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ER Calcium and Alzheimer's Disease: In a State of Flux

Mark P. Mattson

Laboratory of Neurosciences, National Institute on Aging Intramural Research Program,
Baltimore, MD 21224

Mark P. Mattson: mattsonm@grc.nia.nih.gov

Abstract

The calcium ion (Ca^{2+}) plays fundamental roles in orchestrating dynamic changes in the function and structure of nerve cell circuits in the brain. The endoplasmic reticulum (ER) is a particularly intriguing organelle that actively removes Ca^{2+} from the cytoplasm, and can release stored Ca^{2+} through ER membrane receptor channels responsive to either the lipid messenger IP_3 or to cytosolic Ca^{2+} . Emerging findings suggest that perturbed ER Ca^{2+} homeostasis contributes to the dysfunction and degeneration of neurons that occurs in Alzheimer's disease (AD). Interestingly, mutations in presenilin-1 (PS1) (an integral membrane protein in the ER of neurons) that cause early-onset inherited AD increase the pool of ER Ca^{2+} available for release, and enhance Ca^{2+} release through ER IP_3 - and ryanodine-sensitive channels. By enhancing Ca^{2+} flux across the ER membrane, PS1 mutations may exaggerate Ca^{2+} signaling in synaptic terminals and thereby render them vulnerable to dysfunction and degeneration in the settings of aging and amyloid accumulation in AD.

Approximately 5 million Americans and 30 million individuals world-wide are currently afflicted with Alzheimer's disease (AD), and is estimated that these numbers will more than double by the year 2050 because of the rapid increase in individuals who live to an age (65+ years) when AD most commonly strikes (1). Nerve cell circuits involved in short-term memory, including those in the entorhinal cortex, hippocampus, prefrontal cortex and basal forebrain are affected early in the AD process and exhibit the most neuronal loss as the disease progresses. Advancing age is the major risk factor for AD, and quantitative structural magnetic resonance imaging data suggest that many of the same brain regions that degenerate in AD exhibit progressive, albeit slower, atrophy during aging in cognitively normal subjects (2). Additional risk factors for AD include a sedentary lifestyle, diabetes, traumatic brain injury and clinical depression. It is believed that each of these risk factors may render neurons vulnerable to AD by increasing levels of oxidative stress and promoting cellular energy deficits in neurons. Why some individuals with one or more of these risk factors escape AD is unknown, but may involve a "cognitive reserve" and/or increased levels of "neuroprotective factors" (3, 4).

Studies of the brains of living and deceased AD patients, of genetic causes of rare inherited forms of AD, and of experimental models of AD have elucidated the sequence of events that occur in nerve cells that result in their dysfunction and death (5, 6). The accumulation of amyloid β -peptide ($\text{A}\beta$), a 40–42 amino acid self-aggregating peptide that forms compact fibrillar deposits (plaques) and diffuse non-fibrillar aggregates, occurs in affected brain regions early in the disease process. $\text{A}\beta$ is produced when the β -amyloid precursor protein (APP; an integral membrane protein) is cleaved first at the N-terminus of $\text{A}\beta$ by β -secretase and then at the C-terminus of $\text{A}\beta$ by γ -secretase (5). Mutations in APP located within or immediately adjacent to $\text{A}\beta$ are responsible for a few rare cases of dominantly inherited familial AD; in each case the mutation increases the production $\text{A}\beta_{1-42}$ (7). Experiments using cultured neurons and mice that produce excessive amounts of human $\text{A}\beta$ have shown

that A β can cause synaptic dysfunction and neuronal degeneration, and that these adverse effects of A β occur when the peptide is in the early stages of self-aggregation. A β can damage neurons by inducing membrane-associated oxidative stress resulting in disruption of Ca²⁺ regulation in a manner that renders neurons vulnerable to Ca²⁺ overload, particularly under conditions of impaired mitochondrial energy production (8).

While the vast majority of cases of AD occur late in life and are sporadic, approximately 5–10% of cases have an early onset (4th and 5th decades of life) and are inherited in autosomal dominant manner. In 1995 Sherrington et al. reported the discovery of five different missense mutations in a gene on chromosome 14 that co-segregated with early-onset familial AD (FAD); the gene, which was initially named S182, is now known as presenilin-1 (PS1) (9). Later that year a mutation in a highly homologous gene located on chromosome 1 (presenilin-2; PS2) was shown to cause FAD in a Volga German kindred (10). Now more than 100 different FAD mutations in PS1 have been reported and most of these mutations increase the production of A β 1-42 when expressed in cultured cells and transgenic mice. PS1 is itself the aspartyl protease responsible for γ -secretase cleavage of APP and functions in a complex with 3 other protein components (nicastrin, Pen-2 and Aph-1) of the γ -secretase complex. The mechanism by which PS1 mutations cause AD therefore involves increased production of A β 1-42 which then aggregates and damages neurons (11). However, an additional mechanism of mutant PS1 action involving intense sparks of Ca²⁺ emanating from within neurons was then discovered (Figure 1).

It was reported that mutant PS1 (L286V mutation) perturbs Ca²⁺ homeostasis in neuronal cells in a manner characterized by increased release of Ca²⁺ from the ER in response to agonists that activate inositol trisphosphate (IP₃) receptors (12). Similar results were obtained in Ca²⁺ imaging studies of neurons from PS1 mutant (M146V) knockin mice which exhibited enhanced Ca²⁺ responses to glutamate receptor stimulation as a result of increased Ca²⁺ release from ER IP₃ and ryanodine receptors (13, 14). Additional studies showed that levels of ryanodine receptors are elevated and caffeine-induced Ca²⁺ release is enhanced in primary hippocampal neurons from PS1 mutant knockin mice (15). Fibroblasts isolated from mutant PS1 knockin mice also exhibited a marked potentiation in the amplitude of Ca²⁺ transients evoked by IP₃ and ER store-operated Ca²⁺ entry through plasma membrane Ca²⁺ channels was impaired (16). The notion that the size of the ER Ca²⁺ pool is abnormally large in neurons expressing mutant PS1 is supported by evidence suggesting that PS1 normally functions as a Ca²⁺ leak channel in the ER membrane and that FAD PS1 mutations disrupt this leak channel function (17).

In a recent article in *Science Signaling*, Cheung et al. (18) directly recorded ER IP₃ receptor currents in lymphocytes from FAD (PS1 mutant) patients and in neurons from PS1 mutant mice. Mutations in PS1 increased the probability that the IP₃ receptor channels were in an open state resulting in enhanced Ca²⁺ release when cells were stimulated. IP₃ receptor channels in cells expressing mutant PS1 exhibited increased open times and, in many cases, dramatic bursts of repetitive openings for extended time periods suggesting an effect of mutant PS1 on modal gating of the channels. Modal gating has been previously described for ryanodine receptors in the ER of skeletal muscle cells and hippocampal neurons (19), and was recently reported to also occur in IP₃ receptor channels where three modes were detected, a low activity mode, a fast kinetic mode and a burst mode (20). The new findings reveal that similar modal gating of IP₃ receptor channels occurs in neurons and that several different FAD PS1 proteins shift the gating such that fast kinetic and burst modes are increased (18). It remains to be established how this shift in modal gating of IP₃ receptors caused by FAD PS1 impacts on specific physiological processes mediated by Ca²⁺ in neurons. One possibility is that increased release of ER Ca²⁺ in presynaptic terminals enhances glutamate release. Wild type PS may play a role in regulating neurotransmitter

release because long-term potentiation (LTP) and short-term plasticity at CA1 synapses are decreased after presynaptic but not postsynaptic deletion of PSs (21). This presynaptic function of PSs was apparently due to an effect of PSs on ER Ca^{2+} release because depletion of ER Ca^{2+} stores with thapsigargin or blockade of ryanodine receptors mimicks and occludes the effects of presynaptic PS depletion. However, excessive release of Ca^{2+} in presynaptic terminals caused by FAD mutant PS1 may ultimately impair synaptic plasticity by causing depletion of the neurotransmitter or by enhancing long-term depression of the postsynaptic response (22).

In a study that combined whole-cell patch-clamp recordings with flash photolysis and Ca^{2+} imaging in brain slices from wild type and PS1 mutant mice, Stutzmann et al. (23) showed that IP_3 -evoked Ca^{2+} responses were 3 times greater in cortical neurons from PS1 mutant mice compared to wild type mice. Interestingly, electrical excitability of PS1 mutant neurons was decreased as the result of Ca^{2+} -mediated activation of K^+ channels. Because Ca^{2+} release from ER plays important roles in multiple postsynaptic processes including LTP and LTD (24), a second possibility is that FAD PS1 mutations enhance postsynaptic responses by increasing the release of Ca^{2+} from IP_3 - and/or ryanodine-sensitive ER in dendrites. Interestingly, whereas IP_3 receptor activation enhances LTP at hippocampal CA1 synapses (25), NMDA receptor-independent LTP is facilitated in mice lacking the type 3 ryanodine receptor (26). Assuming that FAD PS1 mutations enhance Ca^{2+} release from both IP_3 - and ryanodine-sensitive stores in dendrites, Ca^{2+} -mediated processes involved in postsynaptic plasticity could be altered in ways that impair learning and memory.

The best known biological activity of PS1 is that it is an aspartyl protease that cleaves APP and the Notch receptor resulting in the intracellular release of APP and Notch C-terminal domains (AICD and NICD, respectively) (5). The NICD translocates to the nucleus where it functions as a transcriptional regulator, and this may also be the case with AICD. Notch signaling plays a major role in regulating the fate of neural progenitor cells, and may also be involved in synaptic plasticity and neuron survival (27, 28). There is evidence that γ -secretase-mediated Notch and APP cleavage by PS1 may modulate cellular Ca^{2+} signaling (29), although the details of the underlying molecular mechanism(s) is unknown.

How might the perturbed ER Ca^{2+} release caused by PS1 mutations contribute to the cognitive deficits and neurodegeneration in AD? Electrophysiological recordings of synaptic transmission at CA1 synapses in hippocampal slices from PS1 mutant knockin and control mice revealed age-related changes in two different forms of LTP, the widely-studied early phase of LTP (E-LTP), and late-LTP (L-LTP) which requires gene transcription and protein synthesis (30). Young mice exhibit enhanced E-LTP, but impaired maintenance of L-LTP, while older mice are impaired in both E-LTP and L-LTP. In another study it was shown that cholinergic modulation of hippocampal synaptic plasticity is impaired in PS1 mutant knockin mice (31). Activation of muscarinic acetylcholine receptors induces Ca^{2+} release from IP_3 -sensitive stores and enhances LTP in normal mice, but inhibits LTP in PS1 mutant mice. The NMDA current is decreased in hippocampal CA1 neurons of PS1 mutant mice and is restored by intracellular Ca^{2+} chelation. Muscarinic receptor- and NMDA receptor-mediated components of synaptic plasticity were also impaired in 3xTgAD mice that express PS1, APP and tau mutations and exhibit $\text{A}\beta$ and tau pathologies (31). In 3xTgAD mice there is an aberrantly large Ca^{2+} release through ER ryanodine receptors which may be due to increased levels of the type 2 ryanodine receptor (32). In other studies it was shown that FAD PS1 mutations increase the vulnerability of neurons to reduced energy availability and increased oxidative stress, conditions that occur in normal aging and AD (33, 34). The enhanced ER Ca^{2+} release has been shown to occur in synaptic terminals of PS1 mutant mice in studies that further demonstrated an adverse effect of this perturbation of synaptic Ca^{2+} homeostasis on mitochondrial function (35). Collectively, the findings described above

suggest that perturbed ER Ca²⁺ regulation contributes to synaptic dysfunction and neuronal degeneration in experimental models relevant to AD.

What are the relationships between perturbed ER Ca²⁺ regulation and the A β and tau pathologies in AD. A β has been shown to elevate intracellular Ca²⁺ levels in cultured neurons by impairing Ca²⁺ extrusion and by enhancing Ca²⁺ influx through plasma membrane voltage-dependent and glutamate-activated Ca²⁺ channels (5). Recent in vivo calcium imaging studies in a mouse model of AD have demonstrated aberrant elevations of intracellular Ca²⁺ levels in neurites associated with A β deposits (36). Release of ER Ca²⁺ may also contribute to neuronal degeneration in AD because dantrolene, which blocks ryanodine receptors, can protect neurons from being damaged by A β (37 Guo et al., 1997). A β also directly induces oxidative stress in neurons which may further disrupt Ca²⁺ homeostasis and exacerbate amyloidogenic processing of APP (38 Jo et al., 2008) thereby fostering a viscous neurodegenerative cycle. There is also evidence that elevated intracellular Ca²⁺ levels contribute to tau hyperphosphorylation and self-aggregation to form neurofibrillary tangles. For example, sustained elevations of intracellular Ca²⁺ levels caused by overactivation of glutamate receptors can increase tau phosphorylation in cultured hippocampal neurons (39), and can induce phosphorylation of tau and APP, followed by accumulation of A β inside of cultured neurons (40). Postmortem analysis of brain tissue sections from AD patients have provided evidence for elevated Ca²⁺ levels in tangle-bearing neurons compared to healthier neurons (41).

Future research should clarify the specific contributions of perturbed ER Ca²⁺ handling to the cellular events that underlie synaptic dysfunction and neuronal degeneration in AD. While elevated pools of ER Ca²⁺ resulting from FAD PS1 mutations have been widely documented in a range of cell culture and animal models, the molecular basis of this alteration remains unknown. In addition, it is unclear if and how altered ER Ca²⁺ regulation is involved in the more common late-onset forms of AD. One possibility which merits further investigation is that both age- and disease-related processes impose adverse (oxidative and proteotoxic) stress on the ER (42). The emphasis of translational research on AD has, thus far, focused mainly on reducing A β production, enhancing A β removal, or modulating cholinergic and glutamatergic neurotransmission (5). The findings described above suggest that stabilization of ER Ca²⁺ levels is an additional therapeutic approach that merits testing. This might be achieved using dietary and exercise interventions that increase ER stress resistance (43) or drugs that suppress activation of IP₃ or ryanodine receptors (although side effects of such drugs are likely given the important functions of ER Ca²⁺ release in neuronal plasticity).

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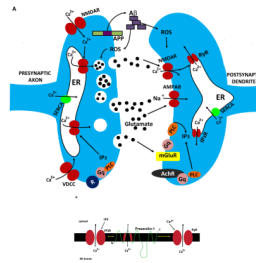


Figure 1.

Mechanisms that regulate synaptic calcium dynamics, and their possible roles in the pathogenesis of Alzheimer's disease (AD). **A.** The endoplasmic reticulum (ER) is present in both presynaptic axon terminals (left) and postsynaptic dendrites (right) where it regulates Ca²⁺-mediated processes involved in synaptic transmission and structural plasticity. In response to membrane depolarization, Ca²⁺ enters presynaptic terminals through voltage-dependent Ca²⁺ channels (VDCC) and N-methyl-D-aspartate (NMDA) glutamate receptors. The elevated cytosolic Ca²⁺ then triggers Ca²⁺ release through ryanodine receptors (RyR), and Ca²⁺ may also be released through IP₃ receptors (IP₃R) in response to activation of metabotropic receptors (R). The elevated Ca²⁺ concentration in the cytosol triggers fusion of glutamate-containing synaptic vesicles with the synaptic plasma membrane resulting in release of glutamate into the synaptic cleft. The β -amyloid precursor protein (APP) is present in the presynaptic membrane, where it can be proteolytically processed to release the amyloid β -peptide (A β). A β then self-aggregates on pre- and post-synaptic membranes where it causes oxidative stress and membrane lipid peroxidation which can disrupt cellular Ca²⁺ homeostasis. Glutamate binds postsynaptic AMPA receptors resulting in sodium influx, membrane depolarization and calcium influx through NMDA receptors and VDCC. Glutamate also binds metabotropic receptors (mGluR) coupled to the GTP-binding protein Gq which then activates phospholipase C (PLC) resulting in generation of IP₃. SERCA, sarco- (smooth-) endoplasmic reticulum Ca²⁺-ATPase. AMPAR (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor). **B.** Presenilin-1 (PS1) is an integral membrane protein that may modulate ER Ca²⁺ dynamics, thereby playing roles in synaptic plasticity and the pathogenesis of AD. PS1 can interact with IP₃R and RyR, and mutations in PS1 that cause early-onset inherited AD enhance the amount of Ca²⁺ released in response to IP₃ or Ca²⁺ influx. PS1 may itself function as a Ca²⁺ leak channel and PS1 mutations may compromise this function of PS1 resulting in an increased intraluminal Ca²⁺ concentration.