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Can calcium hypothesis explain synaptic loss in Alzheimer's disease?

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Abstract

Alzheimer's disease (AD) is the threat of modern humankind that is provoked by increased human lifespan. Despite extensive studies on AD pathology for more than 100 years there are no disease preventing therapies. Growing evidence suggests the role of calcium (Ca2+) in the pathogenesis of AD. The main purpose of the article is to understand whether modern science is able to explain the synapse loss observed in early AD and discuss the role of Ca2+ hypothesis in it. Based on results obtained in our laboratory and others we propose that familial AD-associated mutations in presenilins cause Ca2+ overload of endoplasmic reticulum stores which leads to compensatory downregulation of neuronal store-operated Ca2+ (nSOC) entry pathway. We propose that synaptic nSOC is necessary for stability of mature synaptic spines and that dysfunction of this pathway may play an important role in synaptic and memory loss in AD.

Keywords

Alzheimer's disease; calcium signaling; synapse; mushroom spines; neuronal store-operated channels

Alzheimer's disease (AD) is a well known pathology destroying human brain and the personality. The majority of known facts about AD pathogenesis come from discoveries in mouse models mimicking genetically caused cases of familial AD (FAD). Although FAD covers about 1–2% of all AD cases, the mouse models and clinical data agree that synapse loss is the major hallmark of AD that results in memory loss.

What is the physiological substrate of memory? Expression of long-term potentiation (LTP) in response to brief high frequency stimulation of synaptic ends in the hippocampus is strongly correlated with learning and memory (Bliss and Collingridge, 1993; Trommald et al., 1996). LTP takes place in small dendritic protrusions called dendritic spines. Based on their size and shape spines are divided into three groups: stubby, thin and mushroom. It has been proposed that the mushroom spines are stable "memory spines", therefore, they store memories and that thin spines are "learning spines" that serve as physical substrates for the formation of new memories (Bourne and Harris, 2007; Kasai et al., 2003). Since loss of memories is a hallmark of AD, we and others previously proposed that mushroom spines are more likely to be eliminated during AD progression (Bezprozvanny and Hiesinger, 2013; Popugaeva et al., 2012; Tackenberg et al., 2009).

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What mechanism is responsible for mushroom spine elimination? The dominant amyloid-beta (Aβ)-based hypothesis of AD states that soluble Aβ42 peptides possess synaptotoxic effects. Aβ could mediate the synapse loss through the potentiation of N-methyl-D-aspartate receptor (NMDAR). Stimulation of NMDAR triggers excessive calcium (Ca2+) influx that activates calcineurin (CaN), a Ca2+-activated phosphatase whose activation leads to synapse weakening and AD associated spine loss (Wu et al., 2010). However, many facts speak for early Ca2+ abnormalities that precede or even happen in the absence of Aβ pathology (Bezprozvanny and Mattson, 2008; Stutzmann, 2007). The Ca2+ hypothesis of brain aging and AD states for sustained changes in Ca2+ homeostasis could provide the common pathway for aging and the neuropathological changes associated with AD (Khachaturian, 1989). In particular, multiple evidence points to disregulated endoplasmic reticulum (ER) Ca2+ homeostatsis in aging and, AD neurons (Bezprozvanny and Mattson, 2008; Stutzmann, 2007). There are two channels in the ER that mediate Ca2+ release: ryanodine receptors (RyanR) and inositol triphosphate receptors (IP3R). Taking into account that IP3R predominantly resides in the soma, whereas RyanR-mediated signals are more distinct in dendritic spines and presynaptic terminals (Cheung et al., 2010; Smith et al., 2005), the input of abnormal RyanR function on postsynaptic Ca2+ signaling could be stronger than IP3R-mediated signaling. Thus, blocking RyanR (for example with dantrolene) appears to be a potential way to stabilize Ca+ signals in AD brains. However, inconsistent results were obtained when dantrolene was tested in AD mouse models (Chakroborty et al., 2012; Oules et al., 2012; Peng et al., 2012; Zhang et al., 2010).

In addition to RyanR and IP3R our recent data show that presenilins (PS) (mutations in PS are associated with FAD) could play a role of low conductance ER Ca2+ leak channel and many FAD mutations disrupt this function (Tu et al., 2006). This idea remains controversial (Shilling et al., 2012), but our hypothesis has found a confirmation in a recent breakthrough study that demonstrates the crystal structure of a bacterial homologue of presenilin (PSH) (Li et al., 2013). In agreement with our mutagenesis data (Nelson et al., 2011) the authors found that PSH has a water-filled hole that is large enough to allow passage of small ions, suggesting that PSH may function as an ion channel. Our hypothesis was also supported by a recent unbiased screen for Ca+ homeostasis modulators (Bandara et al., 2013). These authors demonstrated that knocking down presenilin-2 dramatically reduced ER Ca^{2+} leak rate in HEK293 cells, consistent with the “leak channel” hypothesis (Bandara et al., 2013; Bezprozvanny, 2013).

What is the connection between impaired ER Ca2+ leak function, ER Ca2+ overload and synaptic loss in AD? We previously proposed that abnormalities in ER Ca2+ handling may be linked to destabilisation of mushroom postsynaptic spines (Bezprozvanny and Hiesinger, 2013; Popugaeva et al., 2012). Consistent with this idea, in recent experiments we observed a significant downregulation of the synaptic neuronal store-operated Ca2+ (nSOC) entry pathway in presenilin mutant neurons (Sun and Bezprozvanny, unpublished data). In agreement with our findings, impaired SOC was reported by several groups for presenilin mutant cells (Akbari et al., 2004; Bojarski et al., 2009; Herms et al., 2003; Leissring et al., 2000; Yoo et al., 2000; Zhang et al., 2010). Our results further indicate that reduced postsynaptic SOC leads to destabilization and elimination of mushroom spines – sites of memory storage (Sun and Bezprozvanny, unpublished data).

Based on obtained results we propose that synaptic ER Ca2+ overload and compensatory downregulation of synaptic nSOC pathway play an important role in synaptic loss in AD and aging brains. Our results suggest that upregulation of synaptic nSOC pathway may yield therapeutic benefits for treatment of AD and age-related memory problems.

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