HHS Public Access

Author manuscript

Cell Calcium. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Cell Calcium. 2018 March ; 70: 87–94. doi:10.1016/j.ceca.2017.06.008.

Calcium signaling and molecular mechanisms underlying neurodegenerative diseases

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Abstract

Calcium (Ca^{2+}) is a ubiquitous second messenger that regulates various activities in eukaryotic cells. Especially important role calcium plays in excitable cells. Neurons require extremely precise spatial-temporal control of calcium-dependent processes because they regulate such vital functions as synaptic plasticity. Recent evidence indicates that neuronal calcium signaling is abnormal in many of neurodegenerative disorders such as Alzheimer's disease (AD), Huntington's disease (HD) and Parkinson's disease (PD). These diseases represent a major medical, social, financial and scientific problem, but despite enormous research efforts, they are still incurable and only symptomatic relief drugs are available. Thus, new approaches and targets are needed. This review highlight neuronal calcium-signaling abnormalities in these diseases, with particular emphasis on the role of neuronal store-operated Ca^{2+} entry (SOCE) pathway and its potential relevance as a therapeutic target for treatment of neurodegeneration.

Graphical abstract

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Keywords

Alzheimer disease; Parkinson disease; Huntington disease; neurodegeneration; Ca^{2+} signaling; Ca^{2+} homeostasis; neuronal store-operated Ca^{2+} channels; neuronal store-operated Ca2+ entry

Introduction

Calcium ions (Ca^{2+}) are universal second messengers regulating wide range of important eukaryotic cells functions such as differentiation, proliferation, growth, survival, apoptosis, gene transcription and membrane excitability (Capiod, 2016; Clapham, 2007; La Rovere et al., 2016; Toth et al., 2016). Ca^{2+} plays an especially important role in neuronal cells, where it mediates multiple vital physiological processes and plays a central role in control of synaptic plasticity (Berridge, 1998). Neurons require extremely precise control of Ca^{2+} concentration in specific compartments for proper function. Organization of neuronal Ca^{2+} signaling machinery is complex. It includes various calcium-conducting channels and a great number of calcium-dependent proteins as downstream targets including kinases, phosphatases, transcription factors, enzymes and proteins that induce synaptic vesicle fusion (Brini et al., 2014; Clapham, 2007). Calcium-conducting channels in the plasma membrane are voltage-gated Ca^{2+} channels (VGCC), N-methyl-D-aspartate receptors (NMDAR), calcium-conducting α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), canonical transient receptor potential (TRPC) channels and calcium release-activated channels (CRAC). Ryanodine receptors (RyR) and 1,4,5-triphosphate receptors (InsP3R) mediate calcium efflux from the endoplasmic reticulum (ER) - a cellular compartment performing a role of calcium depot. Stromal interacting molecules (STIMs) are calcium-sensor proteins that have an EF-hand Ca^{2+} binding domain located in the ER lumen (Williams et al., 2001). STIMs family includes STIM1 and STIM2 proteins. STIM2 binds Ca^{2+} with higher dissociation constant in comparison to STIM1 and it is more sensitive to luminal Ca^{2+} levels changes (Brandman et al., 2007). During ER calcium store depletion, STIMs oligomerize, subsequently translocate to the plasma membrane and interact with calcium-conducting channels to induce calcium influx and store refilling (Kraft, 2015; Soboloff et al., 2012). This process is called store-operated calcium entry (SOCE) (review in (Majewski and Kuznicki, 2015)). Subsequently calcium ions are transferred from the cytosol of the cell to the ER lumen with help of Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). SOCE calcium fluxes are mediated by highly calcium-selective channels of Orai family (Kraft, 2015) encoding Ca^{2+} release-activated Ca^{2+} current (I_{CRAC}), and non-selective cation channels of TRPC family encoding store-operated current (I_{SOC}) (Parekh and Putney, 2005; Yuan et al., 2007) (Figure 1). It was suggested that Orai binds to TRPC and they form tertiary TRPC-Orai-STIM complex during SOCE activation (Liao et al., 2008; Liao et al., 2009; Zhang et al., 2016a) (Fig. 1). The exact contribution of Orai1 and TRPC channels to SOCE is under investigation (Chen et al., 2011a). SOCE plays an important signaling function in neurons (Majewski and Kuznicki, 2015). This review highlights neuronal SOCE deficiency observed during Alzheimer`s (AD), Huntington`s (HD) and Parkinson`s disease (PD).

Complex calcium signaling system in neuronal cells allows activation of different spatially separated Ca^{2+}-dependent processes at the same time. Neurons are extremely sensitive to calcium concentration levels and even subtle defects in Ca^{2+} homeostasis can lead to destructive consequences and alter normal neuronal activity. Multiple evidence suggest that Ca^{2+} dysregulation plays an important role in aging (Kumar et al., 2009) and neurodegeneration (Bezprozvanny, 2009). Some of the calcium signaling abnormalities that occur in AD, HD and PD neurons are highlighted in this review. Neurodegenerative diseases present an enormous humanity problem, but despite active research efforts, these disorders are still incurable, with most medicine offering only symptomatic relief (Cacabelos, 2017; Cummings et al., 2016; Mason and Barker, 2016). Restoring calcium signaling homeostasis presents an attractive target for drug discovery for neurodegenerative disease treatment.

Calcium dysregulation in Alzheimer`s disease

Alzheimer`s disease (AD) is a neurodegenerative disorder, which affects memory formation and storage processes. In most cases AD appears sporadically and affects people over 60 years of age. Small portion of cases (approximately 1%–2%) refers to familial form of AD, which is characterized by an earlier onset and more severe pathogenesis (Hardy and Selkoe, 2002). Familial form of AD is caused by mutations in genes encoding Presenilin 1 (PS1), Presenilin 2 (PS2) and amyloid-precursor protein (APP) (Bergmans and De Strooper, 2010; Hardy, 2009; Hardy and Selkoe, 2002). Presenilins form the catalytic subunits of the γ-secretase protease complex, which is together with β-secretase are responsible for APP protein cleavage and subsequent production of toxic Aβ peptides (Jellinger, 2009). Several hypothesis about causes of AD have been proposed, but so-called “amyloid cascade hypothesis” is a dominant model of AD pathogenesis. It states that increased production of amyloidogenic Aβ42 peptide (or an increase in Aβ42:Aβ40 ratio) is driving AD, causing reduced number of synapses and neuronal death (Fleming, 2017; Hardy, 2009; Hardy and Selkoe, 2002). Based on this idea, major efforts were spent by the industry on developing agents which can reduce Aβ production or eliminate Aβ from the brain. However, so far these agents did not show benefit in AD clinical trials (Cummings et al., 2014; Karran and Hardy, 2014; Karran et al., 2011). As alternative point of view, “calcium hypothesis of AD” was suggested (Alzheimer's Association Calcium Hypothesis, 2017; Bezprozvanny and Mattson, 2008; Briggs et al., 2016; Khachaturian, 1989). This hypothesis speculates that dysregulation in cellular calcium homeostasis is the main driving force of neurodegeneration in AD (Alzheimer's Association Calcium Hypothesis, 2017; Bezprozvanny and Mattson, 2008; Briggs et al., 2016; Khachaturian, 1989). Several lines of experimental evidence support this idea. ER Ca^{2+} levels are elevated in AD and in aging neurons (Bezprozvanny and Mattson, 2008). Rise in ER Ca^{2+} concentration results in subsequent compensatory alterations and defects in neuronal Ca^{2+} signaling. Altered Ca^{2+} signals shift the balance between Ca^{2+} -dependent phosphatase calcineurin (CaN) and its opponent Ca^{2+} / calmodulin-dependent protein kinase II (CaMKII), which are extremely abundant in synaptic locations. Shift in the balance of CaMKII and CaN activity occludes longterm potentiation and facilitates long-term depression, causing synaptic and memory impairments and leading to synaptic loss and neurodegeneration (Berridge, 2011; Bezprozvanny and Hiesinger, 2013; Popugaeva et al., 2017).

What is a reason for increased calcium content during AD? How do AD-causing mutations induce calcium signaling dysregulation? One possible explanation is that Aβ peptides form Ca^{2+} -permeable pore in the plasma membrane (Arispe et al., 2007; Arispe et al., 1993). Indeed, a part of neurites surrounding β-amyloid plagues have elevated steady-state Ca^{2+} levels (Kuchibhotla et al., 2008). Aβ may induce increased calcium influx via L-type VGCCs (Ueda et al., 1997), but it was also reported that Aβ oligomers suppress P/Q-type VGCCs calcium currents (Nimmrich et al., 2008). NMDAR is another potential source for intracellular calcium, playing important role in excitatory synaptic neurotransmission. Activation of synaptic NMDARs is required for synaptic plasticity and drives LTP generation, but sustained activation of NMDARs can cause subsequent calcium overload and toxicity (Hardingham and Bading, 2010). Role of NMDA receptor in AD and particularly Aβ effects on NMDA receptor were studied intensively (Foster et al., 2017; Mota et al., 2014a). It was proposed that at early AD stages NMDA receptor is overactivated (Parameshwaran et al., 2008; Zhang et al., 2016b). Indeed, recent reports indicate that Aβ oligomers applied on cultured cortical neurons activate GluN2B-containing NMDAR and induce an immediate Ca^{2+} rise (Ferreira et al., 2012). Potentially neuroprotective drugs which block NMDAR has intolerable side effects, presumably because of extreme importance of this receptor for normal neuronal function. An exception is a non-competitive NMDAR inhibitor memantine, which is currently approved for AD treatment (Lipton, 2006). In contrast to other NMDAR blockers, positive effects of memantine administration are likely observed because it preferentially blocks excessively activated NMDARs (Mota et al., 2014b). New generation of drugs which selectively bind to and inhibit only excessivly activated NMDARs are considered for AD treatment (Lipton, 2007). Another adverse effect of Aβ is a reduction in NMDAR expression and its enhanced endocytosis (Snyder et al., 2005). Enhanced endocytosis of NMDARs is in part due to Aβ-mediated activation of STEP61 phosphatase (Snyder et al., 2005). Downregulation of GluN1 subunit of NMDAR was observed in postmortem AD patient's samples (Jacob et al., 2007). It was shown that the specific N-terminal splice cassette containing GluN1 is decreased drastically in AD, suggesting that neurons bearing this isoform are more vulnerable (Hynd et al., 2004). Some data indicate that Aβ may directly bind to and modulate activity of NMDA receptors (De Felice et al., 2007; Lacor et al., 2007; Sinnen et al., 2016; Texido et al., 2011). Reduction of NMDAR activity in AD may also be induced by an oxidative stress, most likely due to oxidation of extracellular NMDAR cysteins and intracellular targets such as calmodulin (Foster et al., 2017). Taking together, we may conclude that Aβ causes dysregulation of NMDAR expression and activity by multiple mechanisms. Disrupted NMDAR signaling further leads to impaired synaptic plasticity, reduced LTP, enhanced LTD and synaptic loss (Foster et al., 2017; Mota et al., 2014a).

In addition to adverse Aβ effects, mutated presenilins directly cause Ca^{2+} dysregulation in AD. Different cellular models expressing AD mutant presenilins show overfilling of the ER with Ca^{2+} and the excessive Ca^{2+} release through the $InsP_3R$ (Ito et al., 1994; Leissring et al., 1999a; Leissring et al., 1999b; Nelson et al., 2007; Stutzmann et al., 2004; Stutzmann et al., 2006; Tu et al., 2006a). To explain these results it has been suggested that mutant presenilins directly affect $InsP_3R1$ gating (Cai et al., 2006; Cheung et al., 2010; Cheung et al., 2008), store-operated Ca^{2+} influx (Leissring et al., 2000; Yoo et al., 2000), RyR (Chan et

al., 2000; Hayrapetyan et al., 2008; Rybalchenko et al., 2008; Stutzmann et al., 2006) or SERCA ER Ca^{2+} pump (Green et al., 2008). Another possible explanation is that presenilin by itself forms ER calcium leaking pore, and most of the AD-causing mutations collapse this pore and induce ER Ca^{2+} overfilling (Nelson et al., 2011; Nelson et al., 2007; Tu et al., 2006a; Zhang et al., 2010b). This idea was initially controversial (Shilling et al., 2012) but it was supported by an unbiased screen for ER Ca^{2+} leak channels (Bandara et al., 2013). Interestingly, presenilins share the fold with chloride channels (Theobald, 2016) and the high resolution crystal structure of archaeal presenilin homologue PSH1 has a hole that traverses through the entire protein and is large enough to allows passage of small ions (Li et al., 2013).

Dysregulation of Ca^{2+} signaling causes excessive Ca^{2+} release via RyR (Briggs et al., 2016). RyR-mediated Ca^{2+} release is enhanced in neurons from presenilin mutant mice (Stutzmann et al., 2006). RyR2 expression levels are elevated in AD brains (Bruno et al., 2012) and activity of RyR is enhanced due to increased ER Ca^{2+} levels. Enhanced Ca^{2+} release via RyR2 affects synaptic plasticity, compensating for changes in LTP and LTD (Chakroborty et al., 2012b). In the spines of AD neurons, NMDA receptor-mediated Ca^{2+} influx triggers supranomal Ca^{2+} responses mediated by RyR2 (Goussakov et al., 2010). Excessive Ca^{2+} release triggers overactivation of Ca^{2+}-dependent SK channels and impairs the induction of synaptic plasticity changes (Chakroborty et al., 2012b). Indeed, SK channels overactivation was at least partially responsible for destablization of mushroom spines and late-phase LTP defects in presenilin knockin (PS1-M146V-KI) neurons (Zhang et al., 2015a). These results suggest that inhibition of RyR2 activity may helps to alleivate AD symptoms. Indeed, previous studies showed that short term treatment with RyR inhibitor dantrolene was able to stabilize Ca^{2+} signals, ameliorate cognitive decline and reduce neuropathology, amyloid load and memory impairments in various AD mouse models (Chakroborty et al., 2012a; Oules et al., 2012; Peng et al., 2012). However, in our previous studies we observed that long-term feeding of the RyR inhibitor dantrolene exacerbated amyloid plaque formation and resulted in the loss of hippocampal synaptic markers and neuronal deterioration in AD mice (Zhang et al., 2010a). One potential problem with interpreting these conflicting results is that specific RyR inhibitors do not exist and the drug dantrolene, used in most studies, has additional targets such as store-operated Ca^{2+} channels (Zhao et al., 2006). Moreover, dantrolene is specific for RyR1 (Krause et al., 2004), and does not block RyR2 and RyR3 effectively. Using genetic knockout approach we found that RyR3 appears to play a dual role in the context of AD pathology, rather than an invariable positive or negative effect (Liu et al., 2014). Our results indicated that RyR3 plays an important protective role in early stages of AD by helping to reduce neuronal excitability and activity-dependent Aβ production. However, in older AD mice deletion of RyR3 resulted in beneficial effects (Liu et al., 2014). Thus, although RyR3 appears to play a protective role in younger mice, these results suggested that in aging brain RyR3 may contribute to AD pathogenesis by amplifying ER Ca2+ release through calcium-induced calcium release (CICR) mechanism and by enhancing the dysregulation of intracellular Ca^{2+}. These results consistent with reports that dantrolene exerted beneficial effects in several AD mouse models (Chakroborty et al., 2012a; Oules et al., 2012; Peng et al., 2012).

Recent results suggest a significant role for neuronal store-operated calcium entry (SOCE) pathway in AD pathogenesis (Fig. 2). SOCE pathway is activated following depletion of ER Ca^{2+} levels. Reduced expression levels of SOCE ER Ca^{2+} sensor STIM2 were discovered in experiments with AD patient fibroblasts (Bojarski et al., 2009). Levels of STIM2 were also reduced in hippocampal samples from PS1-M146V-KI mouse model and in cortical samples from sporadic AD patients (Sun et al., 2014). Hippocampal neurons from PS1-M146V-KI mice displayed reduced mushroom dendritic spines density and almost complete absence of STIM2-gated store-operated calcium entry (SOCE) in dendritic spines (Sun et al., 2014; Zhang et al., 2016a). Following store depletion, STIM2 translocates to neuronal plasma membrane and drives calcium influx into cell through interaction with calcium conducting channels on the plasma membrane. In case of hippocampus, TRPC6 and Orai2 were recently identified as SOCE-forming channels in hippocampal neurons (Zhang et al., 2016a). Orai1 was also implicated as a SOCE channel in developing hippocampal synaptic spines (Korkotian et al., 2017). Reduction of synaptic SOCE was demonstarted in APP mutant mice and following application of Aβ peptides, although effects were less dramatic than for presenilins mutations (Popugaeva et al., 2015; Zhang et al., 2015b). Activation of neuronal SOCE with pharmacological agents or overexpression of SOCE pathway components restored mushroom spines deficiency in hippocampal neurons from presenilin and APP-based AD mice models (Popugaeva et al., 2015; Sun et al., 2014; Zhang et al., 2016a; Zhang et al., 2015b). We proposed that proper SOCE functioning is necessary for the stability of mushroom hippocampal dendritic spines, and that initially protective downregulation of this pathway became toxic with time (Popugaeva et al., 2017; Zhang et al., 2016a). Recent results suggested that presenilin-mediated cleavage of STIM1 may contribute to SOCE dysregulation in AD (Tong et al., 2016). Pharmacological restoration of spine SOCE pathway is one potential way for drug development in AD (Zhang et al., 2016a).

In summary, various calcium signaling mechanisms are dysregulated in AD. The main question for future investigation is to determine the importance of these signaling abnormalities for synaptic and memory loss in AD. These pathways also constitute potential therapeutic targets for treatment of AD.

Calcium signaling alterations in Huntington’s and Parkinson`s diseases

Huntington’s disease is a monogenic autosomal dominant inherited neurodegenerative disorder, caused by CAG trinucleotide repeat expansion in huntingtin (*Htt*) gene (The. et al., 1993). *Htt* gene encodes huntingtin protein, which in mutant form contains expanded polyglutamine tract near the N-terminus. Expansion longer than 35 repeats results in HD, with longer polyglutamine tract leading to the earlier disease onset (Langbehn et al., 2004). GABAergic medium-sized spiny projection neurons (MSNs) of the caudate and putamen nuclei in the striatum are most affected in HD (Vonsattel and DiFiglia, 1998). Huntington’s disease is characterized by movement disorganization, mood and cognition impairments (Bates et al.). Similar to other neurodegenerative disorders Ca^{2+} signaling is dysregulated in HD (Raymond, 2017).

It has been reported that mutant huntingtin protein (mHtt) expression causes increased surface expression and currents of NR2B-bearing NMDARs, by accelerating delivery of

receptors to the plasma membrane (Chen et al., 1999; Fan et al., 2007; Zeron et al., 2002). As a result, a balance between synaptic and extrasynaptic NMDAR is shifted in MSNs (Levine et al., 2010; Milnerwood et al., 2010; Plotkin and Surmeier, 2015). The insertion of extrasynaptic NMDARs depends on activation of calpain protease and STEP phosphatase (Gladding et al., 2014; Gladding et al., 2012). Recent report demonstrated differential changes in function of NMDARs in direct and indirect striatal pathways (Botelho et al., 2014). All these findings lead to the hypothesis that imbalance in activity of synaptic (pro-survival) and extrasynaptic (pro-death) NMDARs is a key pathogenic event in HD (Levine et al., 2010; Milnerwood et al., 2010; Plotkin and Surmeier, 2015). Consistent with this idea, NMDAR inhibitor memantine displayed neuroprotective effect in experiments with HD MSN cultures (Wu et al., 2006) and treatment of HD mice with low doses of memantine ameliorated neuropathological and behavioral phenotype by suppressing activity of extra-synaptic NMDAR (Dau et al., 2014; Okamoto et al., 2009). Overall, it appears that excessive function of extrasynaptic NMDARs is one of the important reasons for synaptic loss in early HD. Indeed, some benefit of memantine was observed in a small scale trial with HD patients (Ondo et al., 2007).

Besides effects on NMDAR, mHtt is reported to bind directly to $InsP_3R1$ (Kaltenbach et al., 2007; Tang et al., 2003) and VGCC (Kaltenbach et al., 2007; Swayne et al., 2005). mHtt binding to $InsP_3R1$ increases its affinity for $InsP_3$ and enhances Ca^{2+} release from ER stores in response to activation of metabotropic glutamate receptors, mGluR1/5 (Tang et al., 2003). Inhibition of $InsP_3R1$ diminishes adverse effects of mHtt and protects striatal neurons (Tang et al., 2009; Tang et al., 2005). In addition to effects of mHtt on $InsP_3R1$, it may cause excessive Ca^{2+} leak through RyR, which also leads to depletion of internal Ca^{2+} stores (Suzuki et al., 2012a). In agreement with this observation, RyR inhibitors showed neuroprotective effects *in vitro* and improved motor behavior in YAC128 HD mice model (Chen et al., 2011b; Suzuki et al., 2012a). Recently our group demonstrated neuronal SOCE enhancement in MSNs from YAC128 HD mice, which likely results from continuous depletion of ER Ca^{2+} stores (Wu et al., 2016b; Wu et al., 2011) (Fig. 3). Moreover, expression of ER-resident protein STIM2 that controls synaptic SOCE pathway is elevated in aged YAC128 striatal cultures and in YAC128 mouse striatum. TRPC1 is a potential SOC channel subunit upregulated in response to mHtt expression (Wu et al., 2011). Inhibition of SOCE or knockdown of STIM2 resulted in neuroprotective effects and rescued dendritic spines deficiency observed in YAC128 HD mice model (Wu et al., 2016b; Wu et al., 2011). Therefore, SOCE inhibitors may constitute a potential new approach for HD treatment.

Parkinson`s disease is a movement disorder, affecting preferentially people of advanced age and characterized by selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Lees et al., 2009). The pathological hallmark of PD is the presence of alfa-synuclein intraneuronal inclusions called Lewy bodies and reduced dopamine secretion due to cell death in substania nigra (Jellinger, 2009). Similar to AD, PD is mostly sporadic disease, but approximately about 10–15% of PD cases are familial (Fleming, 2017). The genes responsible for familial PD are called PARKs, with both recessive and dominant mutations identified (Kumar et al., 2011). Pathogenic mechanisms of sporadic and familial PD are still elusive. Similar to AD and HD, effective disease-modifying therapy for PD is absent (Cacabelos, 2017). Genes associated with PD are implicated in synaptic exocytosis

and endocytosis, endosomal trafficking, autophagy and mitochondrial maintenance processes (Kumar et al., 2011; Trinh and Farrer, 2013). Strongest genetic link is with the mitochondrial biology, suggesting that mitochondrial dysfunction plays a key role in PD pathogenesis (Cieri et al., 2016). Recent data indicate that Ca^{2+} signaling dysregulation is also implicated in PD pathology (Cali et al., 2014; Zaichick et al., 2017).

SNc dopaminergic neurons display spontaneous pacemaking activity in the absence of synaptic input (Guzman et al., 2009; Puopolo et al., 2007). This pacemaking activity leads to sustained Ca^{2+} influx via L-type $Ca_V1.3$ Ca^{2+} channels (Chan et al., 2007). It has been proposed that this continuous Ca^{2+} influx makes SNc neurons selectively vulnerable by leading to basal mitochondrial oxidative stress (Chan et al., 2007; Surmeier et al., 2012; Surmeier et al., 2016). As a result, even subtle changes in intracellular Ca^{2+} homeostasis or in mitochondrial function due to advanced age or environmental factors may lead to neuronal degeneration. L-type Ca^{2+} channels play enhanced role in driving pacemaking activity of aging SNc neurons. Pharmacological inhibition of $Ca_V1.3$ L-type Ca^{2+} channels by izradipine restores Ca^{2+} - independent 'juvenile' pacemaking activity and protects SNc neurons in animal models of PD (Chan et al., 2007; Ilijic et al., 2011). Clinical use of L-type Ca^{2+} channel inhibitors dihydropyridines (DHPs) to treat hypertension has been linked to significant reduction of PD risk in retrospective studies (Becker et al., 2008; Gudala et al., 2015; Pasternak et al., 2012). Phase 3 controlled trial of izradipine in PD patients is currently in progress.

It was recently demonstrated that TRPC1 regulates the L-type Ca2+ channels activity in adult dopaminergic neurons in the SNc region (Sun et al., 2017). Store depletion and subsequent activation of TRPC1 via STIM1 inhibits the frequency and amplitude of the rhythmic activity in dopaminergic neurons (Sun et al., 2017). The death of dopaminergic neurons was induced by loss of either TRPC1 or STIM1 and it was prevented by inhibition of L-type Ca^{2+} channels (Sun et al., 2017). Moreover, application of PD-mimicking neurotoxins induced downregulation of TRPC1 and thapsigargin-mediated Ca^{2+} influx (Arshad et al., 2014; Bollimuntha et al., 2006; Bollimuntha et al., 2005). Activation or overexpression of TRPC1 protects cells against neurotoxin-mediated cytotoxicity (Arshad et al., 2014; Bollimuntha et al., 2006; Bollimuntha et al., 2005). These results suggested that impaired SOC may play a role in PD pathogenesis. Supporting the important role of SOCE for dopaminergic neurons, it was shown that expression of mutant dominant-negative form of Orai1 channel in *Drosophila* leading to downregulation of the tyrosine hydroxylase, an enzyme essential for dopamine synthesis, and the dopamine transporter, which is required for dopamine uptake after synaptic release (Pathak et al., 2015). Even more direct evidence for the role of SOC in PD was provided by the recent studies of PARK14 (Zhou et al., 2016). PARK14 is encoding Ca^{2+}- independent phospholipase A2 group 6 (PLA2g6). It was shown that skin fibroblasts from idiopathic PD patients and patients bearing familial R747W mutation in PLA2g6 gene exhibit depleted stores and reduced SOCE (Zhou et al., 2016). It was previously suggested that Pla2g6 acts as an essential component of signal transduction from the intracellular ER Ca^{2+} stores to the plasma membrane SOCE channels (Bolotina, 2008; Csutora et al., 2006; Smani et al., 2016). Impaired store-operated activation of Pla2g6 leads to SOCE downregulation and subsequent depletion of intracellular ER Ca^{2+} stores during inherited and sporadic PD (Zhou et al., 2016). ER depletion triggers autophagic

dysfunction, leading to progressive SNc neuronal loss and age-dependent PD (Zhou et al., 2016). Based on these findings, it was suggested that that Pla2g6-mediated SOCE pathway constitutes a novel potential therapeutic target for PD treatment (Zhou et al., 2016). Therefore, SOCE pathway present at attractive target for PD drug discovery.

Concluding remarks

Proper work of calcium-signaling machinery is essential for neuronal function. It is clearly demonstrated that calcium signaling dysregulation is a common feature of neurodegenerative diseases. Abnormal Ca^{2+} signaling leads to mitochondrial dysfunction and synaptic instability, and restoration of normal calcium homeostasis is a potential strategy for neurodegenerative diseases treatment. Interestingly, SOCE impairment is observed in AD, HD and PD but the nature of this disruption is unique for each disease. HD and PD both exhibit excessively depleted neuronal ER calcium stores, in contrast ER calcium stores are overfilled in AD neurons. In HD SOCE is overactivated due to ER depletion, while in PD reduced calcium levels in ER is a consequence of impaired SOCE. In AD neurons SOCE is downregulated as a compensatory response to ER Ca^{2+} overfilling. Our previous investigation indicated that synaptic spines in hippocampal and striatal neurons have an opposite sensitivity to SOCE impairments (Sun et al., 2014; Wu et al., 2016b). These differences are probably due to different downstream SOCE targets in different neuronal types. These findings have direct implications for drug discovery. It appears that inhibition of SOCE in HD and activation of SOCE in AD and PD is potentially beneficial strategy, but this approach may result in toxic effects on neuronal cells in non-target region. Molecular identity of SOCE channels in striatal and SNc neurons will be determined in the future. Development of drugs targeting particular SOCE channel isoforms may help to achieve high selectivity and to overcome a potential toxicity.

Acknowledgments

Ilya Bezprozvanny is a holder of the Carl J. and Hortense M. Thomsen Chair in Alzheimer's Disease Research. This work was supported by the R01NS080152, R01NS056224, R01AG055577 and by the Russian Science Foundation Grant 14-25-00024 (IB) (chapter Calcium dysregulation in Alzheimer`s disease, Figure 1), by the state grant 17.1360.2014/K (IB) (Calcium signaling alterations in Huntington's and Parkinson`s diseases, Figure 2), and by the grant of President of Russian Federation 14.Y30.17.1043-MK (EP) (Figure 3).

After ER Ca^{2+} depletion, STIMs oligomerize in the ER and translocate toward PM where they activate calcium entry trough interaction with Orai, TRPC channels or Orai/TRPC channels complex. Calcium current passing through Orai channels is called Ca^{2+} release-activated Ca2+ current (I_{CRAC}), non-selective cation current passing through TRPC channels or TRPC-ORAI channels complexes is called store-operated current (I_{SOC}). Activation of G-protein coupled receptor (GPCR) by extracellular ligand induces activation of phospholipase C (PLC), which subsequently hydrolysis phosphatidylinositol 4,5-bisphosphate (PIP_2) into inositol-1,4,5-trisphospahte ($InsP_3$) and diacylglycerol (DAG). $InsP_3$ activates $InsP_3R$ in the ER, which induces calcium release from the intracellular store. DAG can activate TRPC channels composed of TRPC3/6/7 isoforms directly (Jellinger, 2009). Presenilins (PS) support ER calcium leak (Bezprozvanny, 2009). Ca^{2+} can also be released from ER via ryanodine receptors (RyR) in the process of Ca^{2+} -induced Ca^{2+} release (CICR). Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) transports Ca^{2+} ions from the cytoplasm into the ER using energy of ATP hydrolysis.

In hippocampal dendritic spines SOCE is mediated by TRPC6/Orai2 channels complex (Zhang et al., 2016a). SOCE channels play a critical role in maintenance of hippocampal mushroom dendritic spines (Zhang et al., 2016a). AD-causing mutations in presenilins impair ER Ca^{2+} leak function and lead to elevation of ER Ca^{2+} levels (Tu et al., 2006b). Overfilling of ER Ca^{2+} stores causes excessive Ca^{2+} release through the $InsP_3R1$ and RyR2. It also causes compensatory downregulation of STIM2 expression, SOCE impairment and loss of mushroom spines in AD neurons.

In striatal MSN spines SOCE is gated by STIM2 (Wu et al., 2016b). Molecular identity of TRPC/Orai channels in MSN spines have not been identified yet, with TRPC1 and Orai1/2 are most likely candidates. In HD neurons mutant huntingtin protein (mHtt) binds directly to the $InsP_3R1$ and sensitizes it to basal $InsP_3$ levels (Tang et al., 2003). Ca^{2+} leak via RyR also enhanced in HD neurons (Suzuki et al., 2012b). Enhanced Ca^{2+} efflux from ER leads to chronic ER depletion and overactivation of SOCE pathway (Wu et al., 2016a; Wu et al., 2011), which appears to be toxic to striatal neurons and triggers dendritic spines loss (Wu et al., 2016b).

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Highlights

- Calcium (Ca^{2+}) signaling is dysregulated in aging neurons and in neurons affected by neurodegenerative disorders
- Elevated endoplasmic reticulum (ER) Ca^{2+} levels and reduced neuronal store-operated Ca^{2+} entry (SOCE) are linked with synaptic loss in Alzheimer's disease
- Reduced ER Ca^{2+} levels and enhanced SOCE are linked with synaptic loss in Huntington's disease
- Reduced SOCE and reduced ER Ca^{2+} levels are linked with neuronal cell death in Parkinson's disease

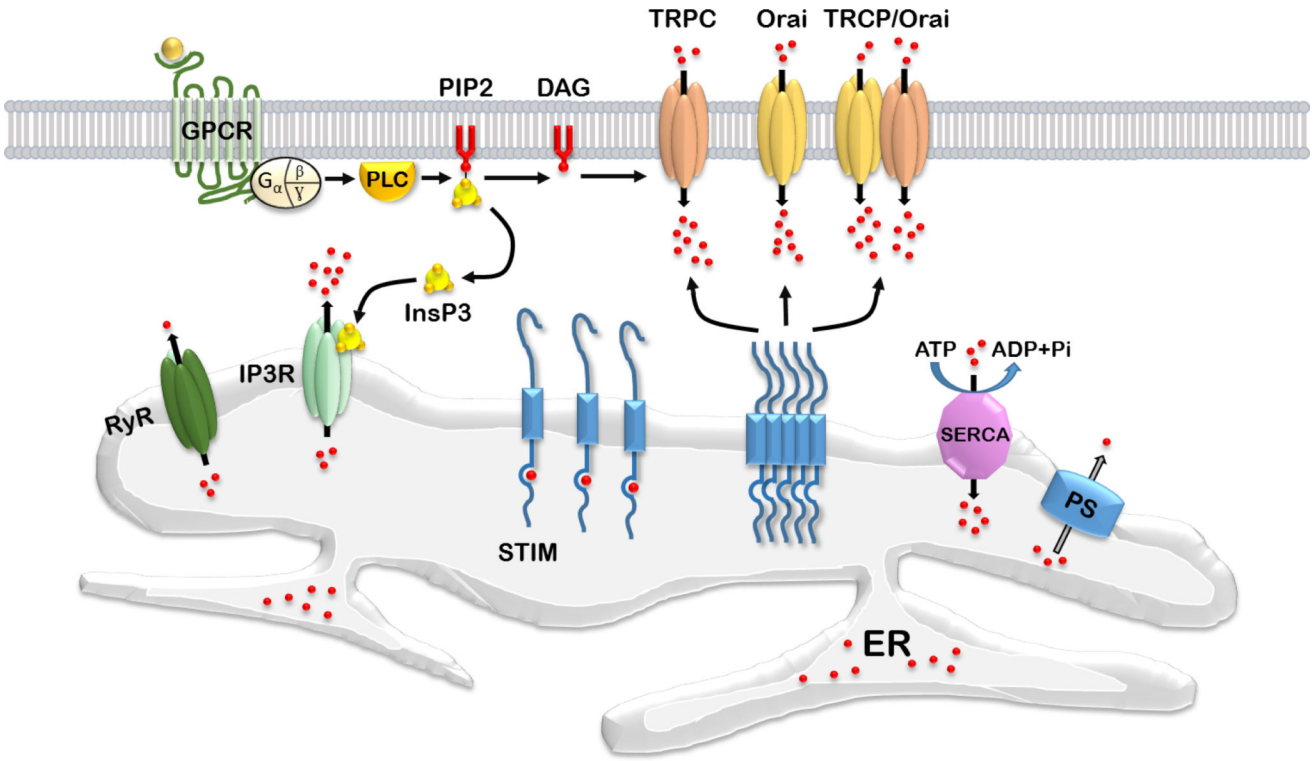

Figure 1.
SOCE in neurons.

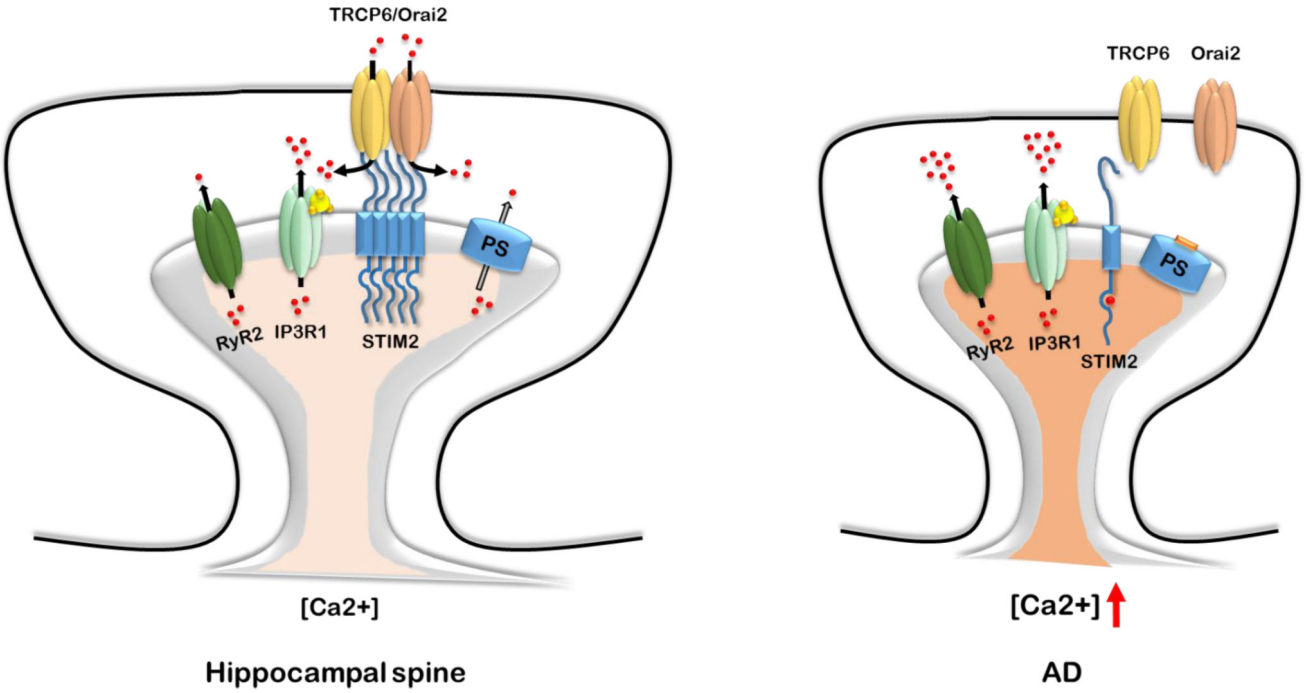

Figure 2.
SOCE impairment in AD.

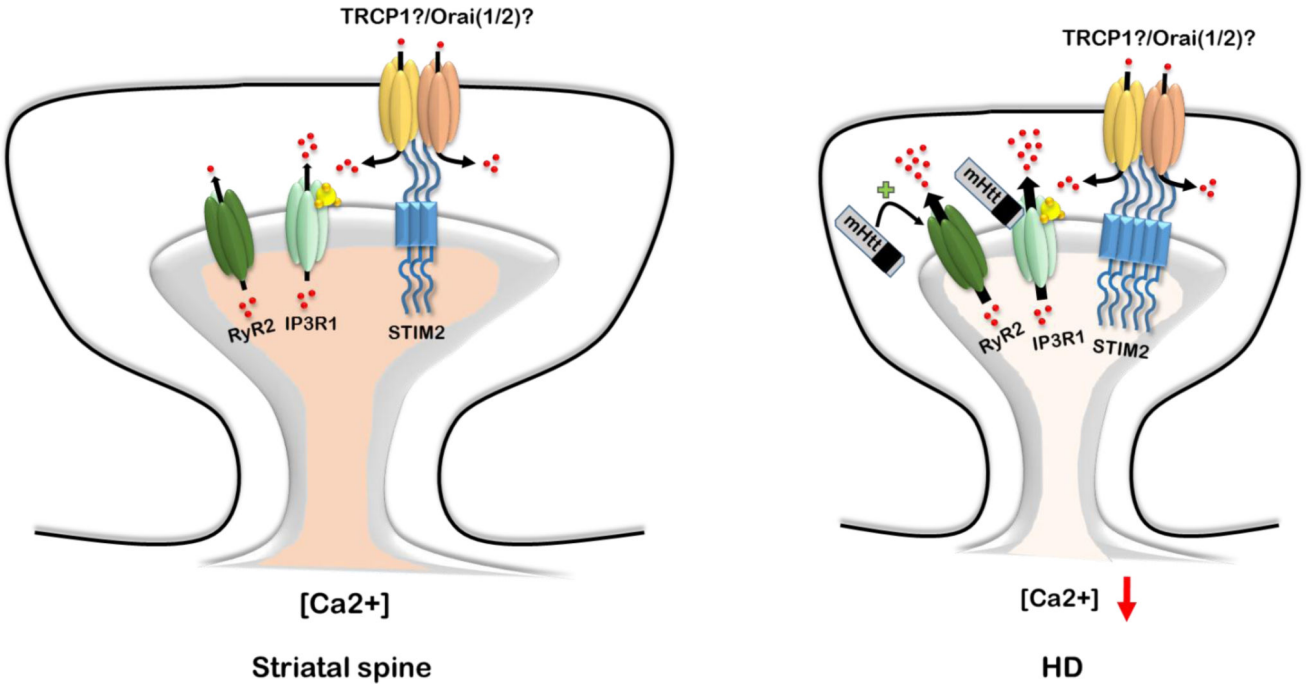

Figure 3.
SOCE impairment in HD.