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Emerging Pathways Driving Early Synaptic Pathology in Alzheimer's Disease

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Abstract

The current state of the AD research field is highly dynamic in some respects, while seemingly stagnant in others. Regarding the former, our current lack of understanding of initiating disease mechanisms, the absence of effective treatment options, and the looming escalation of AD patients is energizing new research directions including a much-needed re-focusing on early pathogenic mechanisms, validating novel targets, and investigating relevant biomarkers, among other exciting new efforts to curb disease progression and foremost, preserve memory function. With regard to the latter, the recent disappointing series of failed Phase III clinical trials targeting A β and APP processing, in concert with poor association between brain A β levels and cognitive function, have led many to call for a re-evaluation of the primacy of the amyloid cascade hypothesis. In this review, we integrate new insights into one of the earliest described signaling abnormalities in AD pathogenesis, namely intracellular Ca²⁺ signaling disruptions, and focus on its role in driving synaptic deficits – which is the feature that does correlate with AD-associated memory loss. Excess Ca²⁺ release from intracellular stores such as the endoplasmic reticulum (ER) has been well-described in cellular and animal models of AD, as well as human patients, and here we expand upon recent developments in ER-localized release channels such as the IP₃R and RyR, and the recent emphasis on RyR2. Consistent with ER Ca²⁺ mishandling in AD are recent findings implicating aspects of SOCE, such as STIM2 function, and TRPC3 and TRPC6 levels. Other Ca²⁺-regulated organelles important in signaling and protein handling are brought into the discussion, with new perspectives on lysosomal regulation. These early signaling abnormalities are discussed in the context of synaptic pathophysiology and disruptions in synaptic plasticity with a particular emphasis on short-term plasticity deficits. Overall, we aim to update and expand the list of early neuronal signaling abnormalities implicated in AD pathogenesis, identify specific channels and organelles involved, and link these to proximal synaptic impairments driving the memory loss in AD. This is all within the broader goal of identifying novel therapeutic targets to preserve cognitive function in AD.

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Keywords

Ca²⁺; endoplasmic reticulum; lysosome; synaptic plasticity; Alzheimer's Disease; SOCE; RyR; IP₃R

Urgency in AD

Among the devastating neurodegenerative diseases, Alzheimer's disease (AD) alone afflicts over 5 million individuals in the U.S., and is feared to grow to nearly 14 million by 2050. Available FDA-approved therapeutics are limited to three cholinesterase inhibitors, approved in 1996–2000, and a low affinity NMDA-R antagonist, approved in 2003. These are symptomatic treatments, not cures, and are not effective in all patients. While the amyloid hypothesis still largely predominates in the field, decades of research and clinic trials addressing A β production and deposition have yet to provide a mechanistic cause of AD or offer new therapeutics. Although expectations and efforts remain high for targeting APP processing as the keystone for AD [136], the amyloid cascade hypothesis is being met with increasing skepticism and scrutiny [20,21,59]. While ongoing clinical trials take a view more towards preventing than reversing AD, clearly it also is time to increase efforts in earlier or upstream mechanisms that may cause or contribute to AD

As recognized since 1989, it is synapse loss which correlates best with cognitive impairment [36,55,128,150]. This association makes intuitive sense and provides a direct cause for the cognitive impairment in AD, as intact synaptic structure and function are required for the synaptic encoding that forms stable memories [56,96]. By extension, it stands to reason that preserving synapses would be an effective means to prevent loss of cognitive functions in at-risk populations. Until recently, there were few tools to measure synaptic integrity in the human brain prior to autopsy, and studies linking synaptic function to cognitive resilience were largely conducted in mouse models or from post mortem human tissue samples [4,24,41]. However, the recent identification of a PET ligand to measure synaptic density in human patients [44] is an exciting new tool, and stands to provide meaningful diagnostic and predictive information related to synapse loss in disease progression.

Most AD patients, over 95%, have sporadic or late-onset forms of the disease where the etiology is unknown, although ApoE4 is a well-characterized genetic risk factor [34,42,99] and more recently variants in TREM2, which normally serves to trigger phagocytosis, have been identified [102]. In familial AD (FAD), the disease-causing mutations identified to date are in *presenilin-1* and *2* (PS1 and PS2) and in *amyloid precursor protein (APP)* genes. Although APP and PS mutations lead to increased A β production or changes in A β 42:40 ratios [136], A β -directed potential therapeutics so far have not met efficacy milestones with regards to memory function in human patients, while multiple lines of evidence connect PS mutations identified in early-onset AD with neuronal dysfunction and apoptosis through Ca²⁺ dyshomeostasis [37,40]. While A β is an obligate diagnostic criterion for AD, it is critically important to expand research in other risk factor mechanisms among cells in the CNS [25,35].

Fundamental and early role of ER Ca^{2+} dysregulation in AD-related synaptic deficits

Ca^{2+} is well known as a principal factor in cytotoxicity and apoptosis, and Ca^{2+} dyshomeostasis is seen in neurons with aging, AD and AD transgenic animal models [17,46,143]. Indeed, PS1 mutations alone, as would occur in FAD, impact Ca^{2+} signaling at early or asymptomatic disease stages in the absence of A β or tau aggregation [25,37,120,122,141,148]. The initiation of this early pathogenic cascade may be due to the γ -secretase independent association of PS with inositol trisphosphate receptors (IP_3R) and ryanodine receptors (RyR), the two major Ca^{2+} release channels in the endoplasmic reticulum. FAD-linked mutant PS can directly increase the gating properties of IP_3R and increase the intracellular Ca^{2+} signaling response to IP_3 -generating GPCR ligands [100,139]. This is seen in cell models, in brain slice pyramidal neurons from multiple AD mouse models mice, and, importantly, in ectodermal cells (fibroblasts) taken directly from human AD patients [80,139,144]. Both PS1 and PS2 influence RyR2 gating through direct interaction with the PS cytosolic domain, with PS1 increasing channel open probability and single channel currents at physiological Ca^{2+} concentrations ($\sim 1 \mu\text{M}$) [131] and PS2 reducing feedback inhibition of RyR2 by Ca^{2+} at pathological concentrations ($\sim 10 \mu\text{M}$) [58,115]. In aged mice, PS1 expression is reduced in cerebellum and PS2 levels are increased in cerebellum and forebrain, potentially contributing to age-related increases in cytosolic Ca^{2+} and cytotoxic elevation of Ca^{2+} through other mechanisms [69].

RyRs are the other major Ca^{2+} release channel in the ER. While both RyR and IP_3R activities are potentiated by Ca^{2+} , it is RyR that is largely responsible for Ca^{2+} -induced Ca^{2+} release (CICR) in neurons as well as skeletal muscle, cardiac muscle and other cells [25,37,133]. As such, RyR are poised to amplify other signals elevating cytoplasmic Ca^{2+} . Indeed, A β has been found to increase Ca^{2+} in AD cell and animal models [38,111,153] and elevated Ca^{2+} can increase A β production [37,66,118,125,142] resulting in a pathogenic feed-forward cycle. RyR-mediated Ca^{2+} release is markedly up-regulated in single AD transgenic mice expressing mutant PS, in AD transgenics expressing a combination of gene mutations, and in APP mutant mice [25,37]. RyR-evoked Ca^{2+} responses are increased in soma cytoplasm 2–3 fold and up to an order of magnitude in dendrite and spines in the presence or absence of A β deposits and from youth throughout life in the transgenic mice [16,50]. Accompanying the elevated responsivity is a 2–5 fold increase in expression of the RyR2 isoform in cell models and transgenic mice at early or asymptomatic disease stages [26,111], and increased RyR3 expression at later stages concomitant with A β_{42} aggregation [149]. Additionally, RyR activity can be further modulated post-translationally through oxidation, nitrosylation, phosphorylation and other mechanisms invoked in AD and other neurodegenerative disorders [37,46,60,120,133,143]. Thus, in AD models, intracellular Ca^{2+} signaling is enhanced through at least two mechanisms: an increase in RyR expression (both at the message and protein levels), and increased Ca^{2+} release across individual channels. As a likely result of increased RyR expression and release dynamics, the RyR are now aberrantly coupling to channels and signaling cascades, such as Ca^{2+} -activated K^+ channels (normally activated by L-type VGCC) which serve to reduce membrane excitability [23,26,27,144,147], and nitric oxide (NO) synthase (normally activated by NMDAR-

mediated Ca^{2+} influx) which generates the gaseous second messenger, NO, and is linked to synaptic activity, excitotoxicity, and neuroprotection [14,23,33,71,101,164]. This potentiated and aberrant ER Ca^{2+} release greatly expands the array of signaling and neurophysiological functions modulated by intracellular Ca^{2+} channels, and in some circumstances, invades other Ca^{2+} signaling pathways contributing to an altered homeostasis, such as that seen in long-term synaptic plasticity expression [23,27].

Ca^{2+} is an essential mediator of basal synaptic transmission, short and long forms of synaptic plasticity, and dendritic spine morphology [9,25,57]. The ER extends throughout the neuron, including both postsynaptic dendritic spines and presynaptic nerve terminals, positioning RyR in key loci to influence these processes [8]. One immediate electrophysiological consequence of Ca^{2+} influx is activation of the hyperpolarizing SK2 Ca^{2+} -dependent K^+ channels. In cortical and hippocampal pyramidal neurons, SK2 channels mediate the medium afterhyperpolarization (mAHP) that reduces neuron excitability and may contribute to the depressed synaptic strength seen in young FAD transgenic mice [26,30,62,67,162]. With aging, expression of the L-type voltage-gated Ca^{2+} channel (VGCC) is upregulated in normal animals and this has been tied to elevated AHP-mediated deficits in cognitive performance [39,108,151]. RyR-mediated Ca^{2+} signaling contributes to SK2 channel/AHP activation and recently it was found that the RyR contribution itself is increased with aging due to decreased expression of an FK506-binding protein that associated with and stabilizes RyR2 activity [46,47], implicating RyR stabilization as a target to normalize depressed pyramidal neuron excitability in aging. Indeed, FK506-binding protein expression was found to be reduced in early-AD patients as well as aged rats [46] and, in aged rats, virally mediated over-expression of FK506-binding protein expression reduced RyR mediated Ca^{2+} signaling and improved spatial memory performance [47]. Thus, in early AD patients, we see evidence for increased RyR expression and destabilization through reduced FK506-binding protein expression, leading to Ca^{2+} signaling dyshomeostasis that can be magnified with age as Ca^{2+} influx through VGCC or other sources increases. In FAD, with further enhancements of RyR and IP_3R Ca^{2+} signaling, the disruption would be more severe and be seen at earlier ages.

In addition to the RyR-generated somatic signaling disruptions, these ER channels also are highly expressed in dendrites, along with IP_3R , and in dendritic spines from which IP_3R appear to be excluded [137]. In dendritic spines, RyR-mediated Ca^{2+} release can be triggered by Ca^{2+} influx through NMDA-R and Ca^{2+} -permeable AMPA-R ligand-gated ion channels as well as VGCC [50,129,160] suggesting a complexity of disruptions resulting from aberrant Ca^{2+} signaling. Homosynaptic NMDA-R dependent long-term potentiation (LTP), a fundamental neuronal mechanism underlying learning and memory, is thought to depend upon depolarization to relieve the Mg^{2+} block of the NMDA-R channel, permitting Ca^{2+} influx, coincident with activation of the NMDA-R by glutamate. Simplistically, up-regulation of Ca^{2+} signaling might be expected to increase LTP. Counterbalancing that, however, is Ca^{2+} dependent activation of SK channels that can reduce synaptic depolarization, limiting NMDA-R Ca^{2+} influx and impeding the induction of LTP [1,43,54,104,127]. Further, elevated Ca^{2+} signaling through RyR and subsequent SK channel activation impairs the post-excitation stabilization of mushroom dendritic spines in cultured neurons and the induction of late-phase LTP in hippocampal brain slices, thus

interfering with the morphological and electrophysiological substrates of learning and memory [166].

Both presynaptic nerve terminals and postsynaptic dendritic spines are particularly vulnerable to dysregulated RyR Ca^{2+} signaling as it influences dendritic structure, function [61,74,77] and neurotransmitter release [90], thus impacting neuronal excitability and short and long term plasticity mechanisms essential for learning and memory [10,22,23,121,166] (Figure 1). The ER extends throughout the neuron including into nerve terminals [8] and there is substantial evidence for presynaptic RyR in the hippocampus including localization by immunohistochemistry and electron microscopy, and function by Ca^{2+} imaging in hippocampal nerve terminals [85,137,154].

Early Transcriptomic and Proteomic Evidence

These findings described above are also consistent with broader proteomic and genomic studies implicating RyR2 in both synaptic functions and AD pathogenesis [19,134,157]. RNA deep sequencing studies show RyR2 transcripts in hippocampal neuropil and dendrites [2,19], and proteomic studies show RyR2 trafficking to synapses [89]. Interestingly, the transcription factor LMO4 (Lim only domain protein 4) is a positive regulator of RyR2 expression, and is one of the genes identified in a GWAS study of aging [157] whose protein expression patterns are altered in the entorhinal cortex and hippocampus, both vulnerable brain regions in AD [82]. Notably, $\text{A}\beta_{42}$ increases expression of LMO4, thus providing a direct mechanism for increased RyR2 in AD brains [6]. Likewise, knockout of LMO4 reduces RyR-mediated Ca^{2+} signaling and reduces its facilitation of CA3-CA1 glutamatergic synaptic transmission and LTP [124]. Because the molecular and protein machinery are uniquely aligned for synaptic RyR2 expression, these collective findings reveal a previously unappreciated role of RyR2 dysregulation in AD pathophysiology and synaptic degeneration.

Ca^{2+} and long and short term plasticity defects in AD

Disrupted synaptic plasticity mechanisms concurrent with memory impairments have been widely recognized and reported in FAD transgenic mice at moderate to severe disease stages [68,92,107,136]. Thus, for the purposes of this review, we will not expand upon this well-covered territory, other than to reiterate that overt deficits in hippocampal LTP are usually reported to occur contemporaneously with $\text{A}\beta$ aggregation. However, there is strong evidence of more insidious or ‘below the radar’ deficits in asymptomatic AD mice, with overt deficits in certain forms of short term plasticity. It is in these more subtle or emergent stages of synaptic plasticity deficits that interventional strategies may be more effectively employed. For example, in young (3 month old) 3xTg FAD mice, the net magnitude of LTP is remarkably similar to that of age-matched non-transgenic mice, but if Ca^{2+} homeostasis is tampered with in the AD mice, a profound and underlying shift towards enhanced long-term synaptic depression (LTD) emerges [25,27]. Indeed, in CA3-CA3 pyramidal neuron synaptic transmission, dual patch-clamp electrophysiological studies implicate presynaptic RyR in the induction of homosynaptic LTD [154] and similar mechanisms may underlie the magnified LTD observed with up-regulated RyR Ca^{2+} signaling in 3xTg FAD mice.

During early stages in 3xTg FAD mice, it is thought that a mixture of NMDA-R dependent and independent mechanisms [30] and enhanced NO signaling boosts postsynaptic RyR-mediated Ca^{2+} signaling and compensates against enhancement of LTD by other mechanisms [14,23,70,86,154]. In older (8 month) AD Tg mice, LTP is reduced compared to age-matched non-transgenic mice due in part to a reduction in the NMDA-R independent mechanisms [30]. At the same time, however, both younger and older AD Tg mice are impaired in spatial working memory perhaps due to a selective dependence on NMDA-R dependent LTP in this task, or perhaps due to an under-appreciated role for short-term plasticity (paired-pulse facilitation) which is impaired in both young and old 3xTg and reflects aberrations in presynaptic RyR Ca^{2+} signaling [26,27,30,154]. Notably, the ER Ca^{2+} signaling abnormalities and plasticity and memory deficits precede detectable amyloid and tau pathology in AD [26,28,144,166].

While seemingly less critical due to its apparent transient nature, short-term plasticity deficits are capable of inflicting long-lasting impairments in memory encoding. While much of the focus has been upon long-lasting changes in synaptic strength, more proximal forms of short-term synaptic plasticity such as synaptic facilitation, post-tetanic potentiation (PTP), paired pulse facilitation (PPF) and early LTP play fundamental roles in stabilizing long term memory encoding. These short forms of synaptic modulation are important in neuronal communication encoding, are impacted by Ca^{2+} signaling, and participate in the critical synaptic tagging mechanisms which underlie long-term forms of stable synaptic plasticity [45,83,98]. Sustainable long-term memory processing is dependent upon Ca^{2+} -mediated short-term plasticity to transform short-term into long-term memory and establish synapse specificity through synaptic tagging and capture mechanisms [45,126]. The timing and strength of synaptic tagging reflects intracellular Ca^{2+} signaling patterns, with RyR activation *during* the plasticity-inducing tetanus serving to increase the duration and durability of the synaptic tag window, thus promoting Hebbian LTP associativity. In contrast, if RyR channels are active *prior to* plasticity induction, as demonstrated in the AD models, this critical associative learning window is shortened and plasticity resilience is reduced [83,132]. Thus, in AD pathogenesis, the increased RyR activity at baseline as well as that generated from synaptic activity can blunt the critical window necessary for transforming and stabilizing long term memory formation, resulting in impaired memory performance such as that observed in 3xTgFAD mice at 2 to 3 months of age [30,98,140]. Indeed, working memory deficits are observed in young 3xTg FAD mice well before $\text{A}\beta$ deposition [30,140] and underlying this may be a shortening of the associative learning window due to elevated Ca^{2+} signaling prior to the plasticity induction [83,132].

In AD mouse models at asymptomatic or early disease stages, several synaptic pathophysiological processes mediated by excessive RyR Ca^{2+} have been observed, such as an increased frequency of spontaneous synaptic potentials, reduced PPF ratios, and increased synaptic depression [16,22,26,27]. Collectively, these would implicate Ca^{2+} -dependent presynaptic mechanisms. PPF, a form of presynaptic Ca^{2+} -dependent short-term plasticity, reflects the probability of neurotransmitter vesicle release, with reduced ratios signifying an increased probability of vesicle release. Existing studies have shown that significant vesicle depletion occurs at synapses with high release probability, which has been demonstrated in several strains of AD mice [50,135]. Thus, presynaptic vesicle release

probability is inversely associated with PTP magnitude and the paired pulse ratio [15,53,75,171]. This is consistent with observations in the AD mice, and implicates a Ca^{2+} -mediated increase in release probability, rectified with RyR inhibitors [22,27], in the reduction of presynaptic vesicle stores and blunting of PTP and hippocampal network function. Notably, since synaptic transmission and strength are dependent upon the 3–4th power of Ca^{2+} concentration within synapses [51], this steep power function is a critical variable influencing synaptic plasticity defects in AD mouse models where synaptically-evoked spine Ca^{2+} levels are 2–3 times higher than in controls [23,49,117]. Under these extreme conditions, upregulated Ca^{2+} signaling can create a depleted or burdened synaptic environment.

Emerging Ca^{2+} sources

Ca^{2+} is necessary for proper ER function and the concentration of Ca^{2+} in the ER is one determinant of the magnitude of Ca^{2+} signaling through IP_3R and RyR channels. While it has been proposed that the effect of FAD PS to increase IP_3R and RyR Ca^{2+} signaling is due to elevated ER Ca^{2+} stores, this mechanism is still under review [12,138]. However, recent modeling studies have demonstrated that knockdown of PS2 can elevate ER Ca^{2+} stores and support the concept that unprocessed forms of PS act as ER Ca^{2+} leak channels [5]. ER Ca^{2+} stores are maintained by store-operated Ca^{2+} entry (SOCE) and by SERCA pumps which move Ca^{2+} from cytosol to ER [10,123,156]. As ER Ca^{2+} levels decrease, Ca^{2+} -sensing stromal interaction molecule (STIM) embedded in the ER membrane associates with the plasma membrane Ca^{2+} channel Orai to refill ER stores, opening a Ca^{2+} influx pathway to cytosol which can be measured electrophysiologically as the Ca^{2+} release activated current I_{CRAC} . Both of the two known STIM homologs (STIM1 and STIM2) are expressed in neurons [97]. In a cultured cortical neuron model, traumatic injury was found to induce an up-regulation of STIM1 and siRNA knockdown of STIM1 reduced the associated increase in Ca^{2+} signaling and apoptotic cell death [64]. Other recent studies have found a down-regulation of STIM2 in cortex from sporadic AD patients and in hippocampus from aged normal mice (12–16 months old) and in FAD transgenic mice (6–12 but not 3 months old) [146,165]. Further, Ca^{2+} entry through this pathway was found to be important in the stabilization of memory-associated dendritic mushroom spines of pyramidal neurons through a calmodulin kinase II mechanism. Thus, here Ca^{2+} influx through ER store-operated channels appears to be favorable for maintaining spine synapses. In striatum from Huntington's disease (HD) transgenic mice, however, STIM2 and SOCE was up-regulated, disrupting spines in medium spiny neurons [163]. Pharmacologic inhibition of SOCE was beneficial to spine synapse maintenance in the HD model [163], but the same compound may be anticipated to be detrimental to cortical and hippocampal pyramidal neurons. Similarly, while up-regulation of SOCE may be beneficial for AD pyramidal neurons, other CNS synapses could be jeopardized. Clearly, these intriguing new results need further mechanistic dissection that may reveal novel therapeutic targets to address the loss of spine synapses in aging and neurodegenerative disease.

Canonical transient receptor potential (TRPC) channels can also complex with STIM or STIM/Orai to form SOCE pathways [109,123], or they can operate independently to promote synaptic or other neurophysiological functions. There are seven members of the

TRPC family with the TRPC1 being the most extensively studied and generally accepted to participate in SOCE. However, TRPC1 was not down- or up-regulated in concert with STIM2 in the aforementioned studies [146,163]. TRPC3, TRPC4 and TRPC5 may also contribute to SOCE alone or in heteromeric complexes with TRPC1, however TRPCs also have the potential to respond more directly to GPCR/diacylglycerol signaling, Ca^{2+} and redox signals [109] and may be a preferred Ca^{2+} channel target [29]. TRPC3 channels have been implicated as a Ca^{2+} source limiting pyramidal neuron firing by activation of the medium and slow AHPs, and the expression of TRPC3 across 23 strains of mice was found to be negatively correlated with learning in the conditioned fear task [103]. Successful learning of the task was associated with down-regulation of TRPC3 and knockdown of TRPC3 improved memory performance. On the other hand, TRPC6 expression improves spatial learning abilities in APP/PS1 mice, and reduces A β production and deposition possibly through an interaction between APP and the second transmembrane domain of TRPC6 [158]. These memory-preserving functions of TRPC6 in AD models are likely related to its critical role in forming excitatory synapses and enhancing dendritic spine formation via Ca^{2+} - regulated pathways [170]. Conversely, FAD PS2 mutations have been found to inhibit TRPC6 [81] and thus may contribute to the demise of synapses that are critical for synaptic and behavioral plasticity. In other neurodegenerative diseases such as Huntington's disease, TRPC5 function is closely linked to cell death [63], further implicating the TRPC channel class broadly in neurodegenerative disorders.

Intracellular organelle sources of Ca^{2+} , may include lysosomes in addition to ER and mitochondria. Lysosome dysfunction is implicated along multiple lines of evidence in neurodegenerative disease - AD, Parkinson's Disease and Huntington's Disease in particular [13,32,48,65,72,93,119]. Among the numerous molecular pathway links to AD, PS knockout and expression of FAD PS1 have been found to increase Ca^{2+} release from lysosomes [31,79]. Recent studies suggest that PS1 deficiency leads to reduction in vacuolar ATPase, increasing lysosomal pH which then causes a switch in the main lysosomal Ca^{2+} efflux pathway from two-pore channels (TPC) to TRPML1 [79]. While the vacuolar ATPase/alkalinization mechanisms remain under investigation is controversial [31,168], there is agreement that PS deficiency increases Ca^{2+} release from lysosomes and reduces their Ca^{2+} content [31,79].

Mitochondria are well known as the "powerhouse" of the cell, important in buffering cytosolic Ca^{2+} , and definitive mediator of cytotoxicity when damaged. Numerous reviews have detailed critical processes in mitochondria that may be involved in AD and other neurodegenerative diseases [18,52,91,110,113,145]. While discussion of these mechanisms is beyond the scope of this minireview, of particular note is the expanding interest in mitochondria-associated ER membrane (MAM) [3,76,112,130]. Among the functions attributed to these areas of contact is Ca^{2+} exchange between ER and mitochondria and the possibility that Ca^{2+} release from ER may help supply Ca^{2+} for the ATP powerhouse under normal conditions, or lead to mitochondrial pathology and apoptosis when ER Ca^{2+} release is aberrant [130].

Opportunities for Therapeutics

RyR are large (>2.2 MDa) allosteric proteins [78,155] in which the intrinsic Ca^{2+} channel activity is modulated through numerous processes including interaction with other proteins (e.g., FK506-binding protein FKBP12 stabilizes RyRs, L-type VGCC activates RyR1 in skeletal muscle), posttranslational modulation (e.g., phosphorylation, oxidation and nitrosylation), endogenous ligands (e.g., Ca^{2+} and calmodulin, cyclic ADP-ribose, ATP), and exogenous ligands (e.g., ryanodine, caffeine, dantrolene) [11,60,105,133]. The ligands act as allosteric modulators rather than classic agonist or antagonist. RyR2 is critical for excitation-contraction coupling in cardiac myocytes and it is thought that the RyR2 N- and C-terminal domains, normally coupled or “zipped”, can be destabilized or “unzipped” under conditions of oxidative stress such as in heart failure [106,159]. Dantrolene is able to normalize RyR2 hyperactivity without blocking function [73,95,106,159]. Other studies find that RyR2 destabilization involves “remodeling” by a combination of oxidation/nitrosylation, phosphorylation by protein kinase A, and loss of interaction with FK506-binding protein “calstabin” [94] that can be reversed by the compound S107 [7]. While there is some controversy surrounding the destabilizing mechanisms, e.g. regarding the kinases and phosphorylation sites involved [11], nevertheless it is apparent that small molecules such as dantrolene and S107 can normalize RyR activity without blocking function. Dantrolene is an approved and highly effective drug for use in human to prevent and rescue malignant hyperthermia where it acts by stabilizing RyR1 hyperactivity [161]. Although in vitro binding of dantrolene to RyR2 is low under normal conditions [169], this depends upon the conformational state of the receptor [114]. In cardiac tissue, where RyR2 is expressed specifically and RyR2 Ca^{2+} release mediates muscle contractility, dantrolene stabilizes aberrant RyR2 function in disease states without blocking normal function [73,152]. Here [106], as in brain [60], oxidative stress may be a key factor in destabilizing RyR2 function in a way that can be normalized by RyR negative allosteric modulators such as dantrolene.

Moreover, treatment of FAD transgenic mice with dantrolene has been found by several laboratories to be effective in reversing a range of AD features, including aberrant ER Ca^{2+} signaling, disrupted hippocampal synaptic plasticity mechanisms, behavioral deficits, and A β plaque deposition [84]. In our laboratory, we found that a 4-week treatment with a brain penetrant nanocrystal formulation of dantrolene normalized the elevated hippocampal RyR2 expression and aberrantly high somatic and dendritic RyR Ca^{2+} responses in pyramidal neurons from 3xTg and APP/PS1 FAD mice, restored normal short-term and long-term synaptic plasticity mechanisms in 3xTg mice, and reduced the levels of soluble and insoluble A β in cortex and hippocampus of APP/PS1 mice [22]. Peng et al. [116] found that memory task performance was improved and A β plaque deposition reduced in 3xTg FAD mice following 11 months of i.c.v. infusion of dantrolene. And in Tg2576 FAD mice, which are transgenic for APP_{sw} but not mutant PS, Oules et al. [111] found that 3 months treatment with dantrolene restored levels of the synapse marker PSD-95 and prevented decline of memory performance in hippocampal and cortical-dependent memory tasks while also reducing production of A β and C99 fragments. In vitro experiments demonstrated that while expression of FAD APP can increase RyR mediated Ca^{2+} release, elevated RyR Ca^{2+} signaling in turn can increase C99 and A β production from APP [111], signaling a feed-

forward pathogenic mechanism between A β and destabilized ER Ca²⁺ release. Indeed, using a restraint stress model in normal mice, Liu et al. [88] found that the RyR2 allosteric modulator, S107, inhibited RyR biochemical and functional remodeling, and normalized hippocampal synaptic plasticity and behavioral performance in Morris Water Maze and open arm tasks.

These studies favor the potential utility of RyR negative allosteric modulators in AD and other neurodegenerative/cognitive disorders. One study, however, found elevated A β plaque load and reduced PSD-95 synaptic marker in APP/PS1 FAD mice fed dantrolene for 6 months [167]. The reasons for this discrepancy are unclear, but may be related to route of administration, low CNS penetration, and low selectivity of dantrolene. Subject age also may be a critical factor, as a knockout study found that RyR3 was protective in young but detrimental in older APP/PS1 FAD mice [87]. Efforts are ongoing to identify superior molecules, as well as further validate the breadth of emerging Ca²⁺ channels and pathways that likely are contributing to the synaptic pathophysiology and resultant devastating loss of cognitive function in AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Aβ	amyloid β
AHP	after-hyperpolarization
AMPA-R	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid sensitive glutamate receptor
ApoE	apolipoprotein E
APP	amyloid precursor protein
CICR	Ca ²⁺ induced Ca ²⁺ release
ER	endoplasmic reticulum
GCPR	G-protein coupled receptor
I_{CRAC}	Ca ²⁺ release activated Ca ²⁺ current
IP₃	inositol trisphosphate
IP₃R	inositol trisphosphate receptor
LMO4	Lim only domain protein 4

LTD	long-term depression
LTP	long-term potentiation
MAM	mitochondria-associated membrane
mGluR	metabotropic glutamate receptor
NMDA-R	N-methyl-D-aspartate sensitive glutamate receptor
PPF	paired-pulse facilitation
PTP	post-tetanic potentiation
RyR	ryanodine receptor
SK	small-conductance Ca^{2+} activated K^{+} channel
SERCA	sarco/endoplasmic Ca^{2+} ATPase
SOCE	store-operated Ca^{2+} entry
TREM	triggering receptor expressed on myeloid cells
VGCC	voltage-gated Ca^{2+} channel

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This review highlights recent findings and insights regarding early mechanisms of synaptic pathology in AD, particularly as it involves neuronal calcium signaling abnormalities and manifests as deficits in synaptic plasticity. This discussion is particularly relevant given the strong relationship between synaptic deficits and memory loss in AD, and the pressing need to investigate alternative mechanisms contributing to AD-associated cognitive impairment.

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Figure 1. Aberrant Ca²⁺ signaling in early Alzheimer's disease

Presynaptically, RyR-mediated CICR can elevate asynchronous release of neurotransmitter vesicles not tied to neuronal action potential. During high frequency activity, VGCC-mediated Ca²⁺ influx can facilitate RyR-mediated CICR and vesicle release probability. In early AD, CICR may be hyperactive due to increased RyR expression, particularly RyR2 and sensitization of RyR through interaction with mutant PS1, reactive oxygen and nitrogen species. This can lead to increased spontaneous neurotransmitter release resulting in depletion of vesicles from readily-releasable and reserve pools. These maladaptive mechanisms may cause metabolic and oxidative stress resulting in neuronal and synaptic

loss. *Postsynaptically*, in dendritic spines, Ca^{2+} influx through AMPAR and NMDAR is amplified by RyR-mediated CICR and is essential for induction of long-term synaptic plasticity. Ca^{2+} also opens Ca^{2+} -dependent potassium (SK) channels which can terminate NMDA-R Ca^{2+} influx, reduce excitability and modulate postsynaptic action potential firing through repolarization. Additionally, mGluR-phospholipase C signaling generates IP_3 , activating IP_3R to stimulate ER Ca^{2+} release and magnify CICR. Activation of IP_3R supports regenerative Ca^{2+} waves which can travel to other dendritic regions and soma, influencing gene expression as well as synaptic plasticity. High levels of RyR and IP_3R activity can reduce ER Ca^{2+} content, triggering store-operated Ca^{2+} entry through STIM2-Orai complexes and TRPC channels. In early AD, increased coupling between RyR2 and SK channels can decrease neuronal excitability and alter the dynamics of synaptic plasticity processes. Altered expression of STIM2 and TRPC3 and TRPC6 can not only disturb store-operated Ca^{2+} entry but can also destabilize dendritic spine structure and morphology, thus disrupting synaptic plasticity processes. SC input: Schaffer Collateral input; VGCC: voltage-gated Ca^{2+} channel; STIM: Ca^{2+} -sensing stromal interaction molecule; TRPC channel: transient receptor potential cation channel