Calcium Dysregulation, IP_3 Signaling, and Alzheimer's Disease

GRACE E. STUTZMANN
Department of Neurobiology and Behavior
University of California, Irvine

Ca^{2+} ions subserve complex signaling roles in neurons, regulating functions ranging from gene transcription to modulation of membrane excitability. Ca^{2+} ions enter the cytosol from extracellular sources, such as entry through voltage-gated channels, and by liberation from intracellular endoplasmic reticulum (ER) stores through inositol triphosphate (IP_3) receptors and/or ryanodine (RyR) receptors. Disruptions of intracellular Ca^{2+} signaling are proposed to underlie the pathophysiology of Alzheimer's disease (AD), and recent studies examining AD-linked mutations in the presenilin genes demonstrate enhanced ER Ca^{2+} release in a variety of cell types and model systems. The development of transgenic AD mouse models provides a means to study the mechanisms and downstream effects of neuronal ER Ca^{2+}-signaling alterations on AD pathogenesis and offers insight into potential novel therapeutic strategies. The author discusses recent findings in both the physiological functioning of the IP_3-signaling pathway in neurons and the involvement of ER-Ca^{2+} disruptions in the pathogenesis of AD. NEUROSCIENTIST 11(2):110–115, 2005. DOI: 10.1177/1073858404270899

KEY WORDS *Presenilin, Endoplasmic reticulum, Neurodegenerative, Transgenic, Ryanodine*

Alzheimer's disease (AD) is a devastating and always fatal neurodegenerative disease that slowly and perniciously destroys neurons and cognitive abilities. Although a variety of drug treatments can delay or temporarily reduce the severity of the disease, there is still no cure or long-term effective treatment. AD can be divided into two categories; the most common is termed *sporadic*, with a relatively late onset (70+ years), moderate to extreme severity, and no known origin or cause for onset. Definitive diagnosis is made through postmortem findings of diffuse β amyloid plaques (Aβ plaques), neurofibrillary tangles, and neuronal cell loss in brain tissue. With inherited familial AD (FAD), the pattern of cognitive decline and histopathological markers are essentially the same as the sporadic form but differ considerably in that the age of onset is markedly younger (as early as 30 years) and the progression of symptoms is more aggressive. FAD is tightly linked to mutations in a select set of genes, namely, the *presenilin 1* and *2* (*PS1, PS2*) and *APP* genes. Although the exact mechanistic link between expression of the mutant genes and onset of AD is not yet known, it is clear that expression of the mutation will lead to onset of FAD (for reviews, see Rossor and others 1996; LaFerla 2002).

Funded by the National Institutes of Health GM 48071 and NIA P50 AG16573. The author thanks Ian Parker and Frank LaFerla for critical review and feedback and Judy Samattasribootr for help in manuscript preparation.

Address correspondence to: Grace E. Stutzmann, 1146 McGaugh Hall, Department of Neurobiology and Behavior, University of California, Irvine, Irvine, CA 92697-4550 (e-mail: grace@uci.edu).

The hallmark features of AD, accumulation of Aβ plaques, neurofibrillary tangles, and neuronal cell loss, are often used as diagnostic markers in conjunction with severe cognitive decline. The accumulation of intra- and extracellular Aβ plaques results from the aberrant proteolysis of the amyloid precursor protein (APP) by enzymatic activity of γ secretase, of which the presenilin protein is an integral constituent. Hyperphosphorylated tau forms the primary component of the intracellular neurofibrillary tangles found in neurites in AD brains. And selective neuronal loss is integral to the disease and is concentrated in brain regions associated with cognition and memory such as the frontal cortex and hippocampus. Much attention has focused on Aβ as a trigger for AD, but accumulating evidence points to disruptions in neuronal Ca^{2+} signaling as a consistent progenitor of AD, occurring prior to the development of the histopathological markers and cognitive decline. Whether the early Ca^{2+} dysregulation is a cause, effect, or an independent parallel track of AD is still being debated. At the very least, enhanced endoplasmic reticulum (ER) Ca^{2+} is believed to exacerbate Aβ and tau formation and alter synaptic signaling and neuronal membrane excitability (Mattson, Lovell, and others 1993; Mattson, Tomaselli, and others 1993; Oddo and others 2003; Stutzmann and others 2004a).

Neuronal Ca^{2+}-Signaling Pathways

Many neuronal functions depend on intracellular Ca^{2+} signals that are precisely regulated in space, time, and magnitude. Maintenance of these Ca^{2+} dynamics is critical for proper neuronal activity: Insufficient levels lead

ISSN 1073-8584

to impaired functioning, whereas excessive cytosolic Ca^{2+} levels cause cell death (Berridge 1998). The resting cytosolic Ca^{2+} concentration in neurons, as in other cells, is maintained very low but can be elevated by Ca^{2+} ions arising from two major sources: extracellular Ca^{2+} ions entering the cell through voltage-, receptor-, or store-operated channels on the plasma membrane and liberation of Ca^{2+} ions sequestered in the ER.

Liberation of Ca^{2+} from intracellular stores occurs through two channels in the ER membrane: the inositol trisphosphate receptor (IP_3R), which is activated by the second messenger IP_3, and the ryanodine receptor (RyR), which is activated by cytosolic Ca^{2+}. IP_3 is generated via agonist stimulation of Gq-coupled receptors found on the plasma membrane (e.g., $5HT_{2A}$, $mGluR_{1,5}$ receptor subtypes) and diffuses from the plasma membrane to its receptor on the ER. In addition to IP_3, Ca^{2+} also serves as a biphasic modulator of IP_3-mediated Ca^{2+} release from the ER, potentiating channel opening at low [Ca^{2+}] and suppressing it higher [Ca^{2+}]. Both IP_3R and RyR can thus be considered as Ca^{2+}-gated channels, mediating a regenerative process of Ca^{2+}-induced Ca^{2+} release (CICR) but with the important exception that the IP_3R has an obligate requirement for IP_3 (Fig. 1). In neurons, it is not clear if the IP_3R and RyR release Ca^{2+} from the same or different ER pools, and depending on cell type, subcellular region, and brain region, the distributions of these two receptors may overlap or be distinct. For example, IP_3R and IP_3-evoked Ca^{2+} signals are predominantly localized in the soma and proximal dendrites of cortical and hippocampal neurons (Sharp and others 1993; Nakamura and others 1999; Stutzmann and others 2003a), whereas RyR-mediated signals are more pronounced in dendritic spines and presynaptic terminals. (Padua and others 1996; Rose and Konnerth 2001, for review).

At rest, the concentration of free Ca^{2+} in the ER lumen is thought to be several hundred µM (~250 µM; Meldolesi and Pozzan 1998; Corbett and Michalak 2000), a thousand times or more greater than the resting cytosolic level. This enormous concentration gradient is maintained by SERCA (sarco-endoplasmic reticulum Ca^{2+} ATPase) pumps that actively transport Ca^{2+} into the ER from the cytoplasm, thereby recycling previously liberated Ca^{2+} and assisting in the clearance of excess Ca^{2+} entering across the plasma membrane. The SERCA pumps are sensitive to cytosolic and ER Ca^{2+} levels and "turn on" in the excess of the former or insufficiency in the latter. Moreover, the ER contains a special set of Ca^{2+} buffers, such as calreticulin, calsequestrin, and calnexin, that help determine and stabilize the free Ca^{2+} level in the ER and determine the total amount of releasable Ca^{2+} (Corbett and Michalak 2000).

Because the ER can function rather independently and maintains its own level of homeostasis, it has thus been christened a "neuron within a neuron" (Berridge and others 1998). It forms a continuous network extending from the nuclear envelope throughout axons and dendrites and even protruding into dendritic spine heads (Verkhratsky 2002). The Ca^{2+} residing within the ER

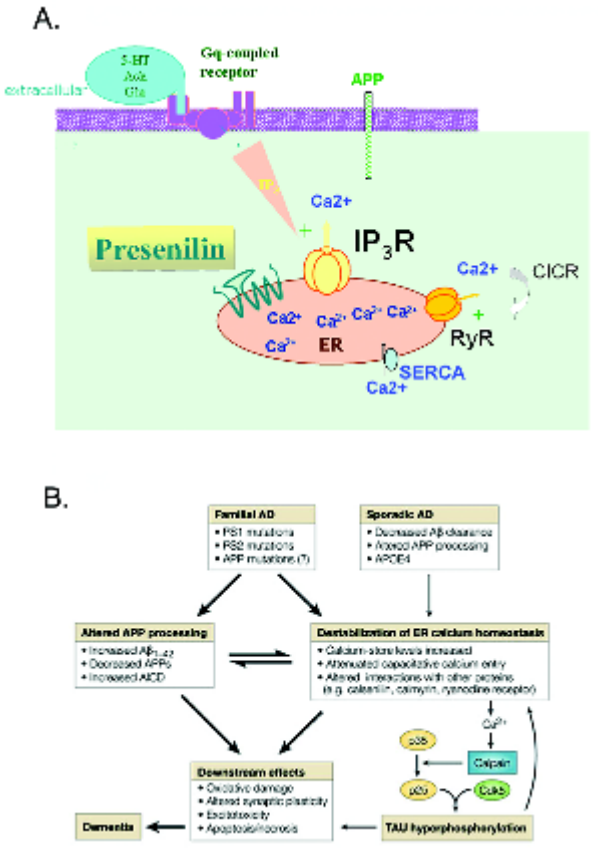

Fig. 1. Endoplasmic reticulum (ER) Ca^{2+} signaling pathways and links to Alzheimer's disease (AD) pathogenesis. *A*, Schematic overview of ER signaling pathways in neurons. Gq-coupled receptors on the plasma membrane transduce a neurotransmitter signal into production of the second messenger inositol triphosphate (IP_3), which binds to IP_3 receptors on the ER causing release of Ca^{2+} from ER stores. Ryanodine receptors (RyR), also found in the ER membrane, are stimulated to release further Ca^{2+} by Ca^{2+} itself, a process termed *Ca^{2+}-induced Ca^{2+} release* (CICR). SERCA pumps use ATP to pump Ca^{2+} back into the ER against its concentration gradient. In addition, presenilin, a transmembrane protein also located in the ER, serves proteolytic functions including cleavage amyloid precursor protein (APP) into Aβ fragments. Its proximity to the IP_3R, RyR, and SERCA, together with evidence functionally linking it to AD Ca^{2+} dysregulation, makes presenilin a strong candidate for involvement in the early pathogenesis of AD. *B*, Relationships between ER Ca^{2+} dysregulation and AD pathology. The diagram outlines the possible contributors to and downstream effects of dysregulated intracellular Ca^{2+} signaling and its role in sporadic and familial AD pathology.

serves many functions, including initiation of gene transcription (Mellstrom and Naranjo 2001), activation of Ca^{2+}-sensitive membrane currents (Yamamoto and others 2002; Stutzmann and others 2003a, 2003b), and modulation of synaptic inputs and plasticity (Nakamura and others 1999; Fujii and others 2000; Nishiyama and others 2000). Although proper functioning of these Ca^{2+}-dependent processes is critical for neuronal viability and synaptic functioning, disruption of Ca^{2+} signaling has been linked to the development of several neuropathologies and degenerative diseases (Mattson and others

2000; Missiaen and others 2000; LaFerla 2002). Here we will discuss the recent data that pertain to dysregulations in intracellular Ca^{2+} signaling, and the neurogenesis of AD.

AD and the Ca^{2+} Hypothesis of AD

The Ca^{2+} hypothesis of AD was first introduced by Khachaturian (1994), who proposed that sustained and accumulated alterations in Ca^{2+} homeostasis are a proximal cause in neurodegenerative diseases such as AD. At that time, there was little supporting evidence, but several subsequent studies now reinforce the validity of the Ca^{2+} hypothesis (for reviews, see Mattson and others 2000; LaFerla 2002). The earliest studies were conducted on fibroblasts taken from familial AD patients and demonstrated enhanced ER Ca^{2+} release upon agonist stimulation of IP_3 receptors. Interestingly, this was also observed in cells obtained from presymptomatic family members who were subsequently shown to express *PS1* and develop AD mutations (Ito and others 1994; Etcheberrigaray and others 1998). These studies were important in demonstrating functional alterations in ER Ca^{2+} signaling in both sporadic and familial cases of AD and in showing that Ca^{2+} disruptions long precede the classical markers of AD.

AD Mutations and Intracellular Ca^{2+} Signaling

There are several mutations within the *PS1*, *PS2*, and *APP* genes that are linked to AD, and all of the mutations studied to date have been linked to alterations in ER Ca^{2+} signaling (see LaFerla 2002, for review). Because the majority of AD-linked mutations are in *PS1*, this gene will be predominantly focused on in this review. Several preliminary studies were critical in formulating the link between *PS* mutations, Ca^{2+} dysregulation, and AD, and they set the groundwork for a series of more detailed investigations. The early expression studies of mutant *PS* in nonneuronal cell lines demonstrated an up-regulation of Ca^{2+} responses mediated by IP_3-linked cell surface receptors and an increased sensitivity to apoptosis (Guo and others 1996; Leissring and others 2000). Additional studies have demonstrated a similar up-regulation of second-messenger-mediated Ca^{2+} signaling in neurons, the primary cell type affected in AD, together with increased vulnerability to excitotoxicity and oxidative stress (Guo and others 1997, 1999). Subsequent expression studies in *Xenopus laevis* oocytes then narrowed down the site of action by using photolysis of caged IP_3 to directly activate ER-Ca^{2+} release and bypass upstream events in the phosphoinositide-signaling pathway. Using this model cell system, overexpression of either mutant *PS1* or *PS2* was found to increase the magnitude of elementary Ca^{2+} release events ("puffs") and to enhance Ca^{2+} activated currents through the plasma membrane (Leissring, Paul, and others 1999; Leissring, Parker, and others 1999; Leissring and others 2001).

Analogous experiments in cortical neurons using whole-cell patch clamp and rapid Ca^{2+} imaging in brain

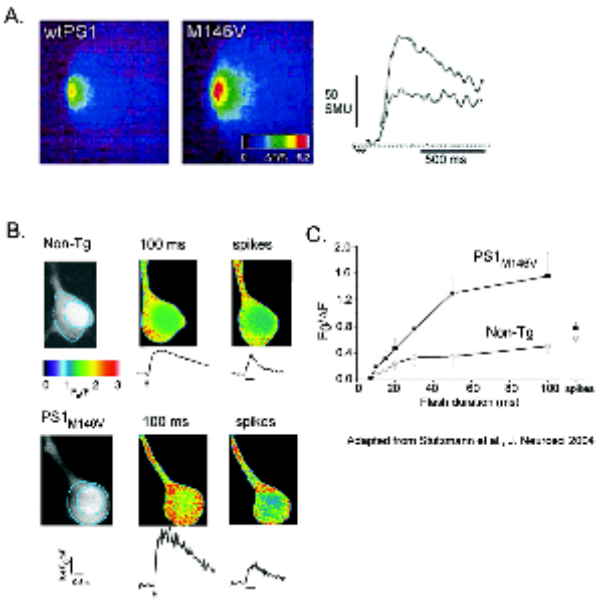

Fig. 2. Effects of PS1 mutations on inositol triphosphate (IP_3)- and voltage-mediated Ca^{2+} signals. *A*, Expression of mutant *PS* (*$PS1_{M146V}$*) in *Xenopus* oocytes results in greatly enhanced local Ca^{2+} signals ("puffs") evoked by flash photolysis of caged IP_3 (*left*). Traces on the right show the corresponding amounts of total Ca^{2+} liberation (signal mass), revealing a twofold increase with expression of mutant PS1 as compared to wild-type PS1. Reproduced with permission from Leissring and others (2001). *B*, Ca^{2+}-dependent fluorescence signals in cortical pyramidal neurons in a brain slice preparation following photorelease of IP_3 (*left panels*) and activation of trains of action potentials by injection of depolarizing current (*right*). Traces show the kinetics of Ca^{2+} signals measured from the cell soma. IP_3-evoked Ca^{2+} signals were greater in the $PS1_{M146V}$ mice (*bottom*) than in nontransgenic controls (*top*), but no appreciable differences were apparent in Ca^{2+} entry through voltage-gated Ca^{2+} channels during action potentials. *C*, Mean peak amplitude of Ca^{2+}-fluorescence signals from the soma measured from non-tg (*open circles*) and $PS1_{M146V}$ neurons (*filled squares*) and plotted as a function of flash duration. Amplitudes of Ca^{2+} signals evoked by trains of action potentials are shown at the right. Reproduced with permission from Stutzmann and others (2004a).

slices from mutant *PS1* knock-in mice also demonstrated a marked (~threefold) exaggeration of ER Ca^{2+} liberation by photoreleased IP_3 and accompanying enhancement of Ca^{2+}-evoked outward membrane currents (Stutzmann and others 2003b, 2004). In contrast, Ca^{2+} signals evoked by entry of extracellular Ca^{2+} through voltage-gated channels were largely unchanged in these mice, indicating that the effects of *$PS1_{M146V}$* mutations are relatively specific to intracellular Ca^{2+} liberation (Fig. 2).

How relevant are these findings to the pathophysiology of ADβ Fibroblasts and *Xenopus* oocytes do not develop AD, and the *PS1* mutant mice fail to show the characteristic histopathological markers of AD. Recently, studies have used a novel triple transgenic mouse model (3Tg; Oddo and others 2003) expressing mutant *$PS1_{M146V}$*, *APPswe*, and *tau*, in which the animals develop plaques and neurofibrillary tangles in an age- and region-specific manner. IP_3-evoked Ca^{2+} signals were

found to be enhanced to an extent similar to that in mice expressing the *PS1* mutant alone. Interestingly, Ca^{2+} signaling was already disrupted at 4 to 6 weeks of age, preceding the appearance of plaques and tangles by several months (Stutzmann and others 2004b; Oddo and others 2003).

How Do AD Mutations Disrupt IP_3-Mediated Ca^{2+} Signaling?

We do not yet know the physiological function(s) of PS or how AD-linked mutations disrupt Ca^{2+} signals. However, when attempting to compile the existing evidence, some good starting points to consider are that 1) the presenilin proteins localize in the ER membrane, 2) they interact with several Ca^{2+}-regulating ER proteins such as RyR and calsenilin (Chan and others 2000; Mattson and others 2000), and 3) overexpression of the wild-type forms enhance IP_3-evoked Ca^{2+} liberation, although to a lesser extent than the mutants. Thus, one obvious possibility is that PS regulates the levels of an ER-Ca^{2+} signaling protein, such as the IP_3R, SERCA, RyR, or luminal Ca^{2+} buffers. However, baseline levels of these proteins are unchanged in the cortex of 4- to 8-week-old *PS1* mutant mice, despite the marked enhancement of IP_3-evoked Ca^{2+} signals at this time point (Stutzmann and others 2004). Moreover, an increase in the sensitivity of the IP_3R is unlikely to be involved because IP_3 dose-response curves in both the PS1 and 3-Tg mice do not show a simple rightward shift, indicating that a straightforward change in receptor affinity is not likely (Stutzmann and others 2004a). On the other hand, *PS1* mutations have been shown to increase levels of the RyR in cultured hippocampal neurons from embryonic mice (Chan and others 2000), which suggests that brain regions with different cellular machinery, and/or cells at different developmental stages, may have variable responses to PS mutations.

Instead, the available evidence suggests a mechanism involving overfilling of ER Ca^{2+} stores. In particular, liberation of ER Ca^{2+}, independent of IP_3R activation, by caffeine activation of RyR or blocking SERCA pumps with CPA or thapsigargin, is also enhanced by PS mutations (Chan and others 2000; Leissring and others 2000). Thus, enhanced intracellular Ca^{2+} release may not be a mechanism specific to the IP_3R but rather reflects an increased ER Ca^{2+} load. How this occurs is also not clear, but one possibility is an increase in the activity of the SERCA pump, whereby the increased flux leads to accelerated and possibly increased Ca^{2+} entry into the ER.

An alternative, but not mutually exclusive, explanation is an increased contribution of the Ry-sensitive stores in response to IP_3-evoked Ca^{2+} release via a CICR mechanism. Evidence for this is demonstrated by blocking the RyR with dantrolene or ryanodine, which results in a return of the exaggerated Ca^{2+} signal back to levels observed in controls (Chan and others 2000; Stutzmann and others 2003b; Stutzmann and others 2004b).

How Do Ca^{2+} Signaling Disruptions Contribute to AD Pathology?

The ER functions as more than a Ca^{2+} store: It is also involved in the synthesis and processing of newly formed membrane proteins and in protein release mechanisms responding to cellular stress. Therefore, alterations in ER-Ca^{2+} signaling can exert a wide array of downstream consequences for neuronal physiology, ranging from altering transcription factors to impairments in synaptic plasticity thought to underlie learning and memory (for reviews, see Rose and Konnerth 2001; Verkhratsky 2002).

Alterations in ER Ca^{2+} signals can interfere with the unfolded protein response (UPR), which is necessary for halting the initiation phase of protein synthesis, resulting in increased protein load and further stress in the ER. In addition, critical proteins that normally play a role in maintaining ER Ca^{2+} levels may be altered due to disrupted sensors of the UPR, such as with the reduced levels of grp78 reported in AD brains or the antiapoptotic bcl-2 protein (Katayama and others 1999; Yasuda and others 2002). Altered Ca^{2+} regulation is also thought to interfere with the normal proteolytic processing of APP, resulting in increased levels of the toxic $A\beta_{42}$ fragments and increase hyperphosphorylated τ (Querfurth and Selkoe 1994). Enhanced Ca^{2+} release from the ER can also sensitize neurons to subsequent stress by increasing phospholipase C activity (Cedazo-Minguez and others 2002) or cell death by up-regulating Ca^{2+}-activated proteins involved in apoptotic cascades such as caspase-12 and m-calpain (Guo and others 1999; Nakagawa and others 2000).

Neuronal activity and plasticity can also be affected by altered ER Ca^{2+} levels. PS1 mutations can enhance an existing Ca^{2+}-activated hyperpolarizing current that further reduces spiking frequency. The exaggerated IP_3-evoked Ca^{2+} release increases the amplitude of a Ca^{2+}-activated hyperpolarizing current that further suppresses membrane excitability, possibly resulting in altering coincidence detection and local circuit activity by increasing the threshold to spike activation (Fig. 3). Analogous findings describe an increase in the medium and late after-hyperpolarization in CA3 pyramidal neurons, which is mediated by Ca^{2+}-sensitive K^+ currents (Barrow and others 2000; Stutzmann and others 2003a, 2004a). In some neurons, the ER extends into the dendrites and dendritic spine heads, placing IP_3-evoked Ca^{2+} release in a prime location to modulate synaptic plasticity by increasing local Ca^{2+} transients in synchrony with Ca^{2+} entry through voltage-gated channels. This combination of Ca^{2+} sources is a very influential mechanism mediating synaptic plasticity because activation of IP_3-sensitive stores has the ability to switch LTP to LTD by liberation of local ER Ca^{2+} stores (Fujii and others 2000). In AD models, alteration of intracellular Ca^{2+} stores can affect synaptic plasticity in other ways. For example, there are several transgenic mouse models of AD

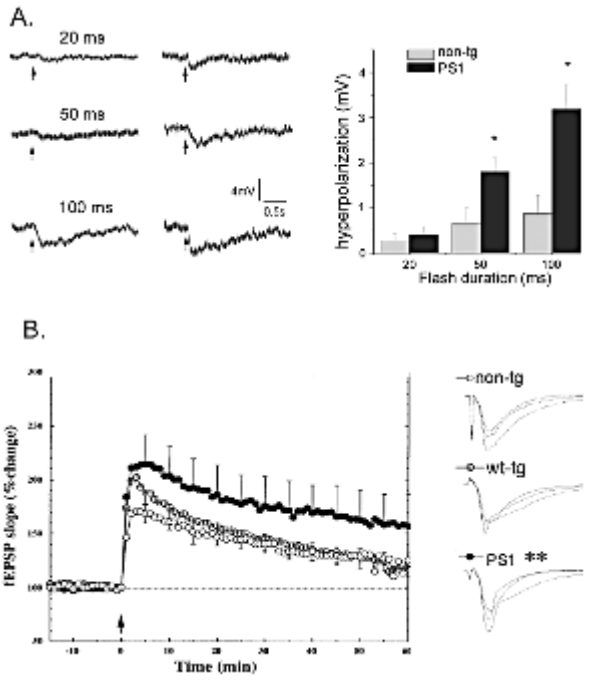

Fig. 3. PS1 mutations alter membrane excitability and synaptic plasticity. *A*, Inositol triphosphate (IP_3)-evoked membrane hyperpolarization is enhanced in mutant PS1 neurons. Traces show representative records of membrane potential changes in a non-tg neuron (*left*) and a mutant PS1 neuron (*right*) in response to photorelease of IP_3 by light flashes with durations as indicated in milliseconds. Bar graph shows average IP_3-evoked hyperpolarizations evoked by these photolysis flashes, pooled from non-tg (gray bars) and mutant PS1 neurons (black bars). Reproduced with permission from Stutzmann and others (2004a). *B*, Field potential recordings in hippocampal slices from control (*open circles and crossed circles*) and PS1 mutant mice (*filled circles*) show enhanced LTP in the mutant mice. Reproduced with permission from Parent and others (1999).

expressing mutant *PS1* that demonstrate enhanced LTP at hippocampal synapses (Parent and others 1999; Barrow and others 2000; Zaman and others 2000; Oddo and others 2003). In addition, basal synaptic transmission and paired pulse facilitation (which is dependent on presynaptic Ca^{2+}) are typically unaffected, which likely reflects a postsynaptic enhancement of Ca^{2+} signaling. This synaptic dysfunction may be related to the cognitive deficits in AD, as well as the pattern of overall cell death.

Ca^{2+}-Signaling Pathways as Potential Targets for Therapeutic Intervention

Given the early and ubiquitous involvement of Ca^{2+} dysregulation in AD pathogenesis, it presents a logical target for therapeutic interventions. However, a difficulty with such a strategy will be to isolate and appropriately modify the correct pathways, given the universal importance of Ca^{2+} for a multitude of functions in neurons and virtually all other cells in the body. Nevertheless, several clinical studies have used specific Ca^{2+} channel blockers with modest results. For example, nimodipine, a voltage-gated L-type Ca^{2+} channel blocker, and memantine, a noncompetitive NMDA receptor antagonist, provided modest symptomatic relief to AD patients (Winblad and Portis 1999; Lopez-Arrieta and Birks 2002). But these treatments target plasma-membrane Ca^{2+} channels rather than the process of intracellular Ca^{2+} liberation that appears to be the principal locus of Ca^{2+} disruption in AD. Improved strategies may include either reversing the exaggerated Ca^{2+} signals (e.g., by reducing intracellular Ca^{2+} release through RyR with dantrolene or using lithium to slow IP_3 turnover) or mitigating the deleterious downstream consequences of elevated Ca^{2+} levels (e.g., by enhancing levels of Bcl-2 levels or grp-78). On an optimistic note, it is likely that more specific strategies will become apparent as we learn more of the molecular mechanisms linking Ca^{2+} homeostasis to AD pathology.

References

Barrow PA, Empson RM, Gladwell SJ, Anderson CM, Killick R, Yu X, and others. 2000. Functional phenotype in transgenic mice expressing mutant human presenilin-1. Neurobiol Dis 7:119–26.

Berridge M. 1998. Neuronal calcium signaling. Neuron 21:13–26.

Berridge M, Bootman M, Lipp P. 1998. Calcium: a life and death signal. Nature 395:645–9.

Cedazo-Minguez A, Popescu BO, Ankarcron M, Nishimura T, Cowburn RF. 2002. The presenilin 1 deltaE9 mutation gives enhanced basal phospholipase C activity and a resultant increase in intracellular calcium concentrations. J Biol Chem 277:36646–55.

Chan SL, Mayne M, Holden CP, Geiger JD, Mattson M. 2000. Presenilin-1 mutations increase levels of ryanodine receptors and calcium release in PC12 cells and cortical neurons. J Biol Chem 275:18195–200.

Corbett EF, Michalak M. 2000. Calcium, a signaling molecule in the endoplasmic reticulum? Trends Biochem Sci 25:307–11.

Etcheberrigaray R, Hirashima N, Nee L, Prince J, Govoni S, Racchi M, and others. 1998. Calcium responses in fibroblasts from asymptomatic members of Alzheimer's disease families. Neurobiol Dis 5:37–45.

Fujii S, Matsumoto M, Igarashi K, Kato H, Mikoshiba K. 2000. Synaptic plasticity in hippocampal CA1 neurons of mice lacking type 1 inositol-1,4,5-trisphosphate receptors. Learn Mem 7:312–20.

Guo Q, Fu W, Sopher BL, Miller MW, Ware CB, Martin GM, and others. 1999. Increased vulnerability of hippocampal neurons to excitotoxic necrosis in presenilin-1 mutant knock-in mice. Nat Med 5:101–6.

Guo Q, Furukawa K, Sopher BL, Pham DG, Xie J, Robinson N, and others. 1996. Alzheimer's PS-1 mutation perturbs calcium homeostasis and sensitizes PC12 cells to death induced by amyloid beta-peptide. Neuroreport 8:379–83.

Guo Q, Sopher BL, Furukawa K, Pham DG, Robinson N, Martin GM, and others. 1997. Alzheimer's presenilin mutation sensitizes neural cells to apoptosis induced by trophic factor withdrawal and amyloid beta-peptide: involvement of calcium and oxyradicals. J Neurosci Res 17:4212–22.

Ito E, Oka K, Etcheberrigaray R, Nelson TJ, McPhie DL, Tofel-Grehl B, and others. 1994. Internal Ca^{2+} mobilization is altered in fibroblasts from patients with Alzheimer disease. Proc Natl Acad Sci U S A 91:534–8.

Katayama T, Imaizumi K, Sato N, Miyoshi K, Kudo T, Hitomi J, and others. 1999. Presenilin-1 mutations downregulate the signalling pathway of the unfolded-protein response. Nat Cell Biol 1:479–85.

Khachaturian ZS. 1994. Calcium hypothesis of Alzheimer's disease and brain aging. Ann N Y Acad Sci 747:1–11.
LaFerla FM. 2002. Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease. Nat Rev Neurosci 3:862–72.
Leissring MA, Akbari Y, Fanger CM, Cahalan MD, Mattson MP, LaFerla FM. 2000. Capacitative calcium entry deficits and elevated luminal calcium content in mutant presenilin-1 knockin mice. J Cell Biol 149:793–8.
Leissring MA, LaFerla FM, Callamaras N, Parker I. 2001. Subcellular mechanisms of presenilin-mediated enhancement of calcium signaling. Neurobiol Dis 8:469–78.
Leissring MA, Parker I, LaFerla FM. 1999. Presenilin-2 mutations modulate amplitude and kinetics of inositol 1, 4,5-trisphosphate-mediated calcium signals. J Biol Chem 274:32535–8.
Leissring MA, Paul BA, Parker I, Cotman CW, LaFerla FM. 1999. Alzheimer's presenilin-1 mutation potentiates inositol 1,4,5-trisphosphate-mediated calcium signaling in *Xenopus* oocytes. J Neurochem 72:1061–8.
Lopez-Arrieta JM, Birks J. 2002. Nimodipine for primary degenerative, mixed and vascular dementia. Cochrane Database Syst Rev (3):CD000147.
Mattson MP, LaFerla FM, Chan SL, Leissring MA, Shepel PN, Geiger JD. 2000. Calcium signaling in the ER: its role in neuronal plasticity and neurodegenerative disorders. Trends Neurosci 23:222–9.
Mattson MP, Lovell MA, Ehmann WD, Markesbery WR. 1993. Comparison of the effects of elevated intracellular aluminum and calcium levels on neuronal survival and tau immunoreactivity. Brain Res 602:21–31.
Mattson MP, Tomaselli KJ, Rydel RE. 1993. Calcium-destabilizing and neurodegenerative effects of aggregated beta-amyloid peptide are attenuated by basic FGF. Brain Res Dev Brain Res 621:35–49.
Meldolesi J, Pozzan T. 1998. The endoplasmic reticulum Ca^{2+} store: a view from the lumen. Trends Biochem Sci 23:10–4.
Mellstrom B, Naranjo J. 2001. Mechanisms for Ca^{2+}-dependent transcription. Curr Opin Neurobiol 11:312–9.
Missiaen L, Robberecht W, van den Bosch L, Callewaert G, Parys JB, Wuytack F, and others. 2000. Abnormal intracellular $Ca^{(2+)}$homeostasis and disease. Cell Calcium 28:1–21.
Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J. 2000. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. Nature 403:98–103.
Nakamura T, Barbara JG, Nakamura K, Ross WN. 1999. Synergistic release of Ca^{2+} from IP_3-sensitive stores evoked by synaptic activation of mGluRs paired with backpropagating action potentials. Neuron 24:727–37.
Nishiyama M, Hong K, Mikoshiba K, Poo MM, Kato K. 2000. Calcium stores regulate the polarity and input specificity of synaptic modification. Nature 408:584–8.
Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, and others. 2003. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron 39:409–21.
Padua RA, Nagy JI, Geiger JD. 1996. Subcellular localization of ryanodine receptors in rat brain. Eur J Pharmacol 298:185–9.
Parent A, Linden DJ, Sisodia SS, Borchelt DR. 1999. Synaptic transmission and hippocampal long-term potentiation in transgenic mice expressing FAD-linked presenilin 1. Neurobiol Dis 6:56–62.
Querfurth HW, Selkoe DJ. 1994. Calcium ionophore increases amyloid beta peptide production by cultured cells. Biochemistry. 33:4550–61.
Rose CR, Konnerth A. 2001. Stores not just for storage: intracellular calcium release and synaptic plasticity. Neuron 31:519–22.
Rossor MN, Fox NC, Freeborough PA, Harvey R. 1996. Clinical features of sporadic and familial Alzheimer's disease. Neurodegeneration 5:393–7.
Sharp AH, McPherson PS, Dawson TM, Aoki C, Campbell K, Snyder SH. 1993. Differential immunohistochemical localization of inositol 1,4,5 triphosphate- and ryanodine-sensitive Ca^{2+} release channels in rat brain. J Neurosci 13:3051–63.
Stutzmann GE, Caccamo A, LaFerla FM, Parker I. 2004. Dysregulated IP_3 signaling in cortical neurons of knock-in mice expressing an Alzheimer's-linked mutation in presenilin1 results in exaggerated Ca^{2+} signals and altered membrane excitability. J Neurosci 24:508–13.
Stutzmann GE, LaFerla FM, Parker I. 2003a. Ca^{2+} signaling in mouse cortical neurons studied by two-photon imaging and photoreleased inositol triphosphate. J Neurosci 23:758–65.
Stutzmann GE, LaFerla FM, Parker I. 2003b. Upregulation of IP3/calcium signaling in cortical neurons from mutant PS1 mice revealed by 2-photon imaging and electrophysiology. Soc Neurosci Abst 295:23.
Stutzmann GE, Oddo S, de Silva I, LaFerla FM, Parker I. 2004b. Differential contributions of ryanodine and IP3-sensitive stores in a novel triple transgenic mouse model of Alzheimer's disease: role of resenilin vs. APP and tau. Soc Neurosci Abst 338:10.
Verkhratsky A. 2002. The endoplasmic reticulum and neuronal calcium signalling. Cell Calcium 32:393–404.
Verkhratsky A, Toescu EC. 2003. Endoplasmic reticulum $Ca^{(2+)}$ homeostasis and neuronal death. J Cell Mol Med 7:351–61.
Winblad B, Portis N. 1999. Memantine in severe dementia: results of the 9M-best study (benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriat Psychiatry 14:135–46.
Yamamoto K, Hashimoto K, Nakano M, Shimohama S, Kato N. 2002. A distinct form of calcium release down-regulates membrane excitability in neocortical pyramidal cells. Neuroscience 109:665–76.
Yasuda Y, Kudo T, Katayama T, Imaizumi K, Yatera M, Okochi M, and others. 2002. FAD-linked presenilin-1 mutants impede translation regulation under ER stress. Biochem Biophys Res Commun 296:313–8.
Yoo A, Cheng I, Chung S, Grenfell TZ, Lee H, Pack-Chung E, others. 2000. Presenilin-mediated modulation of capacitative calcium entry. Neuron 3:561–72.
Zaman SH, Parent A, Laskey A, Lee MK, Borchelt DR, Sisodia SS, and others. 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.