Can the Calcium Hypothesis Explain Synaptic Loss in Alzheimer's Disease?

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Key Words

Alzheimer's disease · Calcium signaling · Synapse · Mushroom spines · Neuronal store-operated channels

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 (Ca^{2+}) 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 Ca^{2+} hypothesis in it. Based on results obtained in our laboratory and others, we propose that familial AD-associated mutations in pre-senilins cause a Ca^{2+} overload of endoplasmic reticulum stores which leads to compensatory downregulation of the neuronal store-operated Ca^{2+} (nSOC) entry pathway. We propose that synaptic nSOC is necessary for the stability of mature synaptic spines and that dysfunction of this pathway may play an important role in synaptic and memory loss in AD.

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Alzheimer's disease (AD) is a well-known pathology destroying the 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 in response to brief high-frequency stimulation of synaptic ends in the hippocampus is strongly correlated with learning and memory [1, 2]. Long-term potentiation 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', and therefore, they store memories, and that thin spines are 'learning spines' that serve as physical substrates for the formation of new memories [3, 4]. 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 [5–7].

What mechanism is responsible for mushroom spine elimination? The dominant amyloid- β ($\text{A}\beta$)-based hy-

pothesis of AD states that soluble A β 42 peptides possess synaptotoxic effects. A β could mediate the synapse loss through the potentiation of the N-methyl-D-aspartate receptor. Stimulation of the N-methyl-D-aspartate receptor triggers excessive calcium (Ca²⁺) influx that activates calcineurin, a Ca²⁺-activated phosphatase whose activation leads to synapse weakening and AD-associated spine loss [8]. However, many facts speak for early Ca²⁺ abnormalities that precede or even happen in the absence of A β pathology [9, 10]. 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 [11]. In particular, multiple evidence points to dysregulated endoplasmic reticulum (ER) Ca²⁺ homeostasis in aging and AD neurons [9, 10]. 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 [12, 13], 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 Ca²⁺ signals in AD brains. However, inconsistent results were obtained when dantrolene was tested in AD mouse models [14–17].

In addition to RyanR and IP3R, our recent data show that presenilins (PS; mutations in PS are associated with FAD) could play the role of a low conductance ER Ca²⁺ leak channel, and many FAD mutations disrupt this function [18]. This idea remains controversial [19], but our hypothesis has found confirmation in a recent breakthrough study that demonstrates the crystal structure of a bacterial homologue of PS (PSH) [20]. In agreement with our mutagenesis data [21], the authors found that PSH has a water-filled hole that is large enough to allow

the passage of small ions, suggesting that PSH may function as an ion channel. Our hypothesis was also supported by a recent unbiased screen for Ca²⁺ homeostasis modulators [22]. These authors demonstrated that knocking down PS2 dramatically reduced the ER Ca²⁺ leak rate in HEK293 cells, consistent with the ‘leak channel’ hypothesis [22, 23].

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 destabilization of mushroom postsynaptic spines [6, 7]. Consistent with this idea, in recent experiments, we observed a significant downregulation of the synaptic neuronal store-operated Ca²⁺ (nSOC) entry pathway in PS mutant neurons [Sun and Bezprozvanny, unpubl. data]. In agreement with our findings, impaired SOC was reported by several groups for PS mutant cells [16, 24–28]. Our results further indicate that reduced postsynaptic SOC leads to destabilization and elimination of mushroom spines – sites of memory storage [Sun and Bezprozvanny, unpubl. data].

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

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