism. The larger volume of the mitochondrial cluster enables the production of higher levels of ATP for efficient PRP production, promoting functional and morphological plasticity. Individual mitochondria are also shown to be able to enter the heads of the mature spines with large head volume and SA, where they possibly feed local translation mechanisms.

Knockout of Sig-1R in hippocampal neurons results in shorter and smaller mitochondria and also causes a decrease in MtMP and release of cytochrome c, which leads to disruption of cytoskeletal networks loss of mature dendritic spines, and formation of immature dendritic spines [63, 64]. Genetic deletion of σ-1R also impairs MAM stability and leads to a decreased number of MERC [65]. A reduced amount of σ-1R has been observed postmortem in the hippocampi of AD patients, and certain σ-1R gene polymorphisms coexist with the well-known risk factor Alzheimer's disease apolipoprotein ε4 (APOE ε4) [66].

Mitochondrial fission and fusion can also be regulated by the ER, for example, by Wnt-5a, a member of the Wingless/integrase (Wnt) secreted glycoprotein family, which induces an increase in Ca^{2+} efflux from the ER via IP3R and RYR. This, in turn, activates Ca^{2+}-dependent signaling molecules, including CaMKII, protein kinase C (PKC), and calcineurin, which may promote phosphorylation of dynamin-related protein 1 (Drp1) associated with increased mitochondrial fragmentation [41]. Although at rest, fragmented dendritic mitochondria are less beneficial for energy production, but they are able to increase ATP production at high levels of arousal through higher H_2O_2 production [67].

8. Functionally and spatially related clusters of spines are served by mitochondria clusters

Modeling and electrophysiological experiments indicate that neighboring synaptic inputs can sum nonlinearly and turn a dendritic compartment or a cluster of spines into a separate summing unit of activity. The experimentally observed signs of synaptic clustering are expressed in the sharing of synaptic inputs from the same axon by two or more neighboring spines. That is, the formation of synapses and their clustering is a consequence of their relative position with the nearest axon (**Figure 2**) [35]. The presence of clustering is also evidenced by the above mechanisms of transfer of intracellular signaling molecules by diffusion from the stimulated spine to a certain distance to neighboring dendritic spines, which can "learn" a similar pattern of activity. There is also evidence for intercluster competition: LTP induction in multiple spines on the same dendritic segment can cause spine contraction and weakening of the synapses of neighboring, more distant, unstimulated spines [34].

It can be expected that the united cluster of spines should have its own stable energy source in the form of a mitochondrial cluster, which will limit Ca^{2+} diffusion and ATP production mainly to this region. The calculations by Rangaraju et al. suggest that mitochondrial clusters spanning about 30 μm of dendritic length are capable of local ATP synthesis to provide energy for 30–300 spines (with a uniform distribution of 1–10 spines per μm of dendrite length) [38]. This co-compartmentalization provides an advantage at the time of obtaining simultaneous excitation for several dendritic spines, in which ATP production from one local mitochondrion or ATP levels in the dendrite would be clearly insufficient, and the expectation of ATP influx from neighboring mitochondria would adversely affect time-dependent plasticity and competitiveness given synaptic cluster. High-frequency excitatory input that leads to a significant increase in the local level of $[Ca^{2+}]i$ also require immediate absorption, which is successfully performed in the case of mitochondrial clustering. Could be supplemented to reformulate Hebbian plasticity into: "Spines that are repeatedly active at the same time with the same inputs will tend to become 'associated' so that

activity in one will facilitate activity in the other. Together, they represent a cluster unit of information in the brain and it will be provided by the own mitochondrial cluster."

What are the advantages of such a clustered mitochondrial service structure for a single spine? Modeling shows that ATP availability in dendrites is directly proportional to mitochondrial length [18]. In the case when several spines of the cluster simultaneously receive excitation, it will cause a more extensive total postsynaptic response, and then such a cluster, which has an extended mitochondrial cluster under it, acting, in this case, as a whole, will be provided with more energy. In pathological cases, the breakdown of such a cluster organization can occur: a decrease in the number of mature functional spines, which will lead to disorganization of the synaptic cluster, and a violation of mitochondrial recruitment and mitochondrial clustering will make energy production more chaotic.

Will an individual spine that receives a local signal be "lost" in such a unified structure? It is known that within a cluster, spines may compete for limited resources (**Figure 2**). After LTP induction, there is a marked loss of small spines, which is accompanied by an increase in the remaining spines, so that the total synaptic surface area per dendrite length remains constant [35]. There are hypotheses, the essence of which is that, despite the apparent morphological integrity of the mitochondrial cluster, the limited spaces represented by the cristae compounds create lateral gradients of critical metabolites and macromolecules within the cristae. Thus, in the mitochondria of the brain, the cristae are connected to the surface of the IMM through narrow long tubular sections. Modeling suggests that such compounds may lead to micro-compartmentation within the mitochondria, which may have important functional implications by creating a barrier to the diffusion of molecules between the cristae and intermembrane spaces. Rearrangements of such barriers change the energy output [68], allowing local ATP targeting.

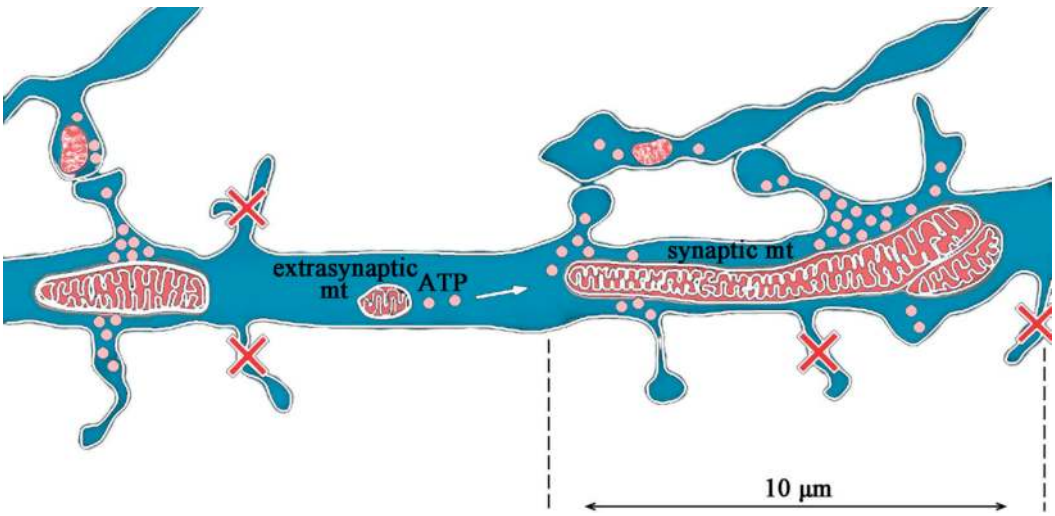

Figure 2.
Stylization based on a real image of the mitochondria distribution in the dendritic shaft. Two clusters of spines are united, each to their axonal presynaptic input, and compete for motile extrasynaptic mitochondrion (arrow). The more active cluster of spines attracts extrasynaptic mitochondrion as well as more efficiently stabilizes adjacent mitochondrial cluster due to an increase in ATP demand. Active spines receive higher levels of ATP from their local synaptic mitochondrial, compared to spines that do not receive sufficient synaptic inputs. Therefore, both intercluster and intracluster spine competition can be proposed.

9. The role of presenilin-1 in interactions between mitochondria and the ER in the neurodegeneration context

The "MAM hypothesis", for AD suggests that this disease is a consequence of a disruption of ER-mitochondrial interactions, since studies show an increased expression of MAM-associated proteins in the brain of humans and mice with AD, up to the appearance of Aβ plaques, which precedes the more common "amyloid hypothesis". For example, fibroblasts obtained from AD patients whose symptoms include impaired lipid metabolism have elongated, up to more than 200 nm MERC and increased lipid traffic [61]. PS1 and PS2 are two highly homologous isoforms of mammalian presenilin, with mutations associated with about 40% of all known cases of familial AD. Their gamma-secretase activity is enriched in MAM where they affect the processing of amyloid precursor protein (APP) to form Aβ. PS-1 plays a key role in the interactions between mitochondria and the ER in the area of synaptic contacts. Presenilin-2 (PS2) in the presence of the mitochondrial fusion protein mitofusin 2 (Mfn-2) located in OMM associated with mitofusin 1 (Mfn-1) on the ER membrane promotes mitochondrial binding to the ER [30]. Mutant presenilins have also been implicated in disrupting Ca^{2+} signaling in neurons due to the release of excess amounts of Ca^{2+} from the stores with the help of RyR and IP3R. RyR expression levels are elevated in cultured neurons expressing mutant PS1 in 3xTg-AD mice starting at a young age [69].

The most interesting and not related to the gamma-secretase activity of presenilins is their participation in the role of channels of passive leakage of Ca^{2+} ER in the hippocampus, shown in the laboratory of Bezprozvanny [70]. The increase in resting Ca^{2+} levels observed in PS1-transfected cells may be due to "leak" storage and the fact that the SERCA pump takes longer to pump the leaked Ca^{2+} back to the store. Calculations predict that under physiological conditions the SERCA pump reaches thermodynamic equilibrium when $[Ca^{2+}]$ER is 2.4 mM, however, visualization gives different values, in the range of 100–500 μM $[Ca^{2+}]$ER. The researchers proposed an explanation for this difference as the presenilin-mediated leak of the ER membrane to Ca^{2+} ions. Then the stationary intraluminal level of Ca^{2+} in the ER is determined by the balance between its injection with SERCA and passive leak into the cytosol. However, the PS1-M146V mutant was not able to function as a Ca^{2+} leak channel, which led to an overflow of Ca^{2+} stores and an increase in the level of released Ca^{2+} upon IP3R activation [70].

According to an alternative hypothesis, presenilins do not necessarily directly regulate the leakage of calcium ions from cisterns in the endoplasmic reticulum. It is possible that they serve as regulators of the family of ryanodine receptors (RyR1–3), which in turn are responsible for the leakage due to CICR [71]. Several studies have established close proximity and molecular linkage between these proteins on the ER membrane [71, 72]. The deep functional relationship between presenilins and RyR is highlighted by the fact that violation of control or mutation of PSs leads to increased expression of RyR2 and RyR3 [71]. Increased levels of RyR expression are found in models expressing PS1 mutants, possibly as a compensatory mechanism associated with loss of PS leakage function [71]. It has been also suggested that N-termini fragments of presenilin-1 or -2 interact with RyR, significantly increasing its sensitivity to cytosolic calcium and the opening probability of this channel (**Figure 3**) [73]. Mutant presenilin can drastically reduce the RyR gating rate and, consequently, the leakage of calcium ions from the ER depo. However, it is important to mention that RyR leakage is directly dependent on cytosolic calcium levels. Consequently, the leak will be

enhanced at high synaptic activity and in those locations on the dendritic shaft where synapses are located. In numerous studies, it is noted that the production of ATP by mitochondria is closely related to the release of calcium through RyR in the MAM region [74, 75]. It is likely that a drop of calcium release through RyR in the MAM zone due to presenilin mutation does not provide the mitochondria with a sufficient calcium signal to initiate ATP production, even in areas of high synaptic activity. Moreover, PS mutations have been found to overload the ER with calcium ions, which are "locked" inside due to reduced leakage in mutant PSs, particularly in Alzheimer's disease (**Figure 3**) [76, 77].

Postsynaptic areas are among the major consumers of energy, which is used to maintain ionic balance, enzymatic processes, and local protein synthesis. Synapses are associated with large and sharp fluctuations in the levels of calcium ions, which are involved in signaling at the junction of the cytosol, ER, and mitochondria. This signaling is aimed at rapid and fine regulation of ATP levels. The energy supply and trafficking of mitochondrial clusters are vital for maintaining synaptic transmission. Thus, in a study by Du et al. [78], it was found that impairment of functionality, permeability, and trafficking of synaptic mitochondria occurs much earlier than among extrasynaptic mitochondria as well as long before the generation of amyloid plaques in a mouse model of AD. Histopathological hallmarks that occur during brain aging or AD are associated with functional insufficiency of synaptic mitochondria. Damaged mitochondria gradually increase and generalize oxidative stress, synaptic dysfunction, loss of contact, and culminate in neuronal degeneration [79, 80].

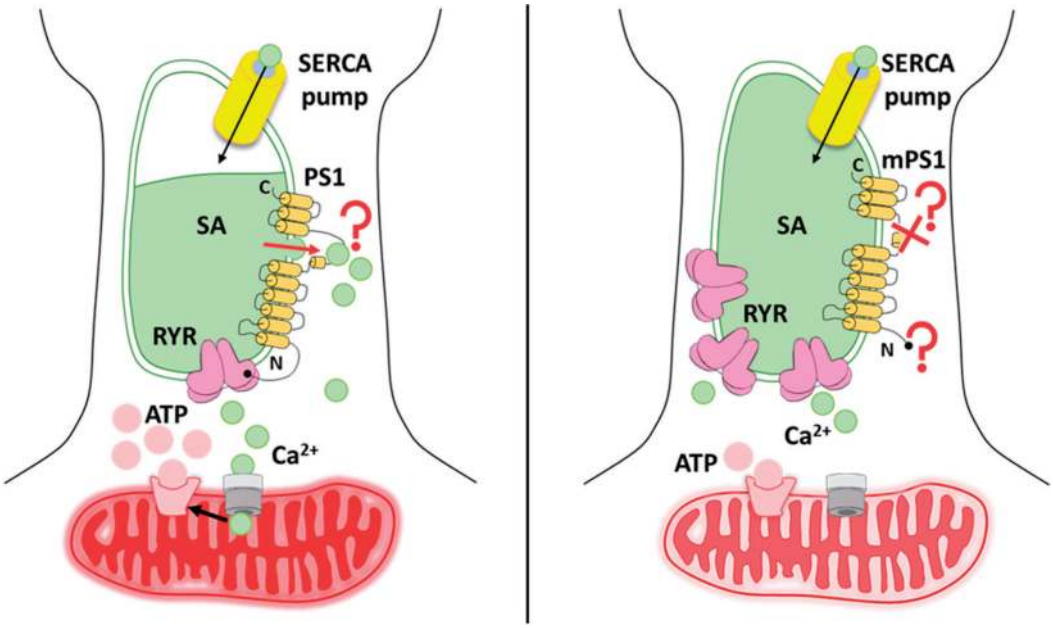

Figure 3.
PS1, possibly, acts as a channel for passive Ca^{2+} leakage from SA and/or may increase Ca^{2+} – induced release of Ca^{2+} by RyR. The N-terminal fragment of PS1 is proposed to bind directly to RyR, increasing its sensitivity to $[Ca^{2+}]i$ and the probability of channel opening. Calcium ions diffuse toward the synaptic mitochondria, entering the matrix through the VDAC/MCU, where they stimulate ATP production. Mutations of PS1 gene possibly abolish the leak function, leading to an overflow of Ca^{2+} reserves in SA. Alternatively, mPS1 may drastically reduce the RyR gating rate and restrict leakage of calcium ions from ER store, through yet unknown mechanisms. Significantly lowered calcium levels released from SA are insufficient for local ATP production by the synaptic mitochondria. The observed increase in RyR expression in mutant PS1 may be a compensatory mechanism to increase calcium leakage from the overfilled store in the absence of correct regulation by presenilin.

Particularly, disruptions of the mitochondrial energy metabolism are associated with proteins responsible for the production of ATP [81]. In all likelihood, it is in disorders of calcium homeostasis between synaptic mitochondrial clusters and regional calcium stores that one should look for the root causes of many, if not all, neurodegenerative pathologies.

10. ER in aging and neurodegeneration

Even in the absence of neurodegeneration, age-related cognitive decline can be observed in association with the loss of synapses in some most active areas of neocortex and hippocampus. Thus, during normal aging, there is a significant decrease in the density of "thin" small-headed spines, which are usually characterized as highly plastic learning spines, in the pyramidal cells of layer III (the most vulnerable cell population in AD) of the prefrontal cortex [82]. The decrease in density, however, has no effect or only minor effect on mushroom spines with normal aging [9]. Whereas in AD, electron microscopy reveals a pathological decrease in the overall density of spines, a decrease in their size along with the presence of abnormally large protrusions in different areas of the brain, as well as morphological abnormalities of the SA and mitochondria (**Figure 4**) [83].

Possibly that a part of the entire pool of thin plastic spines is enriched with ER due to extensive synaptic activation leading to LTP initiation. In its turn, activation could stabilize spine morphology during LTP processes, and increase the head volume, thus, moving them into the pool of mature spines [84, 85]. The remaining poorly activated group of thin spines that did not receive ER, may be completely eliminated. Moreover, the increased and clustered synaptic inputs of such thin highly plastic spines may partially compensate for the bald spots of the synaptic network and improve test performance in plasticity and cognitive abilities [86]. Expectedly, this requires recruiting more mitochondria through local calcium activity. Calcium dysregulation from ER stores may worsen plasticity indicators, reducing the probability of ER penetration into thin, synaptopodin-negative spines, depriving them of the opportunity to achieve energy and mature, while leaving only the perspective of elimination.

In long-term cultured rat hippocampal neurons (15–21 DIV) that mimic physiological aging, a dramatic decrease in SOCE and Orai1/STIM1 is observed, while calcium content in ER stores and the caffeine-induced Ca^{2+} release from the ER are elevated on the contrary. A mechanism of age-dependent SOCE suppression may be proposed to explain the loss of mushroom spines in both physiological aging and cognitive decline in AD [14, 87]. Regulation of the mechanism of SOCE by σ-1R is another important factor in the stabilization of large dendritic spines. Thus, instability of large spines in the hippocampus was observed following dysregulation of the normal SOCE mechanism by σ-1R, in several disorders including AD [88].

Impaired transmission of ER-mitochondrial Ca^{2+} also carries negative physiological consequences for the senescent neurons, since such transmission is necessary to ensure stable ATP flashes from postsynaptic mitochondria upon request. Effective reuptake of Ca^{2+} leakage from ER drops as a result of mitochondrial depolarization in senescent neurons. As a compensatory mechanism for this, cells may develop an increase in the number of MERC contacts, which paradoxically lead to $[Ca^{2+}]$ m overload, disrupting mitochondrial functions and ATP production, respectively [87]. A similar situation is observed in neurodegeneration when the regulation of Ca^{2+} leakage from the ER into mitochondria is disrupted by mutant presenilin,

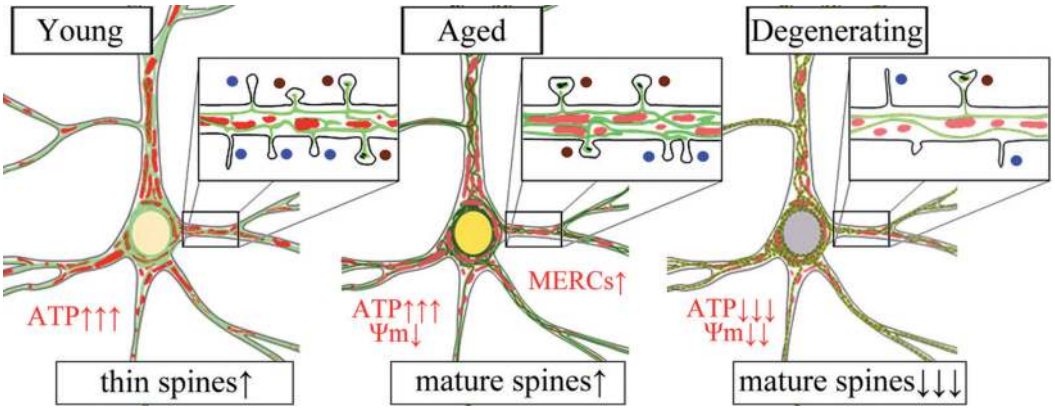

Figure 4.
The ubiquitous mobile ER in young neurons penetrates the pool of thin highly plastic spines more often, thus transforming into spine apparatus and stabilizing the spines. Mitochondria are extensively recruited toward the dendritic region under active postsynaptic compartments to contact ER and make a targeted ATP release. During normal aging, mitochondria drop their resting membrane potential and the ability of addressed ATP production. Consequently, most stable mushroom spines recruit more mitochondria to compensate the lack of ATP/energy by expanding the MERK regions. During neurodegeneration, dysfunctional mitochondria are unable to provide sufficient ATP inflow and calcium sequestration, causing degradation of mature spines and overflow of ER stores with calcium, which leads to a general disruption of ER, malfunction, and, finally, the cell death.

which pathologically overloads the stores with calcium [89]. However, abnormally increased levels of calcium, when released upon activation, may become inefficient and even toxic for mitochondria that "tuned themselves" to poor consumption of Ca^{2+} in MERC. Such disorganization can be superimposed on the already existing aging-induced functional disorders of MERC/MAM and mitochondrial homeostasis (**Figure 4**).

The multidimensionality of subtle changes in the status of ER stores and their consequences, ER dynamic omnipresence in neurons and close functional relationship with mitochondria as well as other membrane organelles, makes it among the main players in the pathological processes of aging and neurodegeneration.

11. Conclusions

1. The spine apparatus is a key structure that is assumed to regulate calcium homeostasis in the postsynaptic region of many synapses. It is characterized by the unique localization of ryanodine receptors, which direct the calcium influx toward the dendritic shaft, the SERCA pumps, and the Orai-STIM complex, which pump calcium ions from the postsynaptic density into the nanoscale store.

2. Synaptic plasticity of many dendritic spines, especially the fraction of the largest ones, depends on stabilization by their spine apparatus. Disturbances in local calcium homeostasis caused by uncoordinated ryanodine/IP_3 receptors and machinery for replenishing calcium stores in the ER can lead to the loss of dendritic spines, changes in their morphology, and a decrease in synaptic connectivity.

3. Synaptic mitochondria are characterized by high spatial stability, most often lying directly under the synapses or, more rarely, penetrating into the heads of some large spines. Synapses are the most active consumers of energy, which is

spent on maintaining ion homeostasis, enzymatic processes, and local protein synthesis.

4. Extrasynaptic mitochondria can be transported toward the most active synapses along microtubules, both in anterograde and retrograde directions. It is likely that postsynaptic calcium gradients play the role of spatial markers for "attracting" extrasynaptic mitochondria.

5. Calcium ions also play a fundamental role as signaling agents for the production of ATP by mitochondria. Both intracluster and intercluster competition of mitochondria for synaptic calcium signals is assumed.

6. In all likelihood, calcium gradients arising in the dendritic shaft are pumped into local mitochondria and buffered by them. Rapid and transient calcium gradients occur via release through ryanodine receptors and are regulated by calcium-dependent calcium release mechanisms. These calcium spikelets in synaptic mitochondria can play the role of signals for ATP release, not in a random direction, but toward the source of the gradient.

7. Synaptic clusters, served by the same axonal branch or by "competing axons" from different neuronal sources, are often associated with a complex and underlying mitochondrial cluster. Particular spines in the cluster may compete for locally released ATP. Moreover, mitochondria can efficiently and rapidly buffer released calcium ions, which highly restrict their spread along the dendrite.

8. Presenilin-1 and -2 modulate RyR and regulate the levels of calcium leak from the local storage in the area of mitochondria-associated endoplasmic reticulum membranes (MAM). Mutant presenilins drastically reduce calcium leak at MAM. It leads to overexpression of RYR and overloads the store. The lack of calcium signals from the ER prevents mitochondria from receiving sufficient signals to modulate ATP production and release. As a result, "energy starvation" in the synapses begins, which leads to synaptic deficiency, spine pruning, and neurodegeneration.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Liliya Kushnireva and Eduard Korkotian*
Department of Brain Sciences, The Weizmann Institute, Rehovot, Israel

*Address all correspondence to: eduard.korkotian@weizmann.ac.il

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