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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), an organelle that actively removes Ca^{2+} from the cytoplasm, can release stored Ca^{2+} through ER membrane receptor channels responsive either to the lipid messenger inositol trisphosphate (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). Presenilin-1 (PS1) is an integral membrane protein in the ER; mutations in PS1 that cause early-onset inherited AD increase the pool of ER Ca^{2+} available for release and also 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.

About 5 million Americans and 30 million individuals worldwide are currently afflicted with Alzheimer's disease (AD), and it is estimated that these numbers will more than double by the year 2050 because of the rapid increase in individuals who live to the 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 life-style, diabetes, traumatic brain injury, and clinical depression. It is believed that each of these risk factors may render neurons vulnerable to AD by increasing oxidative stress and promoting cellular energy deficits. Why some individuals with one or more of these risk factors escape AD is unknown, but the answer may involve a "cognitive reserve (resistance of neurons to being damaged by amyloid, increased numbers or efficacy of synapses, or adaptive remodeling of neural circuits)," increased amounts of "neuroprotective factors," or both (*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 occurs in nerve cells that result in their dysfunction and death (*5*, *6*). The accumulation of β-amyloid peptide (Aβ), a 40– to 42–amino acid self-aggregating peptide that forms compact fibrillar deposits (plaques) and diffuse nonfibrillar aggregates, occurs in affected brain regions early in the disease process. Aβ is produced when the β-amyloid precursor protein (APP, an integral membrane protein) is cleaved first at the N terminus of Aβ by β-secretase and then at the C terminus of Aβ by γ-secretase (*5*). Mutations in APP located within or immediately adjacent to Aβ are responsible for a few rare cases of dominantly inherited familial AD; in each case, the mutation increases the production of Aβ1-42, a product of sequential cleavage of APP by β- and γ-secretases (*7*). Experiments using cultured neurons and mice that produce excessive amounts of human Aβ have shown that Aβ can cause synaptic dysfunction and neuronal degeneration, and that these adverse effects of Aβ occur when the peptide is in the early stages of self-aggregation. Aβ can damage neurons by inducing membrane-associated oxidative stress, resulting in disruption of intracellular Ca^{2+} homeostasis in a manner that renders neurons vulnerable to Ca^{2+} overload, particularly under conditions of impaired mitochondrial energy production (*8*).

Although the vast majority of cases of AD occur late in life and are sporadic, about 5 to 10% of cases have an early onset (during the fourth and fifth decades of life) and are inherited in an autosomal dominant manner. In 1995, Sherrington *et al*. reported the discovery of five different missense mutations in a gene on chromosome 14 that cosegregated 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 homologous gene located on chromosome 1 (presenilin-2; *PS2*) was shown to cause FAD in a Volga German kindred (*10*). More than 100 different FAD mutations in PS1 have now been reported; most of these mutations increase the production of Aβ1-42 when introduced into cultured cells or transgenic mice. PS1 is itself the aspartyl protease responsible for γ-secretase cleavage of APP and functions in a complex with three other protein components [nicastrin, presenilin enhancer 2 (Pen-2), and anterior pharynx-defective 1 (Aph-1)] of the γ-secretase complex. The mechanism by which PS1 mutations cause AD therefore involves increased production of Aβ1-42, which aggregates and damages neurons (*11*). However, an additional mechanism of mutant PS1 action involves intense sparks of Ca^{2+} emanating from within neurons (Fig. 1).

A mutant form of PS1 ($Leu^{286} \rightarrow Val$) perturbs Ca^{2+} homeostasis in neuronal cells in a manner characterized by increased release of Ca^{2+} from the ER in response to agonists that activate inositol trisphosphate (IP_3) receptors (*12*). Similar results were obtained in Ca^{2+} imaging studies of neurons from PS1 mutant ($Met^{146} \rightarrow Val$) knock-in mice, which show enhanced Ca^{2+} responses to glutamate receptor stimulation as a result of increased Ca^{2+} release from ER IP_3 and ryanodine receptors (*13*). Additional studies showed that ryanodine receptor (RyR) abundance is increased and caffeine-induced Ca^{2+} release is enhanced in primary hippocampal neurons from PS1 mutant knock-in mice (*14*). Fibroblasts isolated from PS1 mutant knock-in mice also show a marked increase in the amplitude of Ca^{2+} transients evoked by IP_3, whereas ER store-operated Ca^{2+} entry through plasma membrane Ca^{2+} channels is impaired (*15*). The notion that the size of the ER Ca^{2+} pool is abnormally large in neurons harboring mutant PS1 is supported by evidence suggesting that PS1 normally functions as a Ca^{2+} leak channel in the ER membrane

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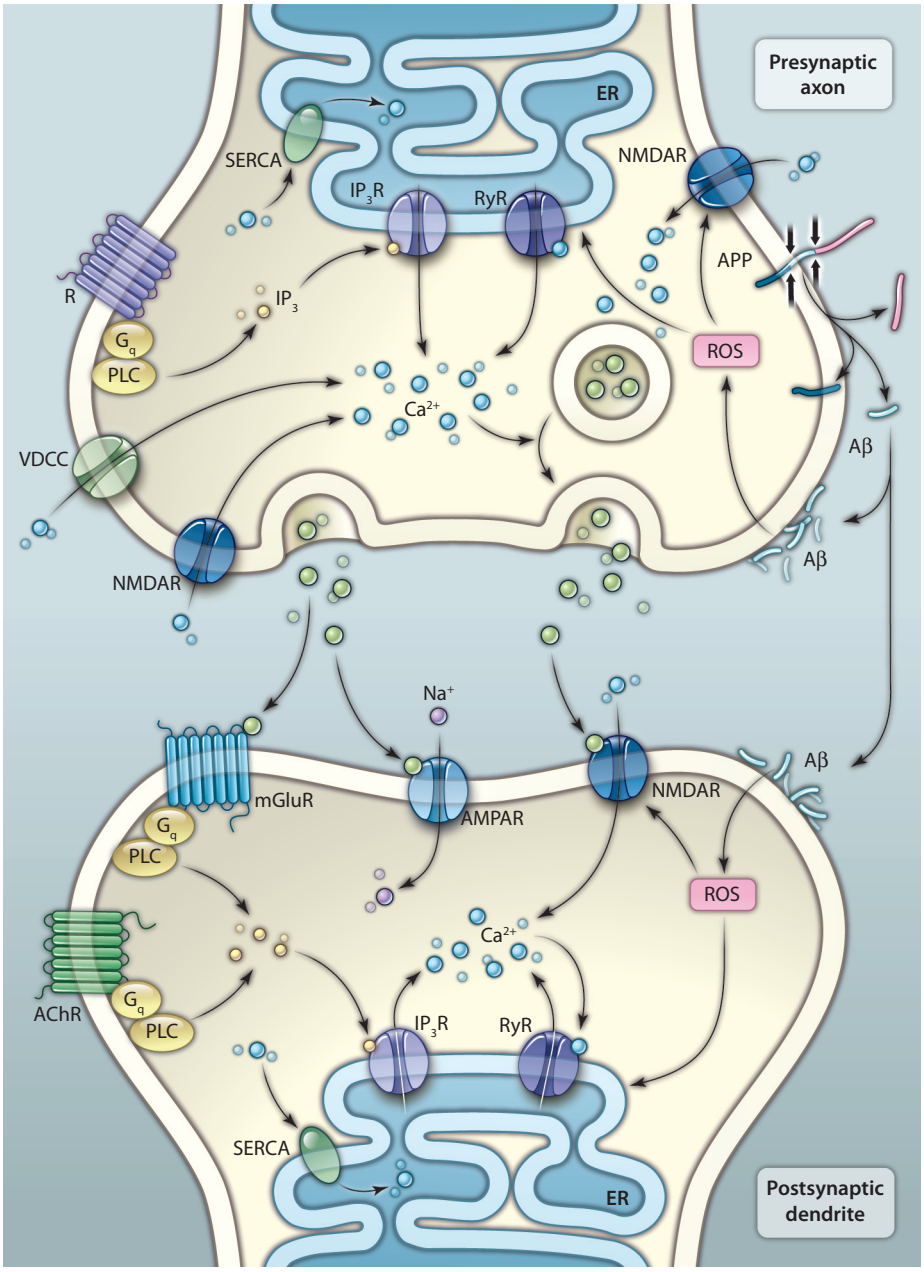

Fig. 1. Mechanisms that regulate synaptic calcium dynamics, with possible roles in the pathogenesis of Alzheimer's disease. The endoplasmic reticulum (ER) is present in both presynaptic axon terminals (top) and postsynaptic dendrites (bottom), where it regulates Ca^{2+}-mediated processes involved in synaptic transmission and structural plasticity. In response to membrane depolarization, Ca^{2+} enters presynaptic terminals through voltage-dependent Ca^{2+} channels (VDCC) and NMDA-type glutamate receptors (NMDAR). The increased cytosolic Ca^{2+} then triggers Ca^{2+} release through ER ryanodine receptors (RyR); Ca^{2+} may also be released through ER IP_3 receptors (IP_3R) in response to activation of metabotropic receptors (R). Increased Ca^{2+} concentration near release sites triggers fusion of glutamate-containing synaptic vesicles with the plasma membrane, leading to 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 β-amyloid peptide (Aβ). Aβ self-aggregates on pre- and postsynaptic membranes, where it causes oxidative stress and membrane lipid peroxidation, thereby disrupting intracellular Ca^{2+} homeostasis, enhancing neurotransmitter release presynaptically and Ca^{2+} influx through the NMDAR postsynaptically. Glutamate binds postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), resulting in sodium influx, membrane depolarization, and calcium influx through the NMDAR and VDCC. Glutamate also binds metabotropic receptors (mGluR) coupled to the guanosine triphosphate–binding protein G_q, leading to activation of phospholipase C (PLC) and generation of IP_3. AChR, acetylcholine receptor; SERCA, sarco-(smooth-) endoplasmic reticulum Ca^{2+}–adenosine triphosphatase; ROS, reactive oxygen species

and that FAD PS1 mutations disrupt this leak channel function (Fig. 2) (*16*).

Cheung *et al*. (*17*) now show that the biophysical properties of IP_3 receptor channels are modified by FAD PS1 mutations, resulting in increased opening of the channels and thereby increased ER Ca^{2+} release. These new findings may explain why synaptic function is perturbed early in the process of AD, and suggest a potential for therapeutic interventions that target IP_3 receptors. By directly recording ER IP_3 receptor currents in lymphoblasts from individuals with FAD (PS1 mutant) and in neurons from PS1 mutant mice, they found that mutations in PS1 increased the probability that IP_3 receptor channels were in an open state, resulting in enhanced Ca^{2+} release when cells were stimulated.

IP_3 receptor channels in cells expressing mutant PS1 showed increased open times and, in many cases, 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 (*18*). It has also been reported in IP_3 receptor channels in insect Sf9 cells, where three modes were detected: a low-activity mode, a fast kinetic mode, and a burst mode (*19*). The new findings reveal that similar modal gating of IP_3 receptor channels occurs in neurons and that several different FAD PS1 proteins shift gating in favor of fast kinetic and burst modes (*17*). It remains to be established how this shift in modal gating of IP_3 receptors caused by FAD PS1 affects specific physiological processes mediated by Ca^{2+} in neurons. One possibility is that increased release of ER Ca^{2+} in presynaptic terminals enhances glutamate release. Long-term potentiation (LTP) and short-term plasticity at CA1 synapses are decreased after presynaptic but not post-

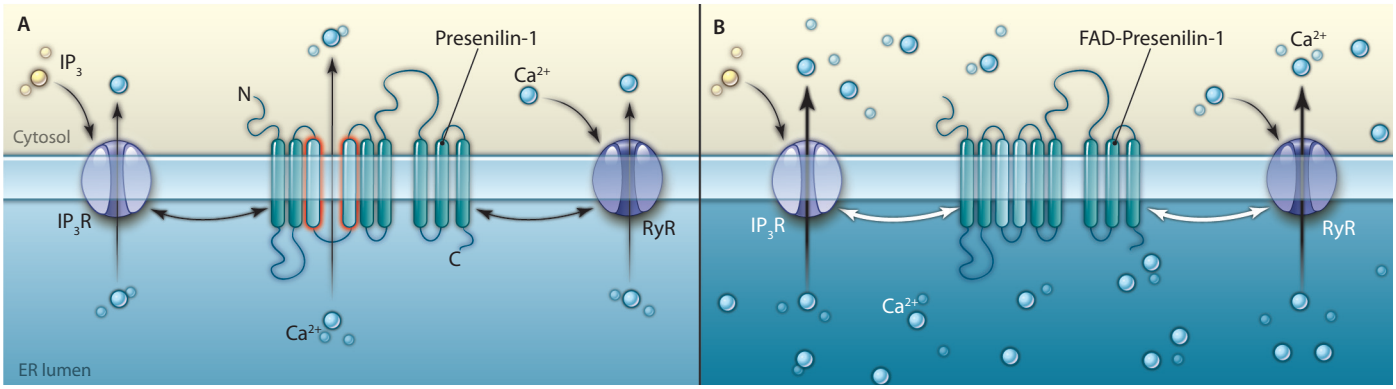

Fig. 2. Presenilin-1 (PS1) regulation of ER Ca^{2+} dynamics. PS1 is an integral membrane protein that may modulate ER Ca^{2+} dynamics, thereby playing roles in synaptic plasticity and the pathogenesis of AD. PS1 can interact with IP_3R and RyR, and mutations in PS1 that cause early-onset inherited AD enhance the amount of Ca^{2+} released in response to IP_3 or Ca^{2+} influx. PS1 may itself function as a Ca^{2+} leak channel, and PS1 mutations may compromise this function of PS1, resulting in an increased intraluminal Ca^{2+} concentration.

synaptic deletion of PSs, which suggests that wild-type PS may play a role in limiting neurotransmitter release (*20*). This presynaptic function of PSs is 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 mimics 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 neurotransmitter depletion or by enhancing long-term depression (LTD) of the postsynaptic response (*21*).

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 (*22*) showed that, relative to responses in cortical neurons from wild-type mice, IP_3-evoked cytosolic Ca^{2+} transients in cortical neurons from PS1 mutant mice were greater in magnitude by a factor of 3. However, the 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 (*23*), FAD PS1 mutations may alter postsynaptic responses by increasing the release of Ca^{2+} from IP_3- or ryanodine-sensitive ER (or both) in dendrites. Whereas IP_3 receptor activation enhances LTP at hippocampal CA1 synapses (*24*), *N*-methyl-D-aspartate (NMDA)–type glutamate receptor–independent LTP is facilitated in mice lacking the type 3 ryanodine receptor (*25*). 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 thus be altered in ways that impair learning and memory.

The best-known biological activity of PS1 is as 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 it may also be involved in synaptic plasticity and neuron survival (*26*).

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 knock-in 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 (*27*). Young mice exhibit enhanced E-LTP but impaired maintenance of L-LTP, whereas older mice are impaired in both E-LTP and L-LTP. Another study showed that cholinergic modulation of hippocampal synaptic plasticity is impaired in PS1 mutant knock-in mice (*28*). 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 are also impaired in 3xTgAD transgenic mice, which express PS1, APP, and tau mutations and exhibit Aβ and tau pathologies (*28*). In 3xTgAD mice, there is aberrantly large Ca^{2+} release through ER ryanodine receptors that may be due to increased levels of the type 2 ryanodine receptor (*29*). Other studies showed that FAD PS1 mutations increase the vulnerability of neurons to reduced energy availability and increased oxidative stress, conditions that occur in both normal aging and AD (*5*). Enhanced ER Ca^{2+} release occurs in synaptic terminals of PS1 mutant mice in studies that further demonstrate an adverse effect of this perturbation of synaptic Ca^{2+} homeostasis on mitochondrial function (*30*). Collectively, these findings suggest that perturbed ER Ca^{2+} regulation contributes to synaptic dysfunction and neuronal degeneration in experimental models relevant to AD.

What are the relationships between perturbed ER Ca^{2+} regulation and the Aβ and tau pathologies in AD? Aβ increases intracellular Ca^{2+} concentrations in cultured neurons both by impairing Ca^{2+} extrusion and by enhancing Ca^{2+} influx through plasma membrane voltage-dependent and glutamate-activated Ca^{2+} channels (*5*). Recent in vivo calcium imaging studies in a mouse model of AD have demonstrated aberrant increases in intracellular Ca^{2+} concentration in neurites in the vicinity of Aβ deposits (*31*). Dantrolene, which blocks ryanodine receptors, can protect neurons from being damaged by Aβ, providing further support for the notion that release of ER Ca^{2+} may also contribute to neuronal degeneration in AD (*32*). Aβ also directly induces oxidative stress in neurons through the production of reactive oxygen species, which may further disrupt Ca^{2+} homeostasis and exacerbate amyloidogenic processing of APP (*33*), thereby fostering a vicious neurodegenerative cycle. Increased intracellular Ca^{2+} concentrations may contribute to tau hyperphosphorylation

and self-aggregation, thereby promoting the formation of neurofibrillary tangles (*5*).

Future research should clarify the specific contributions of perturbed ER Ca^{2+} handling to the cellular events that underlie synaptic dysfunction and neuronal degeneration in AD. Although increased ER Ca^{2+} resulting from FAD PS1 mutations has been documented in various cell culture and animal models, the molecular basis of this alteration remains unknown. In addition, it is unclear whether and how altered ER Ca^{2+} regulation is involved in the more common late-onset forms of AD. One possibility that merits further investigation is that both age- and disease-related processes impose adverse (oxidative and proteotoxic) stress on the ER (*34*). The emphasis of translational research on AD thus far has focused mainly on reducing Aβ production, enhancing Aβ removal, or modulating cholinergic and glutamatergic neurotransmission (*5*). The findings described above suggest that stabilization of ER Ca^{2+} is an additional therapeutic approach that merits testing. This might be achieved with the use of drugs that suppress activation of IP_3 or ryanodine receptors (although side effects of such drugs are likely, given the important functions of ER Ca^{2+} release in neuronal plasticity and outside of the brain).

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