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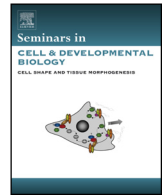

Review

Disturbed calcium signaling in spinocerebellar ataxias and Alzheimer's disease

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ABSTRACT

Neurodegenerative disorders, such as spinocerebellar ataxias (SCAs) and Alzheimer's disease (AD) represent a huge scientific and medical question, but the molecular mechanisms of these diseases are still not clear. There is increasing evidence that neuronal calcium signaling is abnormal in many neurodegenerative disorders. Abnormal neuronal calcium release from the endoplasmic reticulum may result in disturbances of cell homeostasis, synaptic dysfunction, and eventual cell death. Neuronal loss is observed in most cases of neurodegenerative diseases. Recent experimental evidence supporting the role of neuronal calcium signaling in the pathogenesis of SCAs and AD is discussed in this review.

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Abbreviations: AD, Alzheimer's disease; ADCA, autosomal dominant cerebellar ataxia; AMPA receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; APP, amyloid precursor protein; $Atx2^{mut}$, mutant ataxin-2; Aβ peptides, amyloid beta peptides; BACE1, beta site amyloid precursor protein cleaving enzyme 1; CaBPs, calcium-binding proteins; CaMKII, calcium/calmodulin-dependent protein kinase II; CAMTA1, calmodulin-binding transcription activator 1; CaN, calcineurin; Ca^{2+}, calcium; CB, calbindin D-28k; CF, climbing fiber; cGMP, cyclic guanosine monophosphate; Cyt c, cytochrome c; DUB, deubiquitinating enzyme; ER, endoplasmic reticulum; FAD, familial Alzheimer disease; HD, Huntington's disease; IICR, inositol 1,4,5-triphosphate-induced calcium release; $InsP_3$, inositol 1,4,5-triphosphate; $InsP_3R$, inositol 1,4,5-triphosphate receptor; KI, knock-in; LTD, long-term depression; LTP, long-term potentiation; MCU, mitochondrial calcium uniporter; mGluR, metabotropic glutamate receptor; Mito, mitochondria; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; nSOC, neuronal store-operated calcium; OPCA, olivopontocerebellar atrophy; Opt, *opisthotonos*; PC, Purkinje cell; PF, parallel fiber; polyQ, polyglutamine; PS, presenilin; PV, parvalbumin; Q, glutamine; QA, quisqualate; RyRs, ryanodine receptors; SCA, spinocerebellar ataxia; SOCE, store-operated calcium entry; SOC channels, store-operated calcium channels; STIM1, stromal interaction molecule 1; SUMF1, sulfatase modifying factor 1; VDCC, P/Q voltage-dependent calcium channel; 5PP, inositol 1,4,5-triphosphate-phosphatase enzyme.

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1. Spinocerebellar ataxias

Spinocerebellar ataxias (SCAs) represent a group of progressive hereditary neurodegenerative diseases that differ from each other in clinical presentation and genetic basis. At present, about 30 different genes have been identified which can be the cause of these diseases [1]. In the case of some SCAs, molecular cloning methods revealed the expansion of CAG codons that leads to lengthening of polyglutamine (polyQ) tract in appropriate proteins, such as ataxins for SCA1, SCA2, SCA3 and SCA7 or α1A subunit of P/Q voltage-dependent calcium channel (VDCC) $Ca_v2.1$ for SCA6 [2]. These diseases relate to wide group of polyglutamine disorders. In addition to this, there are some types of SCAs caused by other DNA mutations with other trinucleotide repeat expansion, nucleotide repeats in non-coding regions of appropriate genes, or non-repeat mutations and deletions.

1.1. Spinocerebellar ataxia type 2 pathogenesis

In this section we will discuss SCA pathogenesis by the example of SCA2. This disorder is accompanied by a wide spectrum of severe clinical symptoms, such as ataxia of gait and stance, ataxia of limb movements, dysarthria, ophthalmoplegia, pyramidal and extrapyramidal disorders, muscular rigidity and other severe neurological symptoms [2–4]. Clinical investigations have shown that in SCA2 patients olivopontocerebellar atrophy (OPCA) is observed. OPCA is attended with the degeneration of Purkinje cells (PCs) – large neurons located in cerebellar cortex, also with the decay of inferior olive, pontine nuclei and pontocerebellar fibers – fibers that link pons with cerebellum. In clinical trials on humans different diagnostic tests were used: starting with general biochemical analysis, including additional screening-test for paraneoplastic antibodies to PCs and also neuro-ophthalmological examination, electroretinogram and electronystagmogram analysis and in some cases – autopsy [5].

MRI-morphometric examination of infratentorial region of the brain of SCA2 patients revealed significant atrophy of the cerebellar vermis, of the cerebellar hemispheres, of pons base, of middle cerebellar peduncle, of medulla oblongata, of cervical part of spinal cord and also hypertrophy of the fourth ventricle of the brain have been observed in all cases [6].

Some proteins with expanded polyQ tracts are neurotoxic, they disturb nuclear functions by means of misfolding or in other ways. Misfolding is linked with intranuclear inclusion formation. Immunolabeling of intranuclear inclusions revealed the presence of proteosomes, ubiquitin and chaperones and this fact indicates that these inclusions contain misfolded proteins which are exposed to ineffective proteolysis [7]. Ubiquitin-positive neuronal intranuclear inclusions are detected in brains of polyQ diseases patients in the case of Huntington's disease [8], dentatorubral–pallidoluysian atrophy [9], SCA1 [10], SCA3 [11] and SCA7 [12]. However, ubiquitin-positive nuclear inclusions have not been detected in the brain of SCA2 patients [7]. Therefore, misfolding and disturbances in protein metabolism are not essential and there is some other mechanism of neurodegeneration that plays a key role in SCA2 pathogenesis.

1.2. Calcium signaling in cerebellar PCs

The assertion that calcium signaling plays an important role in PCs functioning can be confirmed by the fact that these neurons express a lot of different calcium-dependent proteins and enzymes. Thus, cerebellar PCs contain extremely high amounts of dendritic calbindin D-28k (CB) and somatic parvalbumin (PV). These proteins belong to the large family of EF-hand calcium-binding proteins (CaBPs) [13]. It was demonstrated that the loss of PV and CB leads to the alterations in $Ca_v2.1$ channels (P/Q-type VDCCs), encoded by *CACNA1A* gene [14].

Recently it was reported that regulation of calcium influx to PCs through VDCCs is very important for the right connection from a climbing fiber (CF) to a PC during postnatal development. These data were obtained via simultaneous whole-cell recordings and two-photon calcium imaging from PCs in vivo in wild type and PC-selective P/Q-type VDCC knockout mice [15]. At the same time, in earlier studies with a use of flavoprotein autofluorescence optical imaging and extracellular field potential recordings methods it was shown that derangements in the CF-PC circuitry contribute to neuronal abnormality in SCA1 mice different transgenic lines [16]. PCs also highly express calmodulin-binding transcription activator 1 (CAMTA1) and deletion of *CAMTA1* gene in mice causes severe ataxia with PCs degeneration and cerebellar atrophy [17]. It is commonly thought that long-term depression (LTD) at parallel fiber (PF) on a PC is the main basis for motor learning. PCs express calcium/calmodulin-dependent protein kinase II (CaMKII) and it has been observed that CaMKII activation leads to prolonged increase of cGMP, supporting the signaling mechanism of LTD induction by CaMKII [18].

Summing up, we can conclude that PCs express various calcium sensors to maintain intraneuronal calcium homeostasis. There are two general ways that calcium can get into the cytoplasm of PC. Both include the presence of glutamate, an excitatory neurotransmitter. The first way is calcium influx through VGCCs from the interstitial fluid. These channels are activated by the membrane depolarization, caused by the activation of AMPA receptors. The second way is the activation of metabotropic glutamate receptors (mGluR) which leads to calcium release from the endoplasmic reticulum (ER) via activating inositol 1,4,5-triphosphate receptors ($InsP_3R$) and this calcium influx is called $InsP_3$-induced calcium release (IICR).

1.2.1. $InsP_3$-induced calcium release

$InsP_3R$ is an intracellular calcium channel that mediates ion release mainly from the ER. More often $InsP_3R$ is activated by $InsP_3$ molecules and this leads to IICR. $InsP_3R$ is involved in the regulation of a large number of significant physiological processes including learning and memory, behavior, cell division and proliferation, differentiation, fertilization, development and cell death. There are three $InsP_3R$ subtypes, in neurons a predominant isoform is $InsP_3R$ type 1. There is evidence that dysfunction of $InsP_3R1$ may play a key role in the pathogenesis of certain neurodegenerative diseases. The hyperactivation of $InsP_3R1$ leads to enhanced calcium release from the ER. There is evidence to suggest that deranged neuronal calcium signaling might play an important role in pathogenesis of some neurodegenerative diseases such as Huntington's disease (HD), SCAs and AD. To support this idea, experimental studies on transgenic mice were carried out. This demonstrated a connection between abnormal calcium signaling and neuronal cell death in experiments with HD, SCA2 and SCA3 transgenic mouse models [19]. Additional data in the literature indicate that abnormal neuronal calcium signaling may also play an important role in pathogenesis of SCA1, SCA5, SCA6, SCA14 and SCA15/16. These data suggested that IICR might be one of the causes of pathophysiological processes in neurons, leading to the neurodegeneration.

1.2.2. Mutations in $INSP_3R1$ gene

$InsP_3R$ functions could be clearly identified by the observation of $InsP_3R$ mutant mice. It was demonstrated that most $InsP_3R1$ knockout mice die in the period of prenatal development and mutant mice that managed to survive have severe ataxia and tonic or tonic–clonic seizures and die by the weaning period. An electroencephalogram study with these animals revealed that they suffer

from epilepsy, indicating that $InsP_3R1$ is required for important brain function [20].

In addition to $InsP_3R1$ knock-out mice there is the *opisthotonos* (*opt*) mice colony. The *opt* mutation has appeared spontaneously in a one laboratory mice colony and is the only known, naturally occurring allele of *opt*. This mutant mouse reveals some features of ataxic and convulsive phenotype. Experimental data that were obtained in the results of genetic and molecular assays demonstrated that $InsP_3R1$ is altered in the *opt* mice. The altered protein is believed to have lost several sites of modulation and is presented at significantly decreased levels in *opt* homozygotes. In the experimental study with *opt* mice it was shown that a strong calcium release from intracellular stores can be elicited in cerebellar PCs by the effect of mGluR agonist quisqualate (QA). The calcium response in *opt* homozygotes is less than in control littermates with the same QA application. Obtained results suggest that the ataxia and convulsions phenotype observed in *opt* mice may be caused by the physiological dysfunction of $InsP_3R1$ [21].

Apart from said mutations in *$InsP_3R1$* gene there are Δ18 mice which have an in-frame deletion of 18 base pairs within exon 36 of *$InsP_3R1$* that results in the deletion in the regulatory domain. In order to corroborate the pathogenicity of this mutation, heterozygous Δ18 mice with heterozygous *opt* mice were crossed. Consequently, two litters of mice were obtained. From a total of 15 pups, four pups were affected means $InsP_3R1^{opt/\Delta 18}$ genotype. Remarkably, their phenotype was indistinguishable from that of the homozygous Δ18 and *opt* mice. Moreover, this phenotype was almost the same that in the $InsP_3R1$ knock-out mice case. As with homozygous *opt* mice, translational reading frame was unaffected and the in-frame deletion in the internal coupling domain results in significantly reduction of the level of $InsP_3R1$ expression in cerebellar Purkinje cells. So that these *$InsP_3R1$* mutations or deficiency results in the same autosomal recessive movement disorders [22]. By the way, it is commonly thought that homozygous and heterozygous Δ18 mutant mice represent mouse models for SCA15/16 [23].

1.3. Spinocerebellar ataxia type 15/16

There is evidence that SCA 15/16 is caused by mutations in the *$InsP_3R1$* gene. SCA15 was described in 2001 as rarely occurring autosomal dominant ataxia with slow manifestation. The main sign of this disorder is head tremor. Via neuroradiological methods it was shown that the atrophy of the cerebellum, especially anterior and dorsal vermis, is observed in the case of SCA15. Actually, the significance of point deletions in *$InsP_3R1$* gene to cause SCA15 is not yet confirmed. It was demonstrated that "SCA16" is caused by the *$InsP_3R1$* gene mutation, and this autosomal dominant cerebellar ataxia (ADCA) subtype has now been subsumed into SCA15 [24]. SCA15 was originally detected in an Australian family. Subsequently, two Japanese families were mapped with this ataxia type. After that, partial deletions involving both the *$InsP_3R1$* gene and sulfatase modifying factor 1 (*SUMF1*) gene have been identified in Australian and British families with SCA15. Via gene dosage analysis, array-based comparative genomic hybridization analysis, gene expression and mutational analyses, a Japanese research group identified a 414-kb deletion including the entire *$InsP_3R1$* gene and exon 1 of *SUMF1* in patients from one SCA15 family. The direct consequence of this mutation was around a 2-fold reduction in expression levels of *$InsP_3R1$* and *SUMF1* mRNAs. This data confirmed that *$InsP_3R1$* is the causative gene for SCA15 [25]. The study conducted in UK on unrelated ADCA III families ($n = 38$) by the van de Leemput research group has revealed no *$InsP_3R1$* gene mutations. Based on these results it was concluded that point mutations or deletions in *$InsP_3R1$* gene are infrequent causes of ADCA III (namely, SCA15/16) [26]. In support of this, a deletion of *$InsP_3R1$* gene was found in 6 cases out of 333 (1.8%) families, corresponding to 13 SCA15 patients. Thus based on this research it was concluded that *$InsP_3R1$* gene deletions are rare and provoke around 1% of all ADCA [27].

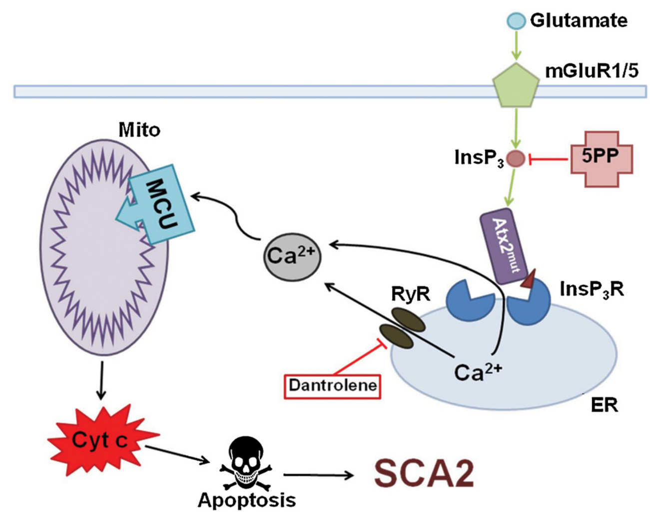

Fig. 1. Calcium hypothesis of SCA2 pathogenesis. Molecules of glutamate activate metabotropic glutamate receptor (mGluR), then inositol 1,4,5-triphosphate ($InsP_3$) molecules release into the cytoplasm and activate inositol 1,4,5-triphosphate receptor ($InsP_3R$) on the endoplasmic reticulum (ER) membrane. Next calcium influx from ER to the cytoplasm is observed and this is $InsP_3$-induced calcium release (IICR). It was shown that mutant ataxin-2 protein ($Atx2^{mut}$), but not wild type Atx2 binds with $InsP_3R$ and increases its sensitivity to $InsP_3$ molecules. Hyperactivation of $InsP_3R$ causes deranged calcium signaling in PCs. Ca^{2+} ions, greatly increased in its number, are pumped to the mitochondria (Mito) through the mitochondrial calcium uniporter (MCU) that leads to mitochondrial swelling, followed later by the rupture of outer mitochondrial membrane and next pro-apoptotic factors like cytochrome c (Cyt c) come into the cytoplasm and initiate apoptosis. Hence, dramatically increased IICR can be suppressed by adenoassociated virus-mediated expression of the $InsP_3$-phosphatase enzyme (5PP) which converts $InsP_3$ into non-active form $InsP_2$. Also calcium release from ER can be reduced via the use of dantrolene, a blocker of ryanodine receptors (RyRs).

1.4. Spinocerebellar ataxias type 2 and 3

SCA2 is an autosomal-dominant neurodegenerative disease caused by an expansion and translation of unstable CAG repeats in the gene encoding ataxin-2 from the normal 22 to more than 31 extra glutamine repeats [28]. Up until now the pathogenesis of SCA2 is not clear. Similar to wild type ataxin-2, polyglutamine-expanded mutant ataxin-2 protein is expressed in every cell type without severe aggregation and formation of inclusion bodies [29], but PCs in SCA2 patients are mostly affected with a loss of over 75% [2].

The experiments conducted by our research group have revealed that mutant ataxin-2 protein, but not wild type ataxin-2, interacts with the carboxyl terminus of the $InsP_3R1$ (Fig. 1). These experiments were performed in a lipid bilayer model system, examining the effect of mutant ataxin-2 expression on $InsP_3R1$ activation in single channel recordings of $InsP_3R1$ co-expressed with mutant ataxin-2. It was discovered in these experiments that the presence of mutant ataxin-2 substantially sensitized $InsP_3R1$ to activation by $InsP_3$ [30]. Consistent with these findings, another group demonstrated that both wild type and mutant ataxin-2 proteins associate with ER membranes [31].

In addition to experiments conducted on lipid bilayers, calcium imaging experiments in primary PCs cultured from SCA2-58Q transgenic and wild-type mice were performed. It was shown that there was a significant increase in calcium release from ER stores via $InsP_3R1$ in the case of mutant mice PCs, but this effect was

not observed in wild-type mice PCs. To block ryanodine receptors (RyRs) and ER calcium release in PC cultures ryanodine or dantrolene were added (Fig. 1). The effect of mutant ataxin-2 expression was immediately reversed as ER calcium release returned to wild type levels. Thus it was suggested that dantrolene and ryanodine provided this protection by inhibiting Ca^{2+} signals that is induced from IICR that is amplified by the RyR [30].

The test the hypothesis that Ca^{2+} release from the PC ER plays a key role in the development of SCA2, chronic suppression of $InsP_3R$-mediated Ca^{2+} signaling was achieved by adeno-associated virus-mediated expression of the $InsP_3$-phosphatase enzyme (5PP) in PCs of a SCA2-58Q transgenic mouse model (Fig. 1) [32]. It was determined that recombinant 5PP overexpression alleviated age-dependent dysfunction in the firing pattern of SCA2 PCs. Further it was discovered that chronic 5PP overexpression also rescued age-dependent motor incoordination and PC death in SCA2 mice. These findings support the important role of supranormal Ca^{2+} signaling in SCA2 pathogenesis and suggest that partial inhibition of IICR could provide therapeutic benefit for the patients afflicted with SCA2 and possibly other SCAs [32].

SCA3 is also an autosomal-dominant neurodegenerative disorder caused by a polyglutamine expansion in the carboxy-terminal of ataxin-3 protein [33]. Morphologically, SCA3 is characterized by degeneration of spinocerebellar tracts, dentate nucleus, pontine and other brainstem nuclei, substantia nigra and pallidum [34]. In SCA3 patients, magnetic resonance imaging (MRI) techniques revealed cerebellar atrophy, which is less pronounced than in SCA2 in combination with brainstem atrophy. It is interesting, that, unlike SCA2 pathogenesis, nuclear inclusions have been found containing mutant ataxin-3 in neurons of affected brain regions. The clinical picture of SCA3 is characterized by a wide range of clinical manifestations, similar to SCA2 symptoms [35]. It was shown that ataxin-3 protein contains 3 ubiquitin-interactions motifs and an amino-terminal Josephin domain, that testifies to ataxin-3 functions as deubiquitinating enzyme (DUB). Moreover, it was demonstrated that the polyQ-expansion has no effect on DUB activity of ataxin-3 [36], so it is likely that neuropathology in SCA3 develops due to gain of toxic function. Normal function of ataxin-3 has been shown to be the repression of transcription via chromatin binding, interaction with histone deacetylase 3, and histone deacetylation [37]. Further in transfected mouse neuroblastoma N2a and human embryonic kidney 293T cells it was discovered that the aggregation of mutant ataxin-3 could be suppressed by the inhibition of the Ca^{2+}-dependent protease, calpain [38]. Similar to mutant ataxin-2, in a lipid bilayer model system it was shown that mutant ataxin-3 but not wild type ataxin-3 binds to and activates $InsP_3R1$. Thus, calcium release from ER through $InsP_3R1$ is rising. Moreover, long-term feeding of SCA3-YAC-84Q transgenic mice with Ca^{2+} stabilizer dantrolene alleviated age-dependent motor coordination deficits in this mice and prevented neuronal loss in affected neurons [39]. Also, just as in the SCA2 case, these improvements can be explained by inhibiting Ca^{2+} signals that is induced from abnormal IICR that is extra amplified by the RyR in neurons.

These results support the hypothesis that abnormal neuronal Ca^{2+} signaling through the $InsP_3R1$ may play a key role in the pathogenesis of many polyglutamine expansion neurodegenerative disorders [19,40]. The same hypothesis also supported by an independent genetic analysis of human ataxias [41].

2. Alzheimer disease

Alzheimer disease (AD) is a neurodegenerative disorder that affects the human brain. AD destroys brain areas that are involved in memory formation, consolidation and storage. There are two forms of AD: sporadic AD, the main risk factor being advanced age; and familial AD (FAD) that is genetically inherited and caused by mutations in genes encoding amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) proteins. Presenilins together with nicastrin, APH-1 and PEN-2 form the γ-secretase complex. This protease complex is transported to the cell surface and endosomes where it cleaves several substrates including APP. Cleavage of APP by β- and γ-secretase constitutes the amyloidogenic pathway that leads to production of toxic amyloid beta (Aβ) peptides. Aβ peptides self-aggregate and form oligomeric species (nowadays considered to be the most toxic species) as well as fibrils. The amyloid hypothesis is the dominant one; however, all attempts that tried to clear the brain of Aβ aggregates have failed. Therefore, other hypotheses including the calcium hypothesis of AD are gaining popularity.

2.1. Deranged calcium signaling in AD

Disruption of calcium (Ca^{2+}) signaling has been proposed to be involved in the pathogenesis of AD [42]. Ca^{2+} is a major second messenger that is involved in many cellular processes starting form dividing of cells during embryogenesis and ending in cell death. Due to the fact that Ca^{2+} is so important for living cells and especially for neurons different questions impugning Ca^{2+} hypothesis arise. For example, is it possible to specifically block Ca^{2+} channels in the brain and do not affect function of similar channels in other excitable tissues such as muscles? To answer this question it is important to understand the full signaling pathway that is disrupted in neurodegenerative disorder, in our case in AD. Moreover, the knowledge of function of every single molecule involved in the signaling pathway is necessary, as the example of the γ-secretase inhibitor semagacestat demonstrates [43]. Semagacestat-treated AD patients displayed significantly worsened functional ability, were predisposed to cancer, infections and inflammation when compared to placebo-treated patients [43]. The reasons of this are (a) APP is not the major substrate for γ-secretase, γ-secretase also cleaves Notch protein, (b) γ-secretase is not a single protease it has four variants [44] probably with different substrate preferences [45]. Eventual blocking of Notch signaling caused the side effects (gastrointestinal, infection, and skin cancer related) observed in treated patients [46].

2.2. Gamma-secretase inhibitors as modifying therapy of AD

Another direction for development of AD modifying therapies is the search of specific inhibitors of β-secretase BACE1 (beta site amyloid precursor protein cleaving enzyme 1). A number of β-secretase inhibitors have been proposed [47–50]. However, after the dramatic story with γ-secretase inhibitors more attention is being put into the investigation of potential side effects of BACE 1 inhibitors. Similarly to γ-secretase, BACE1 has multiple substrates [51–55] and a big catalytic site [56] that make development of pharmaceutical blockers difficult. There are data showing that loss of BACE1 leads to developmental impairments such as peripheral hypomyelination [52,53], defects of axon guidance [54,57,58], disrupted synaptic functions [59,60], retardation of growth, and increased early lethality [61]. Recently it has been shown in mice that blocking of BACE1 with high doses (100 mg/kg) of the inhibitors SCH1682496 (from Merck) or LY2811376 (from Lilly) caused a decrease in spine formation of layer V pyramidal neurons, a reduced rate of spontaneous and miniature excitatory postsynaptic currents in pyramidal neurons and reduced hippocampal long-term potentiation [62]. However, administration of lower doses (30 mg/kg) of the same BACE1 inhibitors did not cause such side effects [62]. Taken together, it seems to be a long way until specific BACE1 inhibitors that could be applied to AD patients will be developed.

2.3. New therapeutic targets in AD treatment

What other directions of the calcium hypothesis may bring new therapeutic targets? We recently have shown that presenilins function as a passive low conductance ER Ca^{2+} leak channels [63,64]. The "leak channel hypothesis" of presenilin function was initially received with skepticism [65], but was recently validated in independent studies [66,67]. Some but not all FAD associated mutations in PS disrupt this function leading to overfilling of ER with Ca^{2+} [63,64,68,69]. To compensate for ER store overloading the neuron can upregulate the function of other ER Ca^{2+} releasing channels such as $InsP_3R1$ and RyRs. Certainly the involvement of these channels in AD pathogenesis has been shown. It has been observed that mutant presenilins activate the $InsP_3R$ [70]. Increased expression of RyR has been reported in multiple studies including FAD models as well as in AD patients [69,71–74]. Consequently it has been proposed that upregulation of RyRs expression at early stages of AD may be a compensatory mechanism for early Ca^{2+} dysregulation and synaptic failure [75], however over the time overactivation of RyRs become toxic. There is a number of studies that administered an antagonist of RyR dantrolene to mouse models of AD and observed a therapeutic effect [76–78]. However, there is another study from our lab showing that long-term oral feeding of dantrolene induced plaques formation and resulted in loss of hippocampal synaptic markers [69]. Since dantrolene does not effectively block neuronal subtypes of RyR 2 and 3, being specific only for skeletal muscle RyR1 [79], the development of highly specific antagonists of neuronal RyRs are needed. In the absence of such inhibitors our laboratory recently took an advantage of RyR3 knockout mice. These genetic experiments with AD mouse models revealed that RyR3 plays protective role at early stages of AD pathology but becomes detrimental at late stages of pathology [80]. These results suggested that RyR inhibitors are likely to be therapeutically useful at late stages but not at early stages of the disease.

Another source of Ca^{2+} for the cell is store-operated calcium entry (SOCE) which has been first observed in non-excitable cells (reviewed in [81]) and lately in neurons [82,83]. SOCE is mediated by SOC channels. Well described SOC channels are STIM1-regulated Orai1/TRPC [84]. SOC channels are unique in the nature of their activation. They are activated in response to lowering of Ca^{2+} content in the ER. Recent evidence suggests that SOCE may play a role in the pathogenesis of neurodegenerative disorders, particularly in AD [85–88]. In our recent publication we have observed that in response to ER Ca^{2+} overload neuronal SOC (nSOC) is downregulated in the M146V-KI (KI) mouse model of AD [89]. Moreover, we observed that the homologue of STIM1, STIM2 plays a dominant role in mediating nSOC in hippocampal spines. Why do neurons need nSOC when they already have so many sources of Ca^{2+} such as NMDAR, AMRAR, VGCC? The answer is that NMDAR, AMRAR, VGCC are sources of fast and massive Ca^{2+} influx and active only when the neuron is depolarized, they are silent at rest. As we observed, neurons need constant Ca^{2+} influx in order to support the stability of mushroom spines [89], neuronal structures involved in memory storage [90]. Such a source of constant Ca^{2+} influx in hippocampal spines is nSOC [89,91]. Our results suggested that nSOC activity is necessary for proper function of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [89]. We discovered that activity of synaptic CaMKII is reduced in response to nSOC decrease [89]. CaMKII is a so called memory molecule. Its activity is associated with formation of long-term potentiation (LTP) and it is highly expressed in synaptic spines. Most likely the decrease in CaMKII expression is mirrored by increased expression of calcineurin (CaN). Indeed, CaN activity is enhanced in aging neurons and plays an important role in increased long-term depression (LTD) [92,93]. The same pathway is disrupted in aging neurons, and in sporadic AD brains [89,94]. Importantly, genetic rescue of this pathway in KI mice restores mushroom spines as well as expression of synaptic proteins PSD95 and rescues CaMKII activity [89]. Thus, we propose that in KI neurons M146V mutation in presenilin 1 causes disruption of ER Ca^{2+} leak function of presenilin 1, which causes ER Ca^{2+} overload, compensatory downregulation of STIM2 protein and inhibition of nSOC. This leads to reduced activity of synaptic CaMKII, loss of mushroom spines and cognitive decline (Fig. 2). Reduction of CaMKII activity could explain impaired late form of LTP observed in KI mice [95]. We propose that the pharmacological activators of STIM2-nSOC constitute attractive therapeutic targets for AD.

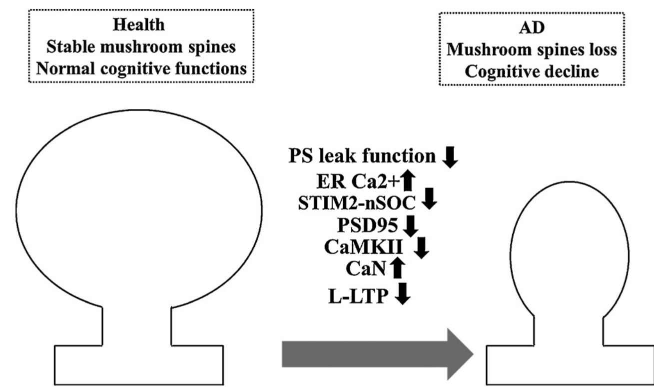

Fig. 2. The schema representing recently discovered signaling pathway that is disrupted in M146V-KI mouse model of AD. M146V mutation in presenilin 1 (PS) causes loss of ER Ca^{2+} leak function of PS that leads to downregulation of neuronal store-operated Ca^{2+} entry mediated by STIM2-dependent nSOC channels. nSOC is necessary for the stability of mushroom spines that store memory. Reduced nSOC causes decrease in expression of CaMKII (well-studied "memory" molecule) [89]. Lowering of CaMKII activity could underlie impaired late form of LTP observed in KI mice [95]. Eventually this leads to mushroom spine loss and cognitive decline.

3. Conclusion

Calcium signaling is involved in the regulation of important physiological processes, including learning and memory, behavior, cell division and proliferation, differentiation, development and cell death. Derangement in calcium signaling plays a significant role in numerous neurodegenerative diseases such as different types of SCAs and AD. In SCAs perturbation of $InsP_3R$ functions results in abnormal Ca^{2+} signaling, more often in the increasing of IICR from ER. So $InsP_3R$ represents a potentially effective drug target for treatment of some polyglutamine neurodegenerative diseases via normalization of the enhanced Ca^{2+} signaling in affected neurons.

To date, attempts have been made to repress IICR in the context of neurodegenerative diseases. Thus, a chronic suppression of IICR was achieved by viral expression of the $InsP_3$-phosphatase enzyme in PCs of the SCA2-58Q mouse model. This resulted in improvement of the neuropathological and behavioral phenotypes of the disease [32]. Also IICR might be pharmacologically inhibited with caffeine [96] and by therapeutic levels of lithium in the presence of neuronal calcium sensor-1 [97]. Of course, there are several other hypothetical approaches that could affect the IICR. So, future studies will provide us more information about physiological functions of $InsP_3R$ in physiology and pathology and will give us new ways to search for treatments for these incurable neurodegenerative diseases.

There is much evidence to suggest that deranged Ca^{2+} signaling plays a significant role in AD pathology. Based on experimental results it can be concluded that the various calcium-dependent channels and pumps in the ER take part in the alterations of intracellular Ca^{2+} signaling in AD. Some changes in the Ca^{2+} signaling observed in AD can lead to neuronal degeneration, but some alterations in calcium level may be compensatory. Further study of the

role of deregulated calcium signaling in neurodegeneration in AD will be very important for the future design of effective disease-modifying therapeutics.

Disclosures

IB is a paid consultant to Ataxion and TEVA in the field of neurodegeneration. Other authors have no financial interests related to this work.

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