Role of endoplasmic reticulum Ca$^{2+}$ signaling in the pathogenesis of Alzheimer disease

Elena Popugaeva$^1$ and Ilya Bezprozvanny$^{1,2,*}$

$^1$ Laboratory of Molecular Neurodegeneration, Saint Petersburg State Polytechnical University, Saint Petersburg, Russia
$^2$ Department of Physiology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

*Correspondence: Ilya Bezprozvanny, Department of Physiology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75358-9040, USA e-mail: ilyabez@southwestern.edu

INTRODUCTION

Calcium (Ca$^{2+}$) is one of the most important second messengers in the nervous system. Ca$^{2+}$-mediated signal transduction connects membrane excitability and biological functions of neurons ranging from proliferation, secretion, gene expression, ATP production, cell death to memory formation and its loss. Acting at the border of electrical and signaling "worlds" of the cell, Ca$^{2+}$-permeable channels play a major role in many key aspects of neuronal functions. Due to the huge importance of the calcium as the second messenger neurons utilize many approaches to regulate intracellular Ca$^{2+}$ content, mainly via local signal transduction pathways. Neuronal Ca$^{2+}$ influx can be maintained by different Ca$^{2+}$-permeable channels, such as voltage-gated Ca$^{2+}$-channels of plasma membrane, N-methyl-d-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, nicotinic receptors, store-operated Ca$^{2+}$-channels (SOC). Ca$^{2+}$ can also be released from intracellular stores of endoplasmic reticulum (ER) via inositol-1,4,5-trisphosphate receptors, ryanodine receptors, presenilins as ER Ca$^{2+}$ leak channels, and neuronal SOC channels. We discuss how function of these channels is altered in AD and how important are resulting Ca$^{2+}$ signaling changes for AD pathogenesis.

Keywords: Alzheimer disease, Ca$^{2+}$ signaling, presenilins, endoplasmic reticulum, inositol trisphosphate receptors, ryanodine receptors, store-operated Ca$^{2+}$ channels, dantrolene

Alzheimer disease (AD) is a major threat of twenty-first century that is responsible for the majority of dementia in the elderly. Development of effective AD-preventing therapies are the top priority tasks for neuroscience research. Amyloid hypothesis of AD is a dominant idea in the field, but so far all amyloid-targeting therapies have failed in clinical trials. In addition to amyloid accumulation, there are consistent reports of abnormal calcium signaling in AD neurons. AD neurons exhibit enhanced intracellular calcium (Ca$^{2+}$) liberation from the endoplasmic reticulum (ER) and reduced store-operated Ca$^{2+}$ entry (SOC). These changes occur primarily as a result of ER Ca$^{2+}$ overload. We argue that normalization of intracellular Ca$^{2+}$ homeostasis could be a strategy for development of effective disease-modifying therapies. The current review summarizes recent data about changes in ER Ca$^{2+}$ signaling in AD. Ca$^{2+}$ channels that are discussed in the current review include: inositol trisphosphate receptors, ryanodine receptors, presenilins as ER Ca$^{2+}$ leak channels, and neuronal SOC channels. We discuss how function of these channels is altered in AD and how important are resulting Ca$^{2+}$ signaling changes for AD pathogenesis.
hypothesis of AD. This hypothesis was first formulated in 1987 by Dr. Zaven Khachaturian who proposed that sustained changes in intracellular calcium homeostasis provide the final common pathway for AD and age-associated changes (Khachaturian, 1987). Since that time many advances in our understanding of Ca\(^{2+}\) signaling in AD have been obtained. New Ca\(^{2+}\) permeable channels have been identified, some of them directly linked to AD. For example, it has been demonstrated that presenilins encode passive ER Ca\(^{2+}\) leak channels (Tu et al., 2006) and a novel Ca\(^{2+}\) channel called Ca\(^{2+}\) homostasis modifier 1 (CALHM1) has been linked to late-onset AD by genetic evidence (Drees-Werringloer et al., 2008). However, as it usually happens with new findings, the existence of these novel Ca\(^{2+}\) channels and their role in AD has been challenged. The main purpose of the current paper is to review recent publications in the field of ER Ca\(^{2+}\) signaling in the context of AD pathology. We will review the role of two well accepted ER Ca\(^{2+}\) channels that release Ca\(^{2+}\) out of the neuronal ER – InsP3R and Ryan. We will also discuss new findings about the role of presenilins and neuronal SOC in neuronal function. Our focus will be on potential role of these channels in AD pathology and as targets for development of disease-modifying therapies.

**INOSITOL TRISPHOSPHATE RECEPTORS**

The first observation of exaggerated InsP3-mediated Ca\(^{2+}\) release from ER in fibroblasts from AD patients has been obtained even before the identification of presenilins (Ito et al., 1994). It was later shown that these fibroblasts (from patients AG06840 and AG06848) harbor A246Q mutation in \(\text{PSEN1}\) (description in Coriell Institute Cell Database). The studies with fibroblasts taken from PS1-M146V knockin mice and with Xenopus oocytes expressing human presenilin proteins 1 and 2 (PS1 and PS2) mutant constructs showed an upregulation of InsP3R-mediated Ca\(^{2+}\) release (Lassang et al., 1999b, 2000). Experiments in cortical neurons using whole-cell patch clamp and rapid Ca\(^{2+}\) imaging in brain slices from mutant PS1-M146V mice also demonstrated almost threefold exaggeration of ER Ca\(^{2+}\) liberation by photolysis of caged InsP3 and accompanying enhancement of Ca\(^{2+}\)-evoked outward membrane currents (Stutzmann et al., 2004). Similar results of enhanced InsP3-evoked Ca\(^{2+}\) signals were observed in Tg2576 mice (Stutzmann et al., 2004). Important to note that the Ca\(^{2+}\) disturbances were already observed in the 3xTg-AD mice at the age of 4–6 weeks that precedes appearance of A\(^{\beta}\) plaques and NFTs by several months (Oddo et al., 2003). Later on it has been taken from PS1-M146V knockin mice and with \(\text{CALHM1}\) (AG06840) (Popugaeva and Bezprozvanny ER calcium and AD 2010). Although detrimental effect of A\(^{\beta}\) oligomers on neurons has been extensively studied and many publications demonstrated that A\(^{\beta}\) aggregates promote the increase in cytosolic Ca\(^{2+}\) content of neurons (Walsh et al., 2002; Demuro et al., 2005, 2010; Deshpande et al., 2006; Simakova and Arispe, 2007; Bezprozvanny and Mattson, 2008; Green and LaFerla, 2008; Kuchibhotla et al., 2008), the exact mechanism how A\(^{\beta}\) contributes to disruption of Ca\(^{2+}\) signaling is not known. Therefore, the studies of Demuro and Parker (2013) and Renner et al. (2010) could potentially provide a connection between amyloid and overactivation of InsP3R-mediated Ca\(^{2+}\) signals.

**RYANODINE RECEPTORS AND EFFECTS OF DANTROLENE**

Ryanodine receptors are expressed in soma, proximal dendrites as well as in distal processes and spines. Ryanodine activity is enhanced in dendrites and synaptic spines from presymptomatic 3xTg-AD and TASTPM (APP/PS1-M146V; Howlett et al., 2004) AD mice (Goussakov et al., 2010). RyanR-mediated Ca\(^{2+}\)-induced Ca\(^{2+}\) release (CICR) in 3xTg-AD mice is exaggerated in response to synaptic stimulation, including NMDAR-mediated Ca\(^{2+}\) influx (Goussakov et al., 2010). These authors proposed that enhanced synaptic CICR may alter synaptic function and may be recognized
as an early pathogenic factor in AD (Gourasak et al., 2016). Increased levels of RyR are at least partially responsible for enhanced CICR in AD neurons. Increased expression of RyR is not limited to AD and has been described in human AD cases and in patients with mild cognitive impairment (MCI, Kelber et al., 1999; Bruno et al., 2012). Elevated RyR expression, cognitive decline, and synaptic loss observed in MCI patients are mirrored by an increase in RyanR2 expression and Ca2+ release in presymptomatic AD mice (Kellih er et al., 1999; Stutzmann et al., 2006; Chakroborty et al., 2009; Zhang et al., 2010b). Recently, it has been suggested that increased RyR expression at early stages of AD might play a role as a compensatory mechanism to stabilize the preexisting synaptic deficits and normalize the depressed synaptic network (Chakroborty et al., 2012b). Similar idea of elevated RyanR expression as a neuroprotective response to AP1–42 toxic effects has been suggested before (Supnet et al., 2010).

Several studies addressed the role of RyanR in the context of AD by using pharmacological agent dantrolene. Dantrolene is an antagonist of the RyanR and is used clinically to treat malignant hyperthermia, neuroleptic malignant syndrome, and muscle spasms (Krause et al., 2004; Inan and Wu, 2010). In the first study the dantrolene was administered to 3xTg-AD mice by intracerebroventricular (ICV) injection for 3 months using an Alzet intracranial ventricular infusion system and then subcutaneously three times per week for 8 month (Peng et al., 2012). The authors stated that dantrolene treatment significantly reduced both memory deficits tested by Morris water maze test and amyloid plaque load in the hippocampus in 13-month-old 3xTg-AD mice (Peng et al., 2012). The second work performed sub-chronically short-term (4 weeks) treatment of AD models (3xTg-AD and TATPSM) with dantrolene (Chakroborty et al., 2012a). Using two-photon Ca2+ imaging and patch clamp recordings authors showed that dantrolene treatment normalized ER Ca2+ signaling within somatic and dendritic compartment in early and late-stage AD mice in hippocampal slice experiments (Chakroborty et al., 2012a). The third study (Oules et al., 2012) was performed with transgenic mice expressing human APP– precursor mutation (Tg2576). These authors observed that dantrolene treatment diminished Aβ load, reduced histological lesions, and slowed down learning and memory deficits in Tg2576 mice (Oules et al., 2012). These studies suggested that inhibition of RyanR with dantrolene may exert beneficial effects in the context of AD pathology. However, opposite conclusion was obtained by September 2013 Volume 6 Article 29 Frontiers in Molecular Neuroscience www.frontiersin.org Popugaeva and Bezprozvanny ER calcium and AD (Krause et al., 2004), and does not block neuronal RyanR2 and RyanR3 subtypes effectively. To resolve this controversy, our laboratory is currently taking a genetic approach to evaluate a role of RyanRs in AD. Our initial results indicate that RyanR may play initially compensatory and later detrimental role in the context of AD pathology.

Taking together, it is clear from multiple studies with various AD cellular and animal models that ER Ca2+ signaling is disturbed in AD and that activity of both InsP3R and RyanR is enhanced. Increased expression of RyanRs at least partially responsible for enhanced CICR in AD neurons. The mechanisms responsible for enhanced activity of InsP3R are less certain and may involve direct gating of InsP3R by presenilins. It is also likely that increased ER Ca2+ levels contribute to enhanced RyanR-mediated and InsP3R-mediated Ca2+ release, as discussed in more details in the following section. It also appears that RyanR is a potential pharmacological target for AD treatment and that dantrolene may provide potential avenue for suppressing RyanR activity in AD.

**Prese-nilins**

There are mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2), and APP genes that are linked to early onset FAD. The majority, nearly 200, of these mutations are within PSEN1. To date many known PSEN1 mutations contribute to Ca2+ disruptions in ER Ca2+ signaling (Berezovska and Mattson, 2008). PS1 and PS2 constitute the catalytic core of the γ-secretase complex, other part- ner of the complex are nicastrin, aph-1, and pen-2 (De Strooper, 2003). The γ-secretase complex cleaves type-1 transmembrane proteins, including Notch receptor protein and APP. One of the main therapeutic approaches to AD is focused on development of γ-secretase inhibitors (GSIs) and modulators, however so far this approach has failed in phase III clinical trials of Eli-Lilly’s Semagacestat, a non-selective GSI (Doody et al., 2013). Semagacestat treatment resulted in worsen cognition scores and increase in the risk of skin cancer (Doody et al., 2013), most likely due to inhibition of Notch processing. As a result, clinical trials of GSIs have been halted.

In addition to contributing to altered γ-secretase function in AD pathogenesis, FAD PS mutations result in disturbed Ca2+ signaling in neurons (reviewed in Stutzmann, 2007; Berezovska and Mattson, 2008; Supnet and Bezprozvanny, 2010a,b). As discussed above, multiple studies demonstrated enhanced InsP3R-mediated and RyanR-mediated ER Ca2+ release in PS-FAD cells. Presenilin mutations also affected SOC, a refilling mechanism for ER stores (Leisring et al., 2000; Ito et al., 2000; Giacomello et al., 2005; Zhang et al., 2010b). To explain these findings, it was sug- gested that gating of InsP3R or RyanRs directly modulated by presenilins (Cheung et al., 2008, 2010; Rybalchenko et al., 2008). It was also suggested that presenilins potenti ate activity of sarco/endoplasmic reticulum Ca2+ ATPase (SERCA; Green et al., 2008), a mechanism that could contribute to the overfilling of ER Ca2+ stores.

Another potential problem with interpreting these results is that specific RyanR inhibitors do not exist and the drug dantrolene used in most studies has additional targets such as store-operated Ca2+ channels (Zhao et al., 2006). Moreover, dantrolene is specific for skeletal muscle RyanR1 (Krause et al., 2004), and does not block neuronal RyanR2 and RyanR3 subtypes effectively. To resolve this controversy, our laboratory is currently taking a genetic approach to evaluate a role of RyanRs in AD. Our initial results indicate that RyanR may play initially compensatory and later detrimental role in the context of AD pathology.
function as ER Ca\[^{2+}\] leak channels (Tu et al., 2006), which function to maintain ER Ca\[^{2+}\] homeostasis by constantly leaking Ca\[^{2+}\] into the cytosol and balancing SECA activity. Our results suggested that presenilin holoprotein function as low conductance passive ER Ca\[^{2+}\] leak channel, and that ER Ca\[^{2+}\] leak function of presenilins does not depend on their \(\gamma\)-secretase activity (Tu et al., 2006). Moreover, we found that some, but not all, FAD PS mutations disrupt Ca\[^{2+}\] leak function (Tu et al., 2006; Nelson et al., 2007, 2010), leading to the overfilling of ER with Ca\[^{2+}\] and exaggerated ER Ca\[^{2+}\] release observed in PSEN1/PSEN2 FAD mutants fibroblasts (Tu et al., 2006; Nelson et al., 2007, 2010), cultured hippocampal neurons from 3xTg AD neurons (Zhang et al., 2010b), and primary lymphoblasts from FAD patients (Nelson et al., 2010). These data suggest that mutations in presenilins directly linked to deranged Ca\[^{2+}\] signaling and neuronal dysfunction in AD by causing ER Ca\[^{2+}\] overload. Our hypothesis has been directly challenged, in particular by the group of Dr. Kevin Foskett (Shilling et al., 2012). These authors claimed that presenilin does not have a pore and cannot act as an ion channel (Cheung et al., 2008; Shilling et al., 2012). As we previously outlined, a number of serious technical and experimental issues exists with their negative arguments (Bezprozvanny et al., 2012). Other experiments that oppose to our hypothesis have also been reported (Zatti et al., 2004, 2006). In contrast to our finding, the authors of these papers observed that FAD-PS expression lower the ER calcium content (Zatti et al., 2004, 2006). Despite existence of these controversial results independent experimental support for leak function of presenilin recently began to accumulate (Das et al., 2012). In a recent study, Bandara et al. (2013) performed an unbiased RNAi-based screen for modulators of calcium homeostasis in HEK293 cells. They transfected 250 candidate short-interfering RNAs (siRNAs) into the cells and used the mathematical model to quantify the effects of knockdown on calcium pump and leak rates, which resulted in the identification of proteins involved in the elusive ER Ca\[^{2+}\] leak pathway. Knocking down presenilin-2 or ORAI2 dramatically reduced ER calcium leak rate, and knocking down PEN-2, encoded by PSENEN, greatly increased calcium leak rate (Bandara et al., 2013). Knockdown of PSENEN would inhibit proteolytic processing of presenilins and thus increase the holoprotein structure of archeal homolog of presenilin (PSH; Li et al., 2013). These authors discovered that PSH has a large hole that transverse Ca\[^{2+}\] from PS1-M146V knock in mice exhibit significant impairments in store-operated Ca\[^{2+}\] entry after stimulation of cells with bradykinin. These authors suggested that impaired SOC in these cells is due to elevated ER Ca\[^{2+}\] levels in PS1-M146V fibroblasts (Leissring et al., 2000). In the same year Yoo et al. (2000) reported alteration in SOC activity in presenilin FAD mutant neurons. Two different mechanisms of mutant PS1-mediated dysregulation of SOC have been proposed (Herms et al., 2003). The first mechanism is linked to direct attenuation of SOC at the cell surface, the second mechanism evokes changes in processing of APP and generation of amyloid peptides (Herms et al., 2003). However, second mechanism cannot explain alteration of SOC observed in the absence of human APP and Aβ42 accumulation. TRP channels may play a role in disruption of neuronal SOC in AD (Santamato et al., 2007), but the mechanisms involved in changes in TRP channel expression or activity in AD are poorly understood.

In addition to TRP channels, important players of SOC in excitable and non-excitable cells are stromal interaction molecule 1 and 2 (STIM1 and STIM2), which mediate Ca\[^{2+}\] entry into the ER. STIM1 and STIM2 proteins reside in ER, and STIM1 knock down in mice leads to a significant decrease in store-operated Ca\[^{2+}\] levels in brain samples, suggesting a possibility of compensatory upregulation of leak pathway in AD neurons in order to reduce ER Ca\[^{2+}\] overload. Where is an ion conductance pore of presenilin leak channel? From the structural-functional analyses we suggested that transmembrane domains 7 and 9 but not transmembrane domain 6 may play a role in forming the ion conductance pore of PS1 (Nelson et al., 2011). Recent publication reported the first crystal structure of archaean homolog of presenilin (PSH, Li et al., 2013).

**Summary**

In the summary we would like to conclude with our working hypothesis for ER Ca\[^{2+}\] dysregulation in AD (Figure 1). FAD

---

**Figure 1**

"fnmol-06-00029" — 2013/9/13 — 18:36 — page 4 — #4
linked mutations in PS cause disruption of PS Ca2+ leak function. As a result Ca2+^2 influx is accumulating inside of the ER. Similar increase in ER Ca2+ levels occur as a result of brain aging. In order to compensate for ER Ca2+ overflow neurons mount two physiological responses: (1) upregulate gating of InP3R and expression/activity of Ryan, and (2) downregulate activity of neuronal SOC (Figure 1). We hypothesize that these initially protective responses with time become toxic and eventually lead to synaptic dysfunction, synaptic loss, impaired plasticity, and learning, loss of memories and neurodegeneration. The role of Ryan in these processes is likely to be more significant than the role of InP3R, as InP3R predominantly localized in the soma, whereas Ryan are abundant in the postsynaptic and presynaptic terminals. Dantrolene provides a possible way to suppress Ryan-mediated Ca2+ release pharmacologically, but there are significant issues with specificity of dantrolene effects and its delivery to the brain. Neuronal SOC pathway provides a novel potential target for AD treatment that should be explored further.

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 Welch Foundation J-1754 (Ilya Bezprozvanny), NIH grant R01NS00152 (Ilya Bezprozvanny), by the contract with the Russian Ministry of Science 11.G34.31.0056 (Ilya Bezprozvanny), and by the Dynasty Foundation grant DB-F-11/13 (Elena Popugaeva).

REFERENCES

Arias, N., Rojas, E., and Pollard, H. B. (1999). Alzheimer disease amyloid beta protein forms calcium channels in bipolar membrane blocks by thrombomodulin and aluminum. Proc. Natl. Acad. Sci. U.S.A. 96, 567–571. doi: 10.1073/pnas.96.2.567
Bandara, S., Malmsjo, S., and Meyer, Y. (2013). Regulators of calcium homeostasis identified by interference of kinetic model parameters from live single cells perturbed by siRNA. Sci. Signal. 6, r66. doi: 10.1126/scisignal.2809649
Bezprozvanny, I. (2013). Presenilins and calcium signaling: systems biology to single cells perturbed by siRNA. J. Biol. Chem. 288, 1072994. doi: 10.1074/jbc.M113.472695
Cheung, K. H., Shineman, D., Muller, A. M., Sircar, S., Malmersjo, S., and Meyer, Y. (2013). Calcium dysregulation and membrane disruption as a ubiquitous neurotoxic mechanism of soluble amyloid oligomers. J. Biol. Chem. 288, 17294–17300. doi: 10.1074/jbc.M113.477944
Demuro, A., Mina, K., Kayed, R., Milon, S. G., Parker, I., and Glabe, C. G. (2010). Gain-of-function beta-amyloid oligomers involve Ca2+ influx from the endoplasmic reticulum by stimulated production of inositol triphosphate. J. Neurosci. 30, 5824–5833. doi: 10.1523/JNEUROSCI.0366-10.2010
Demuro, A., Parker, I., and Stutzmann, G. E. (2010). Calcium signaling and amyloid toxicity in Alzheimer disease. J. Biol. Chem. 285, 12465–12468. doi: 10.1074/jbc.T1001014200.010899
Deshpande, A., Mina, E., Kayed, R., and Glabe, C. G. (2005). Calcium dysregulation and membrane disruption as distinct mechanisms of neurotoxicity by distinct mecha- nisms in human cortical neurons. J. Neurosci. 25, 10111–10116. doi: 10.1523/JNEUROSCI.0535-05.2005
De Strooper, B., and Iwatsubo, T., Vellas, B., Joffe, S., and LaFerla, F. M. (2005). Calcium dysregulation and membrane disruption as a distinct mechanism of neurotoxicity by distinct mechanisms in human cortical neurons. J. Neurosci. 25, 10111–10116. doi: 10.1523/JNEUROSCI.0535-05.2005
Dudley, D. S., Raman, R., Farlow, M., Boutoisse, Y., Vidal, B., Joffe, S., et al. (2005). A phase 3 trial of solasegocat for treatment of Alzheimer’s disease. N. Engl. J. Med. 353, 345–350. doi: 10.1056/NEJMA2005010534534.00295-8
Drewes-Werringloer, U., Lambert, J., Kayed, R., and Glabe, C. G. (2008). A polymorphism in CALHM1 influences Ca2+ homeostasis, A beta levels, and Alzheimer’s disease risk. Cell 135, 1149–1161. doi: 10.1016/j.cell.2008.05.048
Emmerlin, L., Santos, F., and Justin, E. (2006). Alzheimer’s disease mRNA expression profiles of multiple patients show alterations of genes involved with calcium signaling. Neurobiol. Dis. 21, 638–629. doi: 10.1016/j.nbd.2005.09.004
Giannoccaro, M., Barber, L., Zatti, G., Squitti, R., Benetti, G., Pozzan, T., et al. (2005). Reduction of Ca2+ stores and capacitative Ca2+ entry is associated with the familial Alzheimer’s disease presenilin-1 T329A mutation and anticipates the onset of dementia. Neurobiol. Dis. 20, 658–664. doi: 10.1016/j.nbd.2004.10.016
Gonzalez, L., Miller, M. B., and Stutzmann, G. E. (2010). SfMDA-mediated Ca2+ influx in Sf9 cells activates aberrant Ryan receptor activation in dendrites of young Alzheimer’s disease mice. J. Neurosci. 30, 1143–1157. doi: 10.1523/JNEUROSCI.2038-09.2010
Green, K. N., Demuro, A., Akbari, Y., Hitt, B. D., Smith, J. F., Parker, I., et al. (2008). SERCA pump activity is physiologically regulated by presenilin and regulates amyloid beta production. J. Cell Biol. 181, 1107–1117. doi: 10.1083/jcb.200712471
Green, K. N., and LaFerla, F. M. (2008). Linking calcium to Abeta and Alzheimer’s disease. Neurobiol. Dis. 30, 190–194. doi: 10.1016/j.nbd.2007.05.015
Hardy, J., and Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer’s disease: progress and problems on the road to therapeutics. Science 297, 353–356. doi: 10.1126/science.1072994
Hessens, J., Schuelen, I., Deacon, J., Calamante, N., Kreitschmann, H., and...
Kuchibhotla, K. V., Goldman, S. (2008). Alzheimer's Abeta peptide is determinant in regulating calcium homeostasis, synaptic loss and dysfunction in Alzheimer's disease. J. Biol. Chem. 283, 32535–32539. doi: 10.1074/jbc.M804793200

Oddo, S., Caccamo, A., Shepherd, J. D., Sangiovanni, C. L., Lattarulo, C. R., Wu, H. Y., et al. (2004). Dantrolene: a review of its pharmacology, therapeutic use and new developments. Semin. Arthritis Rheum. 34, 355–367. doi: 10.1016/j.semarthrit.2004.07.008

Kira, H., Guo, Y., Sutter, S. T., Tatsuno, K. C., Wu, H. L., Hirman, B., and Baek, J. (2008). Alpha peptide linked to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron 59, 214–225. doi: 10.1016/j.neuron.2008.08.008

Leisering, M. A., Alkhant, Y., Fangon, C. M., Calabani, D. M., Mattoni, M. R., and LaFerla, F. M. (2000). Capacitative calcium entry deficits and elevated luminal calcium content in mutant presenilin-1 knockout mice. J. Cell Biol. 149, 793–798. doi: 10.1083/jcb.149.4.793

Liou, J., Kim, M. L., Heo, W. D., Jones, T., Taya, M., J. W., Forsell, J. E. J., et al. (2005). STIM is a Ca2+ sensor essential for Ca2+ store-depletion-triggered Ca2+ influx. J. Cell Biol. 175, 1225–1234. doi: 10.1083/jcb.200502142

Muller, M., Chuang, K. H., and Fouret, J. K. (2011). Enhanced BOS gene activation mediated by Alzheimer's disease presenilin 3 regulates presenilin 3: effects on endoplasmic reticulum Ca2+ leak function of presenilin 1. J. Cell Sci. 124, 1225–1235. doi: 10.1093/jcs/jgr151

Nelson, O., Suppan, C., Liu, H., and Bresciani, I. (2010). Familial Alzheimer's disease mutations in presenilins: effects on endoplasmic reticulum calcium homeostasis and correlation with clinical phenotypes. J. Alzheimers Dis. 21, 781–791.

Nelson, O., Suppan, C., Tolia, A., Horne, K., De Strooper, B., and Bresciani, I. (2011). Misrouting mapping of the presenilin 1 calcium leak conductance pores. J. Biol. Chem. 286, 22330–22337. doi: 10.1074/jbc.M111.248035

Nelson, O., Liu, H., Lee, T., Batohat, M., De Strooper, B., and Bresciani, I. (2007). Familial Alzheimer disease-linked mutations specifically disrupt Ca2+ leak function of presenilin 1. J. Biol. Chem. 282, 12570–12579. doi: 10.1074/jbc.M700447200

Papogaeva, E., Suppan, C., and Bezprozvanny, I. (2012). Presenilins, deranged calcium homeostasis, synaptic loss and dysfunction in Alzheimer triple transgenic mice. Neuron 71, 274–279. doi: 10.1016/j.neuron.2011.10.008

Papogaeva, E., Suppan, C., and Bezprozvanny, I. (2012). Pharmacological modulation of capacitative calcium entry in familial Alzheimer's disease mice. J. Biol. Chem. 287, 10933–10944. doi: 10.1074/jbc.M112.394141

Popugaeva and Bezprozvanny
Popugaeva and Bezprozvanny (2013) Role of endoplasmic reticulum Ca\(^{2+}\) signaling in the pathogenesis of Alzheimer disease. Front. Mol. Neurosci. 6:29. doi: 10.3389/fnmol.2013.00029

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 June 2013; accepted: 30 August 2013; published online: 18 September 2013.

Citation: Popugaeva E and Bezprozvanny I (2013) Role of endoplasmic reticulum Ca\(^{2+}\) signaling in the pathogenesis of Alzheimer disease. Front. Mol. Neurosci. 6:29. doi: 10.3389/fnmol.2013.00029

This article was submitted to the journal Frontiers in Molecular Neuroscience. Copyright © 2013 Popugaeva and Bezprozvanny. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.