Review
MESSENGER
Vol. 1, 53–62, 2012
www.aspbs.com/messenger

Presenilins, Deranged Calcium Homeostasis, Synaptic Loss and Dysfunction in Alzheimer's Disease

Elena Popugaeva[1], Charlene Supnet[2], and Ilya Bezprozvanny[1, 2, *]

[1] *Laboratory of Molecular Neurodegeneration, St Petersburg Polytechnical University, St Petersburg, 195251, Russia*
[2] *Department of Physiology, UT Southwestern Medical Center, Dallas, Texas 75390, USA*

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder affecting millions of people. Synaptic dysfunction and physical loss of synapses are responsible for memory impairments in AD. The molecular mechanisms responsible for synaptic loss in AD are not understood. The main risk factor for sporadic AD (SAD) is advanced age. Missense mutations in presenilin (PS) proteins and in amyloid precursor protein (APP) are responsible for majority of rare familial AD (FAD) cases. Increased production of Aβ42 amyloidogenic peptide occurs in SAD and FAD. Synaptotoxic effects of Aβ42 may be linked to synaptic loss in AD. FAD mutations in PS proteins disrupt endoplasmic reticulum (ER) calcium (Ca^{2+}) leak function of PSs and result in increased Ca^{2+} levels in neuronal ER. Similar increases in neuronal ER Ca^{2+} levels occur in aging neurons. Increased neuronal ER Ca^{2+} levels lead to a compensatory upregulation of ER Ca^{2+} release channels, the ryanodine receptors (RyanR), and downregulation of the synaptic store-operated Ca^{2+} entry (SOC) pathway. In this review we propose a hypothesis that excessive Ca^{2+} release from the ER and insufficient SOC Ca^{2+} entry lead to destabilization and eventual elimination of mature mushroom spines in PS-FAD neurons and in aging SAD neurons. The proposed Ca^{2+}-dependent spine destabilization mechanism may act in parallel or synergistically with Aβ42 synaptotoxicity mechanisms. The proposed model may help to establish a cause-and-effect connection between abnormal Ca^{2+} and amyloid homeostasis and synaptic loss in AD.

Keywords: Alzheimer's Disease, Amyloid Hypothesis, Calcium Hypothesis, Presenilins, Synaptic Loss, Dysfunction.

CONTENTS

Introduction 53
Presenilins and Deranged Calcium Signaling in Alzheimer's Disease 55
Synaptic Loss in Alzheimer's Disease 55
Contribution of Presenilins and Calcium to Synaptic Loss in Alzhiemer's Disesase 57
Acknowledgments 58
References 59

INTRODUCTION

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder worldwide, accounting for 60–80% of all dementias. Patients experience progressive decline of short-term and working memory, apathy, depression, impaired judgement, disorientation, confusion, changes in behaviour, loss of motor co-ordination, and difficulty speaking. Approximately 5.4 million people in the United States are living with AD now (Alzheimer's Association, 2012) and it is projected that 115 million people worldwide will be affected by 2050 (Alzheimer Disease International, 2011). Current knowledge of the underlying molecular changes leading to AD pathology has resulted from significant scientific advances over the last 30 years. However, effective disease-modifying therapies remain elusive. Given that the greatest risk factor for developing AD is increasing age and the large population of aging baby boomers, the economic toll of AD worldwide is and will continue to be overwhelming. Studies are urgently on-going to develop therapies that can slow, stop, and ultimately prevent AD.

The most prevalent type of AD is sporadic (SAD), with late-onset of symptoms at approximately 60 years old (~95% of cases). A rare form of AD (~1–2%) is genetically inherited, called familial AD (FAD), with an early-onset of 40–50 years of age (Hardy and Selkoe, 2002). More than 50% of autosomal-dominant FAD cases are caused by mutations in the genes encoding presenilin-1 (*PSEN1*), presenilin-2 (*PSEN2*) and amyloid precursor protein (*APP*) (Bergmans and De Strooper, 2010; Hardy, 2009; Hardy and Selkoe, 2002). Both SAD and FAD display the classic pathological hallmarks: extensive atrophy of the median temporal lobe (especially the

*Author to whom correspondence should be addressed.
E-mail: Ilya.Bezprozvanny@UTSouthwestern.edu

hippocampus), parietal lobe, select regions of the frontal cortex, and cingulate gyrus (Giannakopoulos et al., 2009; Wenk, 2003); extracellular senile plaques composed of dense-core deposits of amyloid-β (Aβ) peptide, dystrophic neurites, and activated microglia (Hardy, 2009; Hardy and Selkoe, 2002); and intracellular neurofibrillary tangles (NFTs) comprised of hyper-phosphorylated microtubule-associated protein tau (*MAPT*) (Small and Duff, 2008). All FAD mutations affect the cleavage of APP which leads to either an increase in the overall production of Aβ peptide (Citron et al., 1992; Haass et al., 1995) or an increase in Aβ42/40 ratio (Borchelt et al., 1996; Hardy, 1997). The overproduction of the aggregation prone Aβ42 ultimately triggers the formation of Aβ plaques, synaptic loss, and neurotoxicity (Hardy and Selkoe, 2002), and is the basis for the "amyloid cascade hypothesis of AD." Most past and current efforts to develop AD therapies are based on this hypothesis and agents have been developed to reduce Aβ production or eliminate Aβ from the brain. However, so far all amyloid-based approaches have failed to provide benefit to patients in clinical trials (Hardy, 2009; Karran et al., 2011).

Clearly there is a need to look beyond Aβ to develop effective AD therapies (Seabrook et al., 2007). A number of studies point to dysfunctional endoplasmic reticulum (ER) calcium (Ca^{2+}) homeostasis in AD, particularly in FAD cases that involve PS mutations (Bezprozvanny and Mattson, 2008; Stutzmann, 2007). Preservation of intracellular Ca^{2+} homeostasis is essential for neuronal function and survival, and is a fundamental component of synaptic transmission (Berridge, 1998). Sustained changes in Ca^{2+} homeostasis could provide the common pathway for aging and the neuropathological changes associated with AD, termed the "Ca^{2+} hypothesis of brain aging and Alzheimer's disease" (Khachaturian, 1989). Early changes to intraneuronal Ca^{2+} regulation is a common observation in AD models and patients (Bezprozvanny and Mattson, 2008; Emilsson et al., 2006; Stutzmann, 2007). Increased intracellular Ca^{2+} levels are functionally linked to PS mutations, apoliprotein ε4 (APOE ε4) expression (a

Elena Popugaeva is from Gorno-Altaisk, Russia. Lena received her Diploma in Chemistry (2007) from the Novosibirsk State University and her Ph.D. in Biology (2012) from Humboldt University Berlin, Germany. Since 2012, Lena is a research scientist in the Laboratory of Molecular Neurodegeneration in St Petersburg Polytechnical University, St Petersburg, Russia. Her main current research interests are the molecular pathogenesis of neurodegenerative disorders.

Charlene Supnet is from from Winnipeg, Manitoba, Canada. Charlene received her Ph.D. (2009) in Biomedical Sciences from the University of Prince Edward Island, Charlottetown, Canada. In 2009, Charlene became a postdoctoral research fellow in UT Southwestern Medical Center at Dallas, Texas, USA. Her main current research interest is on the role of abnormal calcium signaling in pathogenesis of Alzheimer's disease.

Ilya Bezprozvanny is from St. Petersburg, Russia. Ilya received M.Sci. in Physics (1989) from the St Petersburg Polytechnical University and Ph.D. in Cell Biology (1992) from the Institute of Cytology Russian Academy of Sciences. He received his postdoctoral training at the University of Connecticut Health Center (1990–1994) and at the Stanford University Medical Center (1994–1996). Since 1996, Ilya is a faculty in the UT Southwestern Medical Center at Dallas, Texas and currently he is a Professor of Physiology and Carl J. and Hortense M. Thomsen Chair in Alzheimer's Disease Research at UT Southwestern. In 2011, Ilya also became the head of the Laboratory of Molecular Neurodegeneration in St Petersburg Polytechnical University, St Petersburg, Russia. His main current research interest is understanding the role of neuronal calcium signaling in pathogenesis of neurodegenerative disorders.

susceptibility gene associated with sporadic AD), amyloid plaques, neurofibrillary tangles, and synaptic dysfunction. It is also thought that loss of synapses and synaptic plasticity are likely to contribute to the disruption of cognition observed in AD. Synapses are lost during AD, which correlates strongly with cognitive decline and illustrates the importance of this process as causative to dementia (Spires and Hyman, 2004; Terry et al., 1991). Are these seemingly independent phenomena somehow interrelated? Could their convergence result in the extensive synaptic damage and cognitive decline in AD? The goal of this review is to highlight how these processes may work together to give rise to AD.

PRESENILINS AND DERANGED CALCIUM SIGNALING IN ALZHEIMER'S DISEASE

Presenilins are aspartyl proteases that mainly reside in the endoplasmic reticulum (ER) membrane (Annaert et al., 1999). Presenilin-1 (PS1) and presenilin-2 (PS2) are structurally and functionally related transmembrane holoproteins with 80% homology and are the catalytic subunit of γ-secretase complex, which is comprised of cleaved PS, nicastrin, anterior pharynx defective 1 (Aph-1), and presenilins enhancer 2 (Pen-2) (De Strooper, 2003). The γ-secretase complex cleaves type-1 transmembrane proteins, including Notch and APP. The majority of genetically-linked FAD is caused by missense mutations in the *PSEN1* and *PSEN2* genes.

In addition to contributing to altered γ-secretase function in AD pathogenesis, FAD PS mutations result in disturbed Ca^{2+} signaling in neurons (reviewed in (Bezprozvanny and Mattson, 2008; Supnet and Bezprozvanny, 2010a, b)). The first observation that presenilins contribute to abnormal Ca^{2+} signaling in AD was demonstrated in Ca^{2+} imaging experiments with fibroblast from patients expressing PSEN1-A246E, where cells displayed augmented intracellular Ca^{2+} responses to both bombesin and bradykinin (Ito et al., 1994). *In vitro* studies showed that cells expressing FAD PS1 mutations display increased release of inositol 1,4,5-trisphosphate ($InsP_3$)-mediated Ca^{2+} from the ER (Leissring et al., 1999; Stutzmann et al., 2004; Tu et al., 2006). Multiple studies followed and reported that altered $InsP_3$ Ca^{2+} signaling caused by PS-M146V and PS2-N141I mutations are linked to increased ryanodine receptor (RyanR) expression, recruitment, and channel function (Chan et al., 2000; Lee et al., 2006; Smith et al., 2005; Stutzmann et al., 2006; Zhang et al., 2010b). Presenilin mutations or genetic deletion attenuate capacitative Ca^{2+} entry (CCE), a refilling mechanism for ER stores (Giacomello et al., 2005; Leissring et al., 2000; Yoo et al., 2000; Zhang et al., 2010b). The gating of $InsP_3R$ can be directly modulated by PS1-M146L and several other PS1-FAD mutants (Cheung et al., 2010, 2008). *Xenopus laevis* oocytes expressing PS1-M146V have increased sarco-/endoplasmic reticulum Ca^{2+} ATPase (SERCA) activity compared to those with WT PS1 (Green et al., 2008), a mechanism that could contribute to the overfilling of ER Ca^{2+} store. It is clear that mutations in PS may greatly alter neuronal ER Ca^{2+} handling in AD.

How do presenilins contribute to the dysregulated ER Ca^{2+} signaling observed in these studies? We recently provided a mechanistic explanation for most of these findings by demonstrating that wild type PSs function as ER Ca^{2+} leak channels (Tu et al., 2006), which functions to maintain ER Ca^{2+} homeostasis by releasing Ca^{2+} into the cytosol and balancing SERCA activity. We found that some FAD PS mutations disrupt Ca^{2+} leak function (Nelson et al., 2010, 2007; Tu et al., 2006), leading to the overfilling of ER with Ca^{2+} and exaggerated ER Ca^{2+} release observed in PS1/PS2 double knock-out (DKO) fibroblasts (Nelson et al., 2010, 2007; Tu et al., 2006), cultured hippocampal neurons from PS DKO and PS1-M146V neurons (Zhang et al., 2010b), and primary lymphoblasts from FAD patients (Nelson et al., 2010). These data suggest that presenilins play a critical role in deranged Ca^{2+} signaling and neuronal dysfunction in AD.

SYNAPTIC LOSS IN ALZHEIMER'S DISEASE

The synapse is essential for neurotransmission or the transport of electrochemical signals from the presynaptic neuron to the postsynaptic partner. Synaptic plasticity, or molecular and structural changes to the synapse to strengthen or weaken neurotransmission in response to neuronal activity, plays a major role in the formation and storage of memories. Changes to postsynaptic dendrites are maintained structurally at the tips of dendritic protrusions called spines, thought to be a structural basis for learning and memory processes. Although the relationship between spine density, spine shape and memory formation is not fully elucidated, there is evidence that spine loss often contributes to deficits in learning and memory (Alvarez and Sabatini, 2007; Fiala et al., 2002; Harris and Kater, 1994; Segal and Andersen, 2000). It follows then that changes to spine structure, spine dysfunction and spine loss may lead to the development of cognitive decline (Nimmrich and Ebert, 2009). In fact, synapses are lost during AD, correlating strongly with cognitive decline, which demonstrates the importance of this process in dementia (Katzman, 1986; Terry et al., 1991). However, the exact mechanisms responsible for synaptic dysfunction and loss in AD are still poorly understood.

Synapses undergo a constant process of formation and elimination, and the stabilization of spines and their presynaptic counterparts are mechanisms of the learning process (Bourne and Harris, 2007, 2008). The accepted neurophysiological correlate to learning and memory are long-term

potentiation (LTP) and long-term depression (LTD). Induction of LTP, the persistent increase in synaptic strength in response to neuronal activity, is thought to be the physiological substrate of information storage in the hippocampus, and causes an increase in spine number and spine size (Bliss and Collingridge, 1993; Popov et al., 2004; Trommald et al., 1996). Induction of LTD, the persistent disruption of synaptic transmission in response to stimulation, results in the shrinkage of spine heads (Matsuzaki, 2007; Zhou et al., 2004). Both LTP and LTD are important in AD pathogenesis (recently reviewed in (Palop and Mucke, 2010)). Spines undergo experience-dependent morphological changes in live animals (Holtmaat and Svoboda, 2009) and even subtle changes in dendritic spines may have significant effects on synaptic function, plasticity and patterns of connectivity in neuronal circuits.

Spines can be classified according to their morphological structure. The most commonly used nomenclature was introduced by Peters and Kaiserman-Abramof in 1970. Thus, spine shapes can be separated in three groups based on the size of spine's head and neck (Peters and Kaiserman-Abramof, 1970). Mushroom spines have a large head and a fine neck, thin spines have a smaller head and a narrow neck, and stubby spines have no obvious distinction between the head size and the attachment to the dendritic shaft. Due to their large head size, mushroom spines have larger post-synaptic density (PSD), a membrane-associated disc of electron dense material which consists of the receptors, channels, and signaling systems involved in synaptic transmission and the coupling of synaptic activity to postsynaptic bio-chemistry (Nimchinsky et al., 2002). It has been shown that the density of AMPA and NMDA receptors is constant within the PSD, thus the number of receptors per synapse is proportional to the PSD area and spine volume (Nimchinsky et al., 2002; Racca et al., 2000; Takumi et al., 1999). Therefore, large (mushroom) spines are the sites of strong synaptic connections likely to be involved in storage of memories. Hence, it is expected that the mushroom spines are those that excessively eliminated during the AD pathogenesis since the memory loss is a hallmark of the disease. This hypothesis is supported by *in vivo* imaging data. It has been demonstrated that dendrites surrounding amyloid plaques in the brain of APPswe/PS1delta9xYFP (B6C3-YFP) transgenic mice showed abnormal curvature and dystrophic swelling (Meyer-Luehmann et al., 2008). Furthermore, spine loss around plaques was due to spine instability, with more spine elimination as compared to control, which reflects defective structural (Spires-Jones et al., 2007) and functional plasticity (Meyer-Luehmann et al., 2009). Simplification of the dendritic arbor has been observed in other models of AD expressing mutant APP (Alpar et al., 2006).

What are the molecular and signaling mechanisms responsible for loss of mature synaptic spines in AD? There is evidence that APP is transported to the presynaptic endings where its function is still under the debate. However, APP may affect dendritic spine formation in mouse brain (reviewed in (Jung and Herms, 2012)). Studies show that lack of APP leads to increased dendritic spine density (Bittner et al., 2009; Priller et al., 2006) and overexpression of human APP sometimes causes decreased formation of dendritic spines (Belichenko et al., 2004; Mucke et al., 2000; Perez-Cruz et al., 2011; Simon et al., 2009; Villar et al., 2005). These data appear to be contradictory. The major affects of APP in the formation of spines appeared at the early stages of the disease, depending on the model used and the region of the brain studied (Belichenko et al., 2004; Bittner et al., 2009; Mucke et al., 2000; Perez-Cruz et al., 2011; Priller et al., 2006; Simon et al., 2009; Villar et al., 2005). Nevertheless, when APP expression is either eliminated or augmented in aged animals, spine density decreases in the hippocampus (Jung and Herms, 2012). The latter observation is in agreement with clinical data showing that in brains of patients suffering from AD, the number of synapses is decreased and synapse loss is a major hallmark of the disease (DeKosky and Scheff, 1990; Terry et al., 1991).

Aβ is produced and accumulated in synaptic regions in activity-dependent manner (Kamenetz et al., 2003; Lazarov et al., 2002; Wei et al., 2010) and itself may contribute to synaptic loss. Aβ induces morphological changes in cultured neurons through the activation of calcineurin (CaN), a Ca^{2+}-activated phosphatase known to affect synaptic plasticity (Celsi et al., 2007; Wu et al., 2010). Furthermore, when AD mice expressed a genetically coded inhibitor of CaN, the plaque-induced changes to dendrites and spines were reversed (Wu et al., 2010). The Aβ-mediated degeneration of spines could be prevented by the application of an NMDA receptor antagonist (Wei et al., 2010). Aβ also causes synaptic clustering and activation of mGluR5 receptors (Lacor et al., 2007; Renner et al., 2010), resulting in excessive Ca^{2+} signals and synaptic loss. Taken together, these data indicate a major role for Ca^{2+} signaling in the Aβ-induced changes to dendritic spine morphology and function.

Synaptic terminals are particularly sensitive to intracellular Ca^{2+} alterations in neurons since they are repeatedly exposed to Ca^{2+} influx and require high levels of energy output to support neuronal homeostasis. In fact, resting intraneuronal Ca^{2+} levels are disrupted around Aβ plaques in AD mice *in vivo*, indicating dysfunctional Ca^{2+} regulation (Kuchibhotla et al., 2008). It is clear that synaptic loss in neurodegenerative diseases such as AD is accompanied or even preceded by altered Ca^{2+} signaling. Presenilins are important regulators of intracellular Ca^{2+} homeostasis (discussed above) and can directly influence the intraneuronal Ca^{2+} signaling. Therefore we will discuss the role of PSs and FAD mutant PSs in synapse function in greater details in the next section.

CONTRIBUTION OF PRESENILINS AND CALCIUM TO SYNAPTIC LOSS IN ALZHIEMER'S DISESASE

Can PSs directly affect dendritic spine formation, morphology and subsequently, synaptic plasticity in AD? A recent study demonstrated that cortical neurons in mice overexpresssing FAD PS1-A246E or wild type human PS1 (hPS1) displayed enhanced dendritic spine density (Jung et al., 2011). Interestingly, the changes in spine density were layer specific. In the 5th layer of cortical dendrites the authors did not find any difference in spine density between mice overexpressing FAD PS1-A246E and hPS1, whereas on 2nd basal layer the overexpression of FAD PS1-A246E increased spine density compared to hPS1 (Jung et al., 2011). After analyzing the shape of the spines, the authors did not observe any significant differences in the relative proportion of mushroom, stubby or thin spines in FAD PS1-A246E or hPS1 mice. However, they reported that the effect on spine density was γ-secretase-independent because they did not observe that FAD PS1-A246E or hPS1 overexpression affected the production of γ-secretase substrates, such as *N*-cadherin, Eph4A-CTF, APPα/β-CTF (Jung et al., 2011). The authors speculate that the effect on spine density they observe is rather related to altered Ca^{2+}-homeostasis, because of the up-regulation of RyanR expression (Jung et al., 2011).

One long-term form of synaptic plasticity, called homeostatic synaptic scaling, is a compensatory type of plasticity that maintains synaptic strength to compensate for the perturbation in activity in both young and adult neurons (Pozo and Goda, 2010; Turrigiano, 2008). Interestingly, this type of plasticity is triggered by changes in intracellular Ca^{2+} levels (Ibata et al., 2008). Recently, it has been shown that homeostatic scaling of excitatory synapses is impaired in primary hippocampal neurons derived from mice either lacking PS1 or expressing PS-M146V (Pratt et al., 2011). Moreover, the authors demonstrate that the impairment of homeostatic synaptic scaling is γ-secretase-independent and is regulated through PI3K/Akt signaling pathway (Pratt et al., 2011).

Can PSs regulate synaptic plasticity and hippocamal LTP in AD mice? There are a limited number of electrophysiological studies in PS-FAD mouse models. One study demonstrated altered contribution of RyanR to synaptic plasticity mechanisms in PS1-M146V mouse model (Chakroborty et al., 2009). Specifically, these authors demonstrated that although hippocampal LTP is induced normally in PS1-M146V mice, the induction of LTP in these mice becomes sensitive to RyanR inhibitor danrolene and RyanR activator caffeine. In contrast, induction of LTP in wild type mice is not affected by dantrolene or caffeine (Chakroborty et al., 2009). In the follow up study the same group reported NMDAR-mediated Ca^{2+} influx triggers supranormal Ca^{2+} responses via RyanR in postsynaptic spines of PS1-M146V mice, suggesting a possible mechanism for altered postsynaptic Ca^{2+} handling and synaptic plasticity in these mice (Goussakov et al., 2010). Another group focused primarily on studies of presynaptic Ca^{2+} signaling mechanisms (Zhang et al., 2009, 2010a). Using a genetic approach, these authors performed conditional knockout of presenilins in either presynaptic (CA3) or postsynaptic (CA1) neurons of the hippocampal Schaeffer-collateral pathway. They discovered that LTP is impaired after presynaptic but not after postsynaptic deletion of presenilins. They further found that short-term plasticity and presynaptic facilitation mechanisms are also altered by genetic deletion of presenlins. In a series of pharmacological experiments, they demonstrated that these long-term and short-term synaptic plasticity alterations are due to deranged ER Ca^{2+} signaling in presenilin knockout neurons (Zhang et al., 2009; 2010a). The studies by these two groups suggest that presenilins play an important role in control of ER Ca^{2+} signaling and synaptic plasticity mechanisms on both "pre" and "post" sides of the synapse.

The functional studies described in above were focused on relatively short-term synaptic plasticity mechanisms. Hippocampal LTP can be categorized into two functionally and mechanistically distinct forms (Bliss and Collingridge, 1993). Short-lasting or early LTP (E-LTP) can be induced by a single high frequency stimulation (HFS), lasts up to 1 h *in vitro* (Huang and Kandel, 1994), and is mediated by the phosphorylation of existing proteins without *de novo* synthesis (Nicoll and Malenka, 1999). Long-lasting (L-LTP) is induced by multiple HFS, lasts at least 4 h, and requires transcription and protein synthesis (Osten et al., 1996; Otani and Abraham, 1989). Early LTP has been extensively studied in various mouse models of AD. Surprisingly, while E-LTP is impaired in APP mutant mice or by Aβ application (Chapman et al., 1999; Walsh et al., 2002), it is increased in mice expressing different mutations of PS1 (Auffret et al., 2009; Dewachter et al., 2008; Parent et al., 1999; Schneider et al., 2001; Zaman et al., 2000). This observation has been problematic and is a consistent criticism when validating the utility of PS1 mice to study AD, implying that they lack the synaptic dysfunction apparent in AD. Nevertheless, PS1 mutant knock-in mice that express the M146V mutation (PS1-M146V) are particularly interesting since they display both exaggerated Ca^{2+} signaling (Chakroborty et al., 2009; Goussakov et al., 2010; Stutzmann et al., 2004) and memory impairment in spatial learning tasks (Sun et al., 2005). Auffret and co-authors showed a transient increase in E-LTP in PS1-M146V and that E-LTP was decreased at 12 month of age (Auffret et al., 2010). Furthermore, they demonstrated for the first time that PS1-M146V induces the early impairment of L-LTP, which is consistent with data showing that PS1-M146V mice display a decline of hippocampal spatial memory as early as 3 month of age (Auffret et al., 2010). It is clear that L-LTP has to be considered when interpreting data obtained from PS1-M146V mice because L-LTP is believed to be critical for the long-term memory storage.

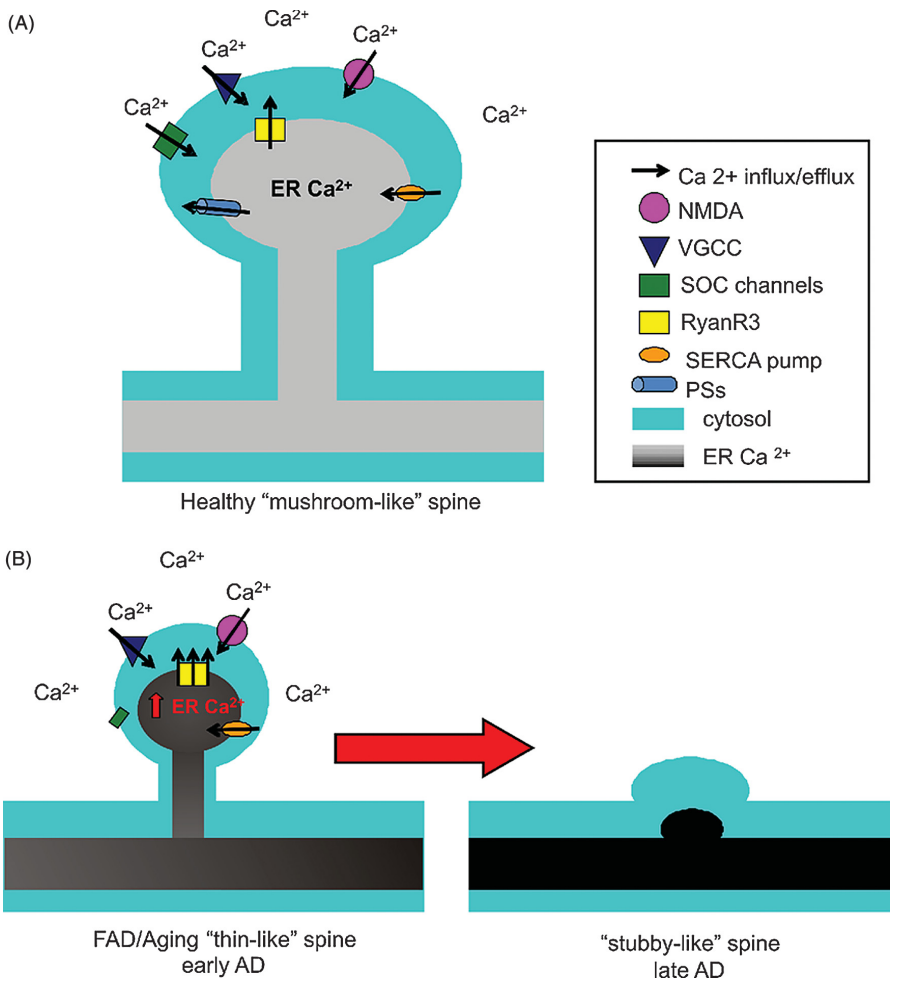

Figure 1. Hypothesis: ER Ca^{2+} signaling changes induced by aging and/or PS-FAD mutations result in destabilization and loss of mushroom spines, causing memory impairment in AD. (A) Cartoon represents mushroom spine shape of healthy "mushroom-like" dendrite. Ca^{2+} channels are present and support intracellular calcium homeostasis. **(B)** The AD affected spine. FAD mutations in PSs disrupt PS-mediated ER Ca^{2+} leak function. That results in Ca^{2+} overfilling of ER store, as a compensate mechanism neurons upregulate RyanR expression and downregulate SOC Ca^{2+} entry pwathway. These events induce spine head shrinkage and eventual spine elimination in AD brain. **Abbreviations**: PSs—presenilins; SOC—store-operated channels; RyanR—ryanodine receptors; IP3R—inositol triphosphate receptor; VGCC—voltage gated calcium channels; SERCA—sarco/endoplasmic reticulum calcium ATPase; ER—endoplasmatic reticulum.

We have demonstrated that some FAD PS1 mutations enhance Ca^{2+} accumulation in the ER. Could these disturbances in Ca^{2+} signaling explain synaptic loss and L-LTP defects in aging PS1-M146V mice? Presenilin mutations can have local adverse effects on Ca^{2+}-mediated synaptic regulation that may result in mitochondrial dysfunction and delayed synaptic degeneration in AD (reviewed in (Supnet and Bezprozvanny, 2010b)). Moreover, FAD PS1 and PS cDKO attenuate capacitative Ca^{2+} entry (Giacomello et al., 2005; Leissring et al., 2000; Yoo et al., 2000; Zhang et al., 2010b). Overexpression of TRPC6 channels, which support store-operated Ca^{2+} entry, resulted in increased density of excitatory spines in transgenic mouse model (Zhou et al., 2008). Based on these results we propose that excessive Ca^{2+} release from the postsynaptic ER and reduced synaptic store-operated Ca^{2+} entry lead to destabilization and eventual elimination of mature mushroom spines in PS-FAD neurons and in aging SAD neurons (Fig. 1). Experimental testing of this hypothesis is one of the key research directions in our laboratory. We hope that these studies will help to clarify the role of deranged neuronal Ca^{2+} signaling in synaptic dysfunction and loss in AD.

Acknowledgments: We would like to thank Drs Hua Zhang and Suya Sun for helpful discussions in the course of writing this review article. IB is a holder of Carl J. and Hortense M. Thomsen chair in Alzheimer's disease research and AD research in his laboratory supported

by the McKnight Neuroscience of Brain Disorders Award, the Welch Foundation, the NIH grant R01AG030746 and the by the contract with the Russian Ministry of Science 14.740.11.0924.

REFERENCES

Alpar, A., Ueberham, U., Bruckner, M. K., Seeger, G., Arendt, T., and Gartner, U. (2006). Different dendrite and dendritic spine alterations in basal and apical arbors in mutant human amyloid precursor protein transgenic mice. Brain. Res. *1099*, 189–198.

Alvarez, V. A., and Sabatini, B. L. (2007). Anatomical and physiological plasticity of dendritic spines. Annu. Rev. Neurosci. *30*, 79–97.

Annaert, W. G., Levesque, L., Craessaerts, K., Dierinck, I., Snellings, G., Westaway, D., George-Hyslop, P. S., Cordell, B., Fraser, P., and De Strooper, B. (1999). Presenilin 1 controls gamma-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons. J. Cell Biol. *147*, 277–294.

Auffret, A., Gautheron, V., Mattson, M. P., Mariani, J., and Rovira, C. (2010). Progressive age-related impairment of the late long-term potentiation in Alzheimer's disease presenilin-1 mutant knock-in mice. J. Alzheimers Dis. *19*, 1021–1033.

Auffret, A., Gautheron, V., Repici, M., Kraftsik, R., Mount, H. T., Mariani, J., and Rovira, C. (2009). Age-dependent impairment of spine morphology and synaptic plasticity in hippocampal CA1 neurons of a presenilin 1 transgenic mouse model of Alzheimer's disease. J. Neurosci. *29*, 10144–10152.

Belichenko, P. V., Masliah, E., Kleschevnikov, A. M., Villar, A. J., Epstein, C. J., Salehi, A., and Mobley, W. C. (2004). Synaptic structural abnormalities in the Ts65Dn mouse model of Down Syndrome. J. Comp. Neurol. *480*, 281–298.

Bergmans, B. A., and De Strooper, B. (2010). Gamma-secretases: From cell biology to therapeutic strategies. Lancet Neurol. *9*, 215–226.

Berridge, M. J. (1998). Neuronal calcium signaling. Neuron. *21*, 13–26.

Bezprozvanny, I., and Mattson, M. P. (2008). Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. Trends Neurosci. *31*, 454–463.

Bittner, T., Fuhrmann, M., Burgold, S., Jung, C. K., Volbracht, C., Steiner, H., Mitteregger, G., Kretzschmar, H. A., Haass, C., and Herms, J. (2009). Gamma-secretase inhibition reduces spine density *in vivo* via an amyloid precursor protein-dependent pathway. J. Neurosci. *29*, 10405–10409.

Bliss, T. V., and Collingridge, G. L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. Nature *361*, 31–39.

Borchelt, D. R., Thinakaran, G., Eckman, C. B., Lee, M. K., Davenport, F., Ratovitsky, T., Prada, C. M., Kim, G., Seekins, S., Yager, D., Slunt, H. H., Wang, R., Seeger, M., Levey, A. I., Gandy, S. E., Copeland, N. G., Jenkins, N. A., Price, D. L., Younkin, S. G., and Sisodia, S. S. (1996). Familial Alzheimer's disease-linked presenilin 1 variants elevate Abeta1–42/1–40 ratio *in vitro* and *in vivo*. Neuron *17*, 1005–1013.

Bourne, J., and Harris, K. M. (2007). Do thin spines learn to be mushroom spines that remember? Curr. Opin. Neurobiol. *17*, 381–386.

Bourne, J. N., and Harris, K. M. (2008). Balancing structure and function at hippocampal dendritic spines. Annu. Rev. Neurosci. *31*, 47–67.

Celsi, F., Svedberg, M., Unger, C., Cotman, C. W., Carri, M. T., Ottersen, O. P., Nordberg, A., and Torp, R. (2007). Beta-amyloid causes downregulation of calcineurin in neurons through induction of oxidative stress. Neurobiol. Dis. *26*, 342–352.

Chakroborty, S., Goussakov, I., Miller, M. B., and Stutzmann, G. E. (2009). Deviant ryanodine receptor-mediated calcium release resets synaptic homeostasis in presymptomatic 3xTg-AD mice. J. Neurosci. *29*, 9458–9470.

Chan, S. L., Mayne, M., Holden, C. P., Geiger, J. D., and Mattson, M. P. (2000). Presenilin-1 mutations increase levels of ryanodine receptors and calcium release in PC12 cells and cortical neurons. J. Biol. Chem. *275*, 18195–18200.

Chapman, P. F., White, G. L., Jones, M. W., Cooper-Blacketer, D., Marshall, V. J., Irizarry, M., Younkin, L., Good, M. A., Bliss, T. V., Hyman, B. T., et al. (1999). Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. Nat. Neurosci. *2*, 271–276.

Cheung, K. H., Mei, L., Mak, D. O., Hayashi, I., Iwatsubo, T., Kang, D. E., and Foskett, J. K. (2010). Gain-of-function enhancement of IP3 receptor modal gating by familial Alzheimer's disease-linked presenilin mutants in human cells and mouse neurons. Sci. Signal. *3*, ra22.

Cheung, K. H., Shineman, D., Muller, M., Cardenas, C., Mei, L., Yang, J., Tomita, T., Iwatsubo, T., Lee, V. M., and Foskett, J. K. (2008). Mechanism of Ca2+ disruption in Alzheimer's disease by presenilin regulation of InsP(3) receptor channel gating. Neuron *58*, 871–883.

Citron, M., Oltersdorf, T., Haass, C., McConlogue, L., Hung, A. Y., Seubert, P., Vigo-Pelfrey, C., Lieberburg, I., and Selkoe, D. J. (1992). Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. Nature *360*, 672–674.

De Strooper, B. (2003). Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-Secretase complex. Neuron *38*, 9–12.

DeKosky, S. T., and Scheff, S. W. (1990). Synapse loss in frontal cortex biopsies in Alzheimer's disease: Correlation with cognitive severity. Ann. Neurol. *27*, 457–464.

Dewachter, I., Ris, L., Croes, S., Borghgraef, P., Devijver, H., Voets, T., Nilius, B., Godaux, E., and Van Leuven, F. (2008). Modulation of synaptic plasticity and Tau phosphorylation by wild-type and mutant presenilin1. Neurobiol. Aging *29*, 639–652.

Emilsson, L., Saetre, P., and Jazin, E. (2006). Alzheimer's disease: mRNA expression profiles of multiple patients show alterations of genes involved with calcium signaling. Neurobiol. Dis. *21*, 618–625.

Fiala, J. C., Spacek, J., and Harris, K. M. (2002). Dendritic spine pathology: Cause or consequence of neurological disorders? Brain Research Brain Research Reviews *39*, 29–54.

Giacomello, M., Barbiero, L., Zatti, G., Squitti, R., Binetti, G., Pozzan, T., Fasolato, C., Ghidoni, R., and Pizzo, P. (2005). Reduction of Ca2+ stores and capacitative Ca2+ entry is associated with the familial Alzheimer's disease presenilin-2 T122R mutation and anticipates the onset of dementia. Neurobiol. Dis. *18*, 638–648.

Giannakopoulos, P., Kovari, E., Gold, G., von Gunten, A., Hof, P. R., and Bouras, C. (2009). Pathological substrates of cognitive decline in Alzheimer's disease. Front Neurol. Neurosci. *24*, 20–29.

Goussakov, I., Miller, M. B., and Stutzmann, G. E. (2010). NMDA-mediated Ca(2+) influx drives aberrant ryanodine receptor activation in dendrites of young Alzheimer's disease mice. J. Neurosci. *30*, 12128–12137.

Green, K. N., Demuro, A., Akbari, Y., Hitt, B. D., Smith, I. F., Parker, I., and LaFerla, F. M. (2008). SERCA pump activity is physiologically regulated by presenilin and regulates amyloid beta production. J. Cell Biol. *181*, 1107–1116.

Haass, C., Lemere, C. A., Capell, A., Citron, M., Seubert, P., Schenk, D., Lannfelt, L., and Selkoe, D. J. (1995). The Swedish mutation causes

early-onset Alzheimer's disease by beta-secretase cleavage within the secretory pathway. Nature Medicine *1*, 1291–1296.

Hardy, J. (1997). Amyloid, the presenilins and Alzheimer's disease. Trends Neurosci. *20*, 154–159.

Hardy, J. (2009). The amyloid hypothesis for Alzheimer's disease: A critical reappraisal. J. Neurochem. *110*, 1129–1134.

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.

Harris, K. M., and Kater, S. B. (1994). Dendritic spines: Cellular specializations imparting both stability and flexibility to synaptic function. Annu. Rev. Neurosci. *17*, 341–371.

Holtmaat, A., and Svoboda, K. (2009). Experience-dependent structural synaptic plasticity in the mammalian brain. Nat. Rev. Neurosci. *10*, 647–658.

Huang, Y. Y., and Kandel, E. R. (1994). Recruitment of long-lasting and protein kinase A-dependent long-term potentiation in the CA1 region of hippocampus requires repeated tetanization. Learn Mem. *1*, 74–82.

Ibata, K., Sun, Q., and Turrigiano, G. G. (2008). Rapid synaptic scaling induced by changes in postsynaptic firing. Neuron *57*, 819–826.

Alzheimer Disease International (2011). World Alzhiemer Report 2011, The benefits of early diagnosis and intervention.

Ito, E., Oka, K., Etcheberrigaray, R., Nelson, T. J., McPhie, D. L., Tofel-Grehl, B., Gibson, G. E., and Alkon, D. L. (1994). Internal Ca^{2+} mobilization is altered in fibroblasts from patients with Alzheimer disease. Proc. Natl. Acad. Sci. USA *91*, 534–538.

Jung, C. K., Fuhrmann, M., Honarnejad, K., Van Leuven, F., and Herms, J. (2011). Role of presenilin 1 in structural plasticity of cortical dendritic spines *in vivo*. J. Neurochem. *119*, 1064–1073.

Jung, C. K., and Herms, J. (2012). Role of APP for dendritic spine formation and stability. Exp. Brain. Res. *217*, 463–470.

Kamenetz, F., Tomita, T., Hsieh, H., Seabrook, G., Borchelt, D., Iwatsubo, T., Sisodia, S., and Malinow, R. (2003). APP processing and synaptic function. Neuron *37*, 925–937.

Karran, E., Mercken, M., and De Strooper, B. (2011). The amyloid cascade hypothesis for Alzheimer's disease: An appraisal for the development of therapeutics. Nat. Rev. Drug Discov. *10*, 698–712.

Katzman, R. (1986). Alzheimer's disease. N. Engl. J. Med. *314*, 964–973.

Khachaturian, Z. S. (1989). Calcium, membranes, aging, and Alzheimer's disease. Introduction and overview. Ann. NY Acad. Sci. *568*, 1–4.

Kuchibhotla, K. V., Goldman, S. T., Lattarulo, C. R., Wu, H. Y., Hyman, B. T., and Bacskai, B. J. (2008). Abeta plaques lead to aberrant regulation of calcium homeostasis *in vivo* resulting in structural and functional disruption of neuronal networks. Neuron *59*, 214–225.

Lacor, P. N., Buniel, M. C., Furlow, P. W., Clemente, A. S., Velasco, P. T., Wood, M., Viola, K. L., and Klein, W. L. (2007). Abeta oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. J. Neurosci. *27*, 796–807.

Lazarov, O., Lee, M., Peterson, D. A., and Sisodia, S. S. (2002). Evidence that synaptically released beta-amyloid accumulates as extracellular deposits in the hippocampus of transgenic mice. J. Neurosci. *22*, 9785–9793.

Lee, S. Y., Hwang, D. Y., Kim, Y. K., Lee, J. W., Shin, I. C., Oh, K. W., Lee, M. K., Lim, J. S., Yoon, D. Y., Hwang, S. J., and Hong, J. T. (2006). PS2 mutation increases neuronal cell vulnerability to neurotoxicants through activation of caspase-3 by enhancing of ryanodine receptor-mediated calcium release. FASEB J. *20*, 151–153.

Leissring, M. A., Akbari, Y., Fanger, C. M., Cahalan, M. D., Mattson, M. P., and LaFerla, F. M. (2000). Capacitative calcium entry deficits and elevated luminal calcium content in mutant presenilin-1 knockin mice. J. Cell Biol. *149*, 793–798.

Leissring, M. A., Paul, B. A., Parker, I., Cotman, C. W., and LaFerla, F. M. (1999). Alzheimer's presenilin-1 mutation potentiates inositol 1,4,5-trisphosphate-mediated calcium signaling in Xenopus oocytes. J. Neurochem *72*, 1061–1068.

Matsuzaki, M. (2007). Factors critical for the plasticity of dendritic spines and memory storage. Neuroscience Research *57*, 1–9.

Meyer-Luehmann, M., Mielke, M., Spires-Jones, T. L., Stoothoff, W., Jones, P., Bacskai, B. J., and Hyman, B. T. (2009). A reporter of local dendritic translocation shows plaque- related loss of neural system function in APP-transgenic mice. J. Neurosci. *29*, 12636–12640.

Meyer-Luehmann, M., Spires-Jones, T. L., Prada, C., Garcia-Alloza, M., de Calignon, A., Rozkalne, A., Koenigsknecht-Talboo, J., Holtzman, D. M., Bacskai, B. J., and Hyman, B. T. (2008). Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. Nature *451*, 720–724.

Mucke, L., Masliah, E., Yu, G. Q., Mallory, M., Rockenstein, E. M., Tatsuno, G., Hu, K., Kholodenko, D., Johnson-Wood, K., and McConlogue, L. (2000). High-level neuronal expression of abeta 1–42 in wild-type human amyloid protein precursor transgenic mice: Synaptotoxicity without plaque formation. J. Neurosci. *20*, 4050–4058.

Nelson, O., Supnet, C., Liu, H., and Bezprozvanny, I. (2010). Familial Alzheimer's disease mutations in presenilins: Effects on endoplasmic reticulum calcium homeostasis and correlation with clinical phenotypes. J. Alzheimers Dis. *21*, 781–793.

Nelson, O., Tu, H., Lei, T., Bentahir, M., de Strooper, B., and Bezprozvanny, I. (2007). Familial Alzheimer disease-linked mutations specifically disrupt Ca2+ leak function of presenilin 1. J. Clin Invest. *117*, 1230–1239.

Nicoll, R. A., and Malenka, R. C. (1999). Expression mechanisms underlying NMDA receptor-dependent long-term potentiation. Ann. NY Acad. Sci. *868*, 515–525.

Nimchinsky, E. A., Sabatini, B. L., and Svoboda, K. (2002). Structure and function of dendritic spines. Ann. Rev. Physiol. *64*, 313–353.

Nimmrich, V., and Ebert, U. (2009). Is Alzheimer's disease a result of presynaptic failure? Synaptic dysfunctions induced by oligomeric beta-amyloid. Reviews in the Neurosciences *20*, 1–12.

Osten, P., Valsamis, L., Harris, A., and Sacktor, T. C. (1996). Protein synthesis-dependent formation of protein kinase Mzeta in long-term potentiation. J. Neurosci. *16*, 2444–2451.

Otani, S., and Abraham, W. C. (1989). Inhibition of protein synthesis in the dentate gyrus, but not the entorhinal cortex, blocks maintenance of long-term potentiation in rats. Neurosci. Lett. *106*, 175–180.

Palop, J. J., and Mucke, L. (2010). Synaptic depression and aberrant excitatory network activity in Alzheimer's disease: Two faces of the same coin? Neuromolecular Medicine *12*, 48–55.

Parent, A., Linden, D. J., Sisodia, S. S., and Borchelt, D. R. (1999). Synaptic transmission and hippocampal long-term potentiation in transgenic mice expressing FAD-linked presenilin 1. Neurobiol. Dis. *6*, 56–62.

Perez-Cruz, C., Nolte, M. W., van Gaalen, M. M., Rustay, N. R., Termont, A., Tanghe, A., Kirchhoff, F., and Ebert, U. (2011). Reduced spine density in specific regions of CA1 pyramidal neurons in two transgenic mouse models of Alzheimer's disease. J. Neurosci. *31*, 3926–3934.

Peters, A., and Kaiserman-Abramof, I. R. (1970). The small pyramidal neuron of the rat cerebral cortex. The perikaryon, dendrites and spines. Am. J. Anat. *127*, 321–355.

Popov, V. I., Davies, H. A., Rogachevsky, V. V., Patrushev, I. V., Errington, M. L., Gabbott, P. L., Bliss, T. V., and Stewart, M. G. (2004). Remodelling of synaptic morphology but unchanged synaptic density during late phase long-term potentiation (LTP): A serial section electron micrograph study in the dentate gyrus in the anaesthetised rat. Neuroscience *128*, 251–262.

Pozo, K., and Goda, Y. (2010). Unraveling mechanisms of homeostatic synaptic plasticity. Neuron *66*, 337–351.

Pratt, K. G., Zimmerman, E. C., Cook, D. G., and Sullivan, J. M. (2011). Presenilin 1 regulates homeostatic synaptic scaling through Akt signaling. Nat. Neurosci. *14*, 1112–1114.

Priller, C., Bauer, T., Mitteregger, G., Krebs, B., Kretzschmar, H. A., and Herms, J. (2006). Synapse formation and function is modulated by the amyloid precursor protein. J. Neurosci. *26*, 7212–7221.

Racca, C., Stephenson, F. A., Streit, P., Roberts, J. D., and Somogyi, P. (2000). NMDA receptor content of synapses in stratum radiatum of the hippocampal CA1 area. J. Neurosci. *20*, 2512–2522.

Renner, M., Lacor, P. N., Velasco, P. T., Xu, J., Contractor, A., Klein, W. L., and Triller, A. (2010). Deleterious effects of amyloid beta oligomers acting as an extracellular scaffold for mGluR5. Neuron *66*, 739–754.

Alzheimer's Association (2012). 2012 Alzheimer's disease facts and figures. Alzheimers Dement *8*, 131–168.

Schneider, I., Reverse, D., Dewachter, I., Ris, L., Caluwaerts, N., Kuiperi, C., Gilis, M., Geerts, H., Kretzschmar, H., Godaux, E., Moechars, D., Van Leuven, F., and Herms, J. (2001). Mutant presenilins disturb neuronal calcium homeostasis in the brain of transgenic mice, decreasing the threshold for excitotoxicity and facilitating long-term potentiation. J. Biol. Chem. *276*, 11539–11544.

Seabrook, G. R., Ray, W. J., Shearman, M., and Hutton, M. (2007). Beyond amyloid: The next generation of Alzheimer's disease therapeutics. Mol. Interv. *7*, 261–270.

Segal, M., and Andersen, P. (2000). Dendritic spines shaped by synaptic activity. Curr. Opin. Neurobiol. *10*, 582–586.

Simon, A. M., Schiapparelli, L., Salazar-Colocho, P., Cuadrado-Tejedor, M., Escribano, L., Lopez de Maturana, R., Del Rio, J., Perez-Mediavilla, A., and Frechilla, D. (2009). Overexpression of wild-type human APP in mice causes cognitive deficits and pathological features unrelated to Abeta levels. Neurobiol. Dis. *33*, 369–378.

Small, S. A., and Duff, K. (2008). Linking Abeta and tau in late-onset Alzheimer's disease: A dual pathway hypothesis. Neuron *60*, 534–542.

Smith, I. F., Hitt, B., Green, K. N., Oddo, S., and LaFerla, F. M. (2005). Enhanced caffeine-induced Ca^{2+} release in the 3xTg-AD mouse model of Alzheimer's disease. J. Neurochem. *94*, 1711–1718.

Spires-Jones, T. L., Meyer-Luehmann, M., Osetek, J. D., Jones, P. B., Stern, E. A., Bacskai, B. J., and Hyman, B. T. (2007). Impaired spine stability underlies plaque-related spine loss in an Alzheimer's disease mouse model. Am. J. Pathol. *171*, 1304–1311.

Spires, T. L., and Hyman, B. T. (2004). Neuronal structure is altered by amyloid plaques. Reviews in the Neurosciences *15*, 267–278.

Stutzmann, G. E. (2007). The pathogenesis of Alzheimers disease is it a lifelong "calciumopathy"? Neuroscientist *13*, 546–559.

Stutzmann, G. E., Caccamo, A., LaFerla, F. M., and Parker, I. (2004). Dysregulated IP3 signaling in cortical neurons of knock-in mice expressing an Alzheimer's-linked mutation in presenilin1 results in exaggerated Ca2+ signals and altered membrane excitability. J. Neurosci. *24*, 508–513.

Stutzmann, G. E., Smith, I., Caccamo, A., Oddo, S., Laferla, F. M., and Parker, I. (2006). Enhanced ryanodine receptor recruitment contributes to Ca^{2+} disruptions in young, adult, and aged Alzheimer's disease mice. J. Neurosci. *26*, 5180–5189.

Sun, X., Beglopoulos, V., Mattson, M. P., and Shen, J. (2005). Hippocampal spatial memory impairments caused by the familial Alzheimer's disease-linked presenilin 1 M146V mutation. Neuro-Degenerative Diseases *2*, 6–15.

Supnet, C., and Bezprozvanny, I. (2010a). The dysregulation of intracellular calcium in Alzheimer disease. Cell Calcium *47*, 183–189.

Supnet, C., and Bezprozvanny, I. (2010b). Neuronal calcium signaling, mitochondrial dysfunction, and Alzheimer's disease. J. Alzheimers Dis. *20 (Suppl 2)*, S487–498.

Takumi, Y., Ramirez-Leon, V., Laake, P., Rinvik, E., and Ottersen, O. P. (1999). Different modes of expression of AMPA and NMDA receptors in hippocampal synapses. Nat. Neurosci. *2*, 618–624.

Terry, R. D., Masliah, E., Salmon, D. P., Butters, N., DeTeresa, R., Hill, R., Hansen, L. A., and Katzman, R. (1991). Physical basis of cognitive alterations in Alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. Ann. Neurol. *30*, 572–580.

Trommald, M., Hulleberg, G., and Andersen, P. (1996). Long-term potentiation is associated with new excitatory spine synapses on rat dentate granule cells. Learn Mem. *3*, 218–228.

Tu, H., Nelson, O., Bezprozvanny, A., Wang, Z., Lee, S.-F., Hao, Y. H., Serneels, L., De Strooper, B., Yu, G., and Bezprozvanny, I. (2006). Presenilins form ER calcium leak channels, a function disrupted by mutations linked to familial Alzheimer's disease. Cell *126*, 981–993.

Turrigiano, G. G. (2008). The self-tuning neuron: Synaptic scaling of excitatory synapses. Cell *135*, 422–435.

Villar, A. J., Belichenko, P. V., Gillespie, A. M., Kozy, H. M., Mobley, W. C., and Epstein, C. J. (2005). Identification and characterization of a new Down syndrome model, Ts[Rb(12.1716)]2Cje, resulting from a spontaneous Robertsonian fusion between T(171)65Dn and mouse chromosome 12. Mamm. Genome *16*, 79–90.

Walsh, D. M., Klyubin, I., Fadeeva, J. V., Cullen, W. K., Anwyl, R., Wolfe, M. S., Rowan, M. J., and Selkoe, D. J. (2002). Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation *in vivo*. Nature *416*, 535–539.

Wei, W., Nguyen, L. N., Kessels, H. W., Hagiwara, H., Sisodia, S., and Malinow, R. (2010). Amyloid beta from axons and dendrites reduces local spine number and plasticity. Nat. Neurosci. *13*, 190–196.

Wenk, G. L. (2003). Neuropathologic changes in Alzheimer's disease. J. Clin. Psychiatry *64 (Suppl 9)*, 7–10.

Wu, H. Y., Hudry, E., Hashimoto, T., Kuchibhotla, K., Rozkalne, A., Fan, Z., Spires-Jones, T., Xie, H., Arbel-Ornath, M., Grosskreutz, C. L., Bacskai, B. J., and Hyman, B. T. (2010). Amyloid β induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation. J. Neurosci. *30*, 2636–2649.

Yoo, A. S., Cheng, I., Chung, S., Grenfell, T. Z., Lee, H., Pack-Chung, E., Handler, M., Shen, J., Xia, W., Tesco, G., Saunders, A. J., Ding, K., Frosch, M. P., Tanzi, R. E., and Kim, T. W. (2000). Presenilin-mediated modulation of capacitative calcium entry. Neuron *27*, 561–572.

Zaman, S. H., Parent, A., Laskey, A., Lee, M. K., Borchelt, D. R., Sisodia, S. S., and Malinow, R. (2000). Enhanced synaptic potentiation in transgenic mice expressing presenilin 1 familial Alzheimer's disease mutation is normalized with a benzodiazepine. Neurobiol. Dis. *7*, 54–63.

Zhang, C., Wu, B., Beglopoulos, V., Wines-Samuelson, M., Zhang, D., Dragatsis, I., Sudhof, T. C., and Shen, J. (2009). Presenilins are essential for regulating neurotransmitter release. Nature *460*, 632–636.

Zhang, D., Zhang, C., Ho, A., Kirkwood, A., Sudhof, T. C., and Shen, J. (2010a). Inactivation of presenilins causes pre-synaptic impairment prior to post-synaptic dysfunction. J. Neurochem. *115*, 1215–21.

Zhang, H., Sun, S., Herreman, A., De Strooper, B., and Bezprozvanny, I. (2010b). Role of presenilins in neuronal calcium homeostasis. J. Neurosci. *30*, 8566–8580.

Zhou, J., Du, W., Zhou, K., Tai, Y., Yao, H., Jia, Y., Ding, Y., and Wang, Y. (2008). Critical role of TRPC6 channels in the formation of excitatory synapses. Nat. Neurosci. *11*, 741–743.

Zhou, Q., Homma, K. J., and Poo, M. M. (2004). Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron *44*, 749–757.

Received: 6 May 2012. Accepted: 25 May 2012.