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The dysregulation of intracellular calcium in Alzheimer disease

Charlene Supnet and **Ilya Bezprozvanny**[#]
Department of Physiology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX

Abstract

Alzheimer disease (AD) is the most common neurodegenerative disorder worldwide and is at present, incurable. The accumulation of toxic amyloid-beta (Aβ) peptide aggregates in AD brain are thought to trigger the extensive synaptic loss and neurodegeneration linked to cognitive decline, an idea that underlies the 'amyloid hypothesis' of AD etiology in both the familal (FAD) and sporadic forms of the disease. Mutations causing FAD also result in the dysregulation of neuronal calcium (Ca^{2+}) handling and may contribute to AD pathogenesis, an idea termed the 'calcium hypothesis' of AD. In particular, Ca^{2+} dysregulation by the endoplasmic reticulum (ER) in AD mouse models results in augmented cytosolic Ca^{2+} levels which can trigger signaling cascades that are detrimental to neuronal function and health. However, there is growing evidence to suggest that not all forms of Ca^{2+} dysregulation in AD neurons are harmful and some of them instead may be compensatory. These changes may help modulate neuronal excitability and slow AD pathology, especially in the early stages of the disease. Clearly, a better understanding of how dysregulation of neuronal Ca^{2+} handling contributes to neurodegeneration and neuroprotection in AD is needed as Ca^{2+} signaling modulators are targets of great interest as potential AD therapeutics.

Introduction

Alzheimer's disease (AD) is characterised clinically by the progressive impairment of higher cognitive function, loss of memory and altered behaviour that follows a gradual progression. The pathological hallmarks of the disease are characterised at autopsy; the presence of senile plaques composed of extracellular amyloid-beta (Aβ) protein aggregates, intracellular neurofibrillary tangles (NFTs) composed of hyper-phosphorylated tau (τ) protein deposits, and the shrinkage of the cerebral cortex due to extensive neuronal loss [1]. The cause of AD is unknown but it is widely accepted that Aβ, particularly the highly fibrillogenic fragment 1–42 and its various assemblies, plays a central role in both familial, early-onset AD (FAD) and sporadic, late-onset AD (LOAD) neuropathology, termed "the amyloid hypothesis of AD" [2]. The study of Aβ-related mechanisms that occur prior to irreversible cognitive impairment and neurodegeneration in AD could reveal targets for therapeutic intervention and disease prevention.

Marked and sustained changes to intracellular calcium Ca^{2+} signalling occurs prior to cognitive decline and extensive neuronal death in AD [3]. The regulation of intracellular Ca^{2+} by the endoplasmic reticulum (ER) has been a focus of study since it was reported that fibroblasts from asymptomatic patients at risk for AD had enhanced cytosolic Ca^{2+} levels after application

#Corresponding author: Dr. Ilya Bezprozvanny, Department of Physiology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75390-9040, USA, Phone: 214-645-6017, Fax: 214-645-6018, ilya.bezprozvanny@utsouthwestern.edu.

of bradykinin, a G-protein-coupled receptor agonist that increases intracellular Ca^{2+} by generating inositol-1,4,5-trisphosphate (IP_3) and activation of IP_3 receptors (IP_3Rs) on the ER [4,5]. Ryanodine receptors (RyanRs) receptors are the other major Ca^{2+} release channels found on the ER. Neuronal RyanRs activated via Ca^{2+}-induced Ca^{2+} release (CICR) mechanism [6]. The sarco/endoplasmic reticulum ATPase (SERCA) pump refills depleted ER Ca^{2+} stores. The goal of this review is to discuss how changes in intracellular Ca^{2+} signalling by the ER may contribute to neurodegeneration in AD.

Calcium signalling in neurons

Calcium signalling is utilized by neurons to control a variety of functions, including membrane excitability, neurotransmitter release, gene expression, cellular growth, differentiation, free radical species formation and cell death [6]. Because of the ubiquitous nature of Ca^{2+} in second-messenger signalling, neurons have strict mechanisms to maintain low concentrations (50–300 nM) of cytosolic Ca^{2+} ($[Ca^{2+}]_{cyto}$) when neurons are at rest or have minimal activity [7]. Calcium-ATPases and the sodium/calcium (Na^+/Ca^{2+}) exchanger on the plasma membrane (PM) extrude Ca^{2+} into the extracellular space while the sarco/endoplasmic reticulum ATPase (SERCA) on the endoplasmic reticulum (ER) membrane pumps Ca^{2+} from the cytosol into intracellular stores. Thus, a large electrochemical gradient is created across the PM and ER membrane. Upon activation, Ca^{2+} can flux into the cytosol through channels on the PM that are either voltage-gated and/or ligand-gated (eg. *N*-methyl-D-aspartate (NMDA) receptors) or store-operated (eg. transient receptor potential channels, TRPC). Stimulation of G-protein-coupled receptors (eg, metabotrophic glutamate receptors, mGluR) can activate phospholipase C and increase the generation of inositol-1,4,5-trisphosphate (IP_3), which can bind receptors IP_3 receptors (IP_3R) on the ER to release Ca^{2+} into the cytosol. The ER-resident ryanodine receptors (RyanR) are Ca^{2+} sensitive and serve to amplify the Ca^{2+} signals from IP_3Rs or the extracellular pool, termed Ca^{2+}-induced Ca^{2+} release (CICR) [6]. In response to stimulation neuronal $[Ca^{2+}]_{cyto}$ can be elevated to 1–5 μM and trigger Ca^{2+}-dependent cellular signalling cascades. The specific pathway activated will depend on the source of Ca^{2+}, the spatio-temporal pattern of cytosolic Ca^{2+} accumulation and the resulting $[Ca^{2+}]_{cyto}$. Cytosolic Ca^{2+} can also flux into mitochondria and activate Ca^{2+}-dependent mitochondrial matrix dehygrogenases and ATP production [8,9]. The overall effect of these Ca^{2+} fluxes can range from the modulation of membrane excitability, enzyme/kinase activity, gene expression, mitochondrial function, reactive oxygen/nitrogen species (ROS/RNS) formation and apoptosis/necrosis.

Calcium regulation in neurons and aging

It is thought that as neurons age, their ability to maintain such tight regulation of Ca^{2+} gradients across the PM and ER membrane becomes compromised, likely due to inefficient energy metabolism and accumulating oxidative stress. Compared to young neurons, old neurons display Ca^{2+} dysregulation, or changes in Ca^{2+} regulation that lead to sustained increases in $[Ca^{2+}]_{cyto}$ [10]. This observation has inspired the hypothesis that such changes in Ca^{2+} signalling could contribute to brain aging, neuronal dysfunction and neurodegeneration [11, 12]. Such age-dependent changes to Ca^{2+} handling in brain have been recently reviewed [10]. Ca^{2+} influx associated with action potentials induces larger Ca^{2+}-dependent after hyperpolarizations (AHPs) [13–15] and impaired short-term synaptic plasticity [16] in aged neurons from rats and rabbits compared to young neurons. Pharmacologically isolated Ca^{2+} action potentials, whole-cell Ca^{2+} currents and Ca^{2+} transients during repetitive spike trains are larger in hippocampal neurons from aged animals [15–17]. Aging enhanced the activity of large (L-type) voltage-gated Ca^{2+} channels (L-VGCC) in partially dissociated hippocampal slices [18]. Functionally, antagonists of L-VGCC appear to improve learning and memory in aged animals [19] and in some patients with dementia [20]. Clearly, there are changes to different components of Ca^{2+} handling with aging and such alterations lead to the augmented susceptibility to induction of long-term depression (LTD) and an increase in the threshold

frequency for induction of long-term potentiation (LTP) in aging neurons [21]. LTD and LTP refer to activity-dependent changes to synaptic strength and remodelling and are proported to be the basis for memory formation and storage [21].

Calcium and neurodegeneration in Alzheimer disease

Alzheimer disease (AD) is the most common form of progressive dementia in the elderly. Most cases of AD are sporadic but approximately 1–2% are genetically linked or familial (FAD) and are distinguished by the early onset of dementia (< 65 years old). Missense mutations in the amyloid precursor protein (APP), the presenilin-1 (PS1) and the presenilin-2 (PS2) genes [22] result in a shift in the proteolysis of APP by the γ-secretase complex such that the ratio of Aβ42/40 protein fragments in the brain is increased [23,24] (Figure 1). This leads to the aggregation and formation of toxic Aβ42 oligomers that induce the loss of synapses and neuronal toxicity in AD [2]. Because FAD is pathologically identical to sporadic AD, it is thought that Aβ42 over-production is the causative factor in AD, dubbed the “amyloid cascade hypothesis”.

In addition to changes in Aβ42/40 ratio, a number of studies point to dysfunctional endoplasmic reticulum (ER) Ca^{2+} signalling in AD, particularly those involving PS mutations [3]. In 1989, Khachaturian proposed that sustained changes in Ca^{2+} homeostasis could provide the common pathway for aging and the neuropathological changes associated with AD, termed the “calcium hypothesis of brain aging and Alzheimer’s disease” [25] and the evidence to support the hypothesis came soon after. Fibroblasts from asymptomatic patients at risk for AD displayed enhanced IP_3R-mediated Ca^{2+} signalling [4]. Expression of Ca^{2+}-handling genes are significantly altered in brain tissue from AD patients [26]. Recently, memantine has been approved by the FDA for use in the treatment of patients with moderate to severe AD. Because memantine antagonizes the Ca^{2+}-permeable NMDA receptor by blocking open, over-activated channels [27], its efficacy illustrates the potential involvement of altered Ca^{2+} signalling in the clinical manifestation of AD. Nimodipine, a dihydropyridine derivative and L-VGCC antagonist, has beneficial effects in AD patients and slows the progression of the disease [28]. A nimodipine derivative, MEM-1003, has completed Phase II clinical trials [29]. Finally, a single nucleotide polymorphism in a newly identified plasma membrane Ca^{2+} channel, CALHM1, interferes with Ca^{2+} permeability and slightly increases susceptibility to sporadic, late-onset AD [30,31]. It should be noted, however, that the role of CALHM1 in AD is controversial, with several studies showing no association between the two [32–34]. Further study of CALHM1 function in neuronal Ca^{2+} signaling is clearly required. In any case, there is a universal agreement that Ca^{2+} dysregulation in neurons appears to be a genuine consequence AD pathology (Figure 1).

Do changes in Ca^{2+} homeostasis affect Aβ production? If so, changes in Ca^{2+} handling could be the trigger of AD pathology. Past studies have addressed this question but there are conflicting conclusions. The earliest study reported that cultured human embryonic kidney cells expressing APP had increased Aβ production after treatment with the Ca^{2+} ionophore, A23187 [35]. The same result was obtained after treating the cells with caffeine, a RyR agonist, suggesting that both Ca^{2+} influx and release of Ca^{2+} from intracellular stores promoted Aβ production [36]. However, after treatment with thapsigargin, which irreversibly blocks SERCA activity and increases cytosolic Ca^{2+} levels, cultured cells showed dose-dependent decreases in their production of Aβ [37]. More recently it was demonstrated that influx of Ca^{2+} from L-VGCC and elevated $[Ca^{2+}]_{cyto}$ increased intraneuronal Aβ42 production, while release of ER Ca^{2+} was inadequate for Aβ production [38]. Conversely, it has been shown that loss of Ca^{2+}influx through plasma membrane channels due to polymorphisms increases Aβ42 formation and Aβ42/40 ratio in CHO cells expressing APP [30]. The processing of APP is complex and is clearly affected by altered cytosolic Ca^{2+} signalling but further study,

particularly in neuronal systems, is required to determine which Ca^{2+} sources are important for Aβ production.

The effects of APP and its metabolites on cytosolic Ca^{2+} signalling are well established and have been reviewed recently [39]. Aβ40 and Aβ42 can form Ca^{2+}-permeable pores on the plasma membrane, generally leading to an increase in $[Ca^{2+}]_{cyto}$ [40]. Pore formation is enhanced by exposure of phosphatidylserine on the cell surface; an indication that a cell will undergo apoptosis [41,42]. Because destabilization of cytosolic Ca^{2+} levels can trigger free radical formation [43], lipid peroxidation [44] and apoptosis [45], such mechanisms could be involved in Aβ neurotoxicity. Aβ oligomers can modulate NMDA receptor activity [46–48] and sensitivity to NMDA-mediated excitotoxicity [47,49]. Aβ oligomers can also suppress activity of presynaptic P/Q-type (neuronal) VGCC [50] and direct modulation of L-type Ca^{2+} VGCC activity by APP was recently reported [51]. Secreted APPs have neuroprotective qualities because they attenutate the elevated $[Ca^{2+}]_{cyto}$ evoked by Aβ [52] and moderate glutamate-induced cytosolic Ca^{2+} levels in hippocampal neurons by increasing cyclic GMP [53]. Changes in Ca^{2+} dynamics are thought to contribute to the altered synaptic transmission observed in PDAPP mice [54]. More recently, *in vivo* Ca^{2+} imaging experiments with Tg2567 mice displayed elevated $[Ca^{2+}]_{cyto}$, or Ca^{2+} overload, in neurites and spines that were in close proximity to Aβ plaques [55] and induction of Ca^{2+} waves in astrocytes [56]. Ca^{2+} disturbances observed in both cases were most likely caused by direct effects of soluble Aβ oligomers on Ca^{2+} signaling in neurons and astrocytes [57].

Downstream effects of sustained dysregulated cytosolic Ca^{2+} is activation of Ca^{2+}-dependent phosphatase calcineurin and neuritic atrophy [55]. Activation of calcineurin also has profound effects on synaptic plasticity [58]. Excessive Ca^{2+} signals also activate Ca^{2+}-dependent proteases calpains which degrade signaling enzymes involved in learning and memory [59, 60]. Prolonged Ca^{2+} dysregulation causes accumulation of ROS, mitochondrial dysfunction and neuronal death. Increases in $[Ca^{2+}]_{cyto}$ can cause excessive Ca^{2+} flux into mitochondria and increase ROS production [43,45,61]. Evidence of ROS, reduced energy metabolism and decreased cytochrome *c* oxidase activity have been described in the brains of AD patients [62,63]. These processes could ultimately lead to the extensive cortical and hippocampal atrophy and neurodegeneration characteristic of AD [64] (Figure 1).

ER Ca^{2+} and neurodegeneration in AD

The role of the ER in the dysregulation of cytosolic Ca^{2+} in AD has been a major focus of research because mutations that cause AD also affect ER Ca^{2+} signalling. Skin fibroblasts from human patients that harbour a mutation in presenilin 1 (PS1)-A246E, a transmembrane protein that is the catalytic component of the γ-secretase complex, showed exaggerated Ca^{2+} release from IP_3-gated stores compared to controls after treatment with bombesin and bradykinin [4]. These alterations in Ca^{2+} signalling were detected before the development of overt clinical symptoms and such changes were not present in cells from subjects that failed to develop AD [5]. Cells expressing mutant PS1 [65] and primary cortical neurons from mice expressing mutant PS1 displayed similar alterations in signalling [66,67]. Clinical mutations of the PS2 gene also enhanced Ca^{2+} release from IP_3R-gated ER stores [68]. Much data have been generated since these early studies to suggest that in addition to their γ-secretase function, PS mutations have a significant impact on Ca^{2+} signalling in AD models. It has been reported that mutations in PS can modulate capacitative Ca^{2+} entry, a refilling mechanism for depleted Ca^{2+} stores [66,69,70]. Explanation to these results has been provided by a recent discovery that PS also functions as ER Ca^{2+} leak channels and that FAD mutations in PS1 disrupts this function [71,72], resulting in overloaded ER Ca^{2+} stores and exaggerated ER Ca^{2+} release in PS double knockout fibroblasts and in fibroblasts transfected with mutant PS1 and PS2 constructs. The PS1-M146V mutation augmented Ca^{2+} release from IP_3- and caffeine- gated

stores in hippocampal and cortical neurons in 3XTg-AD mice [14,73]. The gating of IP_3R was reported to be directly modulated by PS1-M146L in overexpression system [74], providing another potential mechanism for connection between mutations in presenilins and ER Ca^{2+} signaling. *Xenopus laevis* oocytes expressing PS1-M146V have increased SERCA activity compared to those with wild-type PS1 [75], a mechanism that could additionally contribute to the overfilling of ER Ca^{2+} store. It is clear that familial AD mutation in presenilins affect the activity and/or expression of many proteins involved in ER Ca^{2+} signalling and predominately results in enhanced release of Ca^{2+} from ER stores.

Several mouse models of AD demonstrate that RyanRs are up-regulated in expression and function in cultured neurons and in brain. For example, the exaggerated IP_3- and caffeine-evoked Ca^{2+} responses in 3XTg-AD hippocampal and cortical neurons were attributed to increased RyanR expression and recruitment [14,67,73]. RyanRs are responsible for the amplification of intracellular Ca^{2+} signals from IP_3R stores or Ca^{2+} influx from the plasma membrane by CICR. Given the involvement of RyanRs in CICR, modulation of membrane excitability [76,77], neuronal function [78,79] and hippocampal learning and memory [80, 81], it is rational to hypothesize that the up-regulation of the RyanRs could contribute to AD pathology. In human post-mortem tissue, ryanodine binding is elevated in hippocampal regions (subiculum, CA2 and CA1) of AD brain in the early stages of the disease prior to extensive neurodegeneration and overt Aβ plaque deposition [82]. Furthermore, it has been reported that RyanR levels are increased in 3 different mouse models of AD; PS1-M146V, PS2-N141I, 3XTg-AD and TgCRND8 [83–86]. Finally, increased RyR levels enhanced Ca^{2+} release from the ER and sensitized cortical neurons from PS1-M146V and PS2-N141I mice to neurotoxic insults, such as treatment with high glutamate concentration [83,84] (Figure 1).

ER Ca^{2+} and neuroprotection in AD

Are all changes to neuronal ER Ca^{2+} signaling in AD detrimental? Recent evidence has revealed new insight into potential importance of enhanced Ca^{2+} release from neuronal ER in the context of AD. Chakroborty, et al. 2009, demonstrated that while pre-symptomatic 3XTg-AD mice had aberrant ryanodine-evoked Ca^{2+} responses in CA1 pyramidal neurons compared to non-Tg, due to increased RyanR type 2 expression, they displayed seemingly normal synaptic transmission [73]. These results suggest a mechanism by which neurons might maintain Ca^{2+} homeostasis and neuronal function in the early stages of the disease. Furthermore, TgCRND8 mice displayed increased RyanR type 3 expression and function and increased Ca^{2+} release from ryanodine-gated stores in primary cortical neurons [86] but showed no changes in global Ca^{2+} handling [87]. It followed that Tg neurons were no more susceptible to neurotoxicants, such as glutamate, compared to non-Tg and suppression of RyanR3 up-regulation sensitized neurons to death in culture [87].

Given the importance of Ca^{2+} signalling to synaptic plasticity [88] and that mouse models of AD display neuronal hyperexcitability, epileptiform activity and functional disruption of neuronal networks [55,89–92], perhaps alterations in ER Ca^{2+} handling are utilized to depress membrane excitability and prevent excitotoxicity. RyanRs are appropriately situated in the dendritic spines of CA1 hippocampal neurons to contribute to the CICR required to induce synaptic changes [73]. Recently, it has been shown that RyanR3 plays a substantial role in mediating the slow AHP current in hippocampal CA1 pyramidal neurons, important for the depression of membrane excitability [79]. Up-regulation of RyR3 could prove important for the modulation of excitability in cortical neurons of TgCRND8 mice, due to accumulating Aβ *in vitro*, and neurons that are unable to up-regulate RyR3 due to siRNA treatment could be more vulnerable to the excitotoxicity, oxidative stress and death related to Aβ exposure [93]. Such a role for RyanR3 could be relevant in brain as well. Adult (4–4.5 month old) TgCRND8 mice have increased expression of RyanR3 in the cortex and hippocampus compared to controls

[86]. It is interesting to note that pre-plaque TgCRND8 mice display presynaptic depression of basal synaptic transmission in hippocampal CA1 mediated by large current Ca^{2+}-activated K^+ (BK) channels, which participate in AHP and are activated in epilepsy [94]. Altered neuronal excitability and epileptic activity in AD are thought to be a manifestation of neuronal circuit remodelling that can occur very early in the disease. In AD patients, seizures may accompany the onset of mild cognitive impairment and can occur at the time of diagnosis prior to extensive neurodegeneration [95]. This is an emerging area of study in AD and changes to RyanR-mediated Ca^{2+} signalling could be an important factor in these phenomena.

Furthermore, when AD-related mutations negate the ability of PS to "leak" Ca^{2+} from the ER [71], the results are damaging to neuronal function and health. The up-regulation of RyanR function in hippocampal neurons from the 3X-TgAD mice expressing PS1-M146V knockin mutation appear to partially compensate for the loss of ER Ca^{2+} leak function in these neurons [96]. It was demonstrated that when up-regulated RyanRs were blocked by RNA interference or dantrolene in hippocampal neurons from 3X-TgAD mice, the results were significantly overloaded ER Ca^{2+} pools [96]. Moreover, when APPPS1 transgenic mice harbouring the FAD PS1-L166P mutation were chronically fed dantrolene, Aβ plaque load was increased by 3-fold and PSD95 expression, a marker for excitatory synapse formation, was decreased in brain from 8 month old mice compared to control [96]. Such data indicate that the loss of ER Ca^{2+} leak function of presenilins can be partially compensated by an increased RyanR-mediated Ca^{2+} flux from the ER.

These findings prompt us to suggest that perhaps some forms of dysregulated ER Ca^{2+} signalling are a response to the adverse conditions of AD, such as for example the accumulation of Aβ peptides or increased neuronal excitability, and are an effort to maintain intracellular Ca^{2+} and cellular homeostasis (Figure 2). If such compensatory mechanisms exist, they may slow down the progression of disease but can not stop it completely, as TgCRND8, APPPS1 and 3X-TgAD mice go on to develop cognitive dysfunction and plaque formation [97–100]. Possibly such subtle alterations to neuronal Ca^{2+} regulation are only effective in the early stages of the disease. Another possibility is that these small changes to ER Ca^{2+} signalling are intended for the short-term and when they are sustained over the duration of AD progression, they may actually contribute to neuronal dysfunction and aberrant neuronal network formation leading to cognitive deficits [90]. The mechanisms by which changes to intracellular Ca^{2+} could be protective in AD are still not clear and further studies are required to determine how they may affect neuronal function and viability (Figure 2).

Conclusion

There is much evidence to suggest that dysregulated Ca^{2+} signalling has a significant role to play in the pathology of AD. Evidence suggests that the various Ca^{2+} handling channels and pumps in the ER are prominent contributors to the alterations of intracellular Ca^{2+} signalling in AD. Some of the Ca^{2+} signaling changes observed in AD appear to be detrimental to neuronal health, but some may be compensatory. A more comprehensive understanding of the role of dysregulated Ca^{2+} handling in neurodegeneration and neuroprotection in AD will be imperative for the future design of effective disease-modifying therapeutics.

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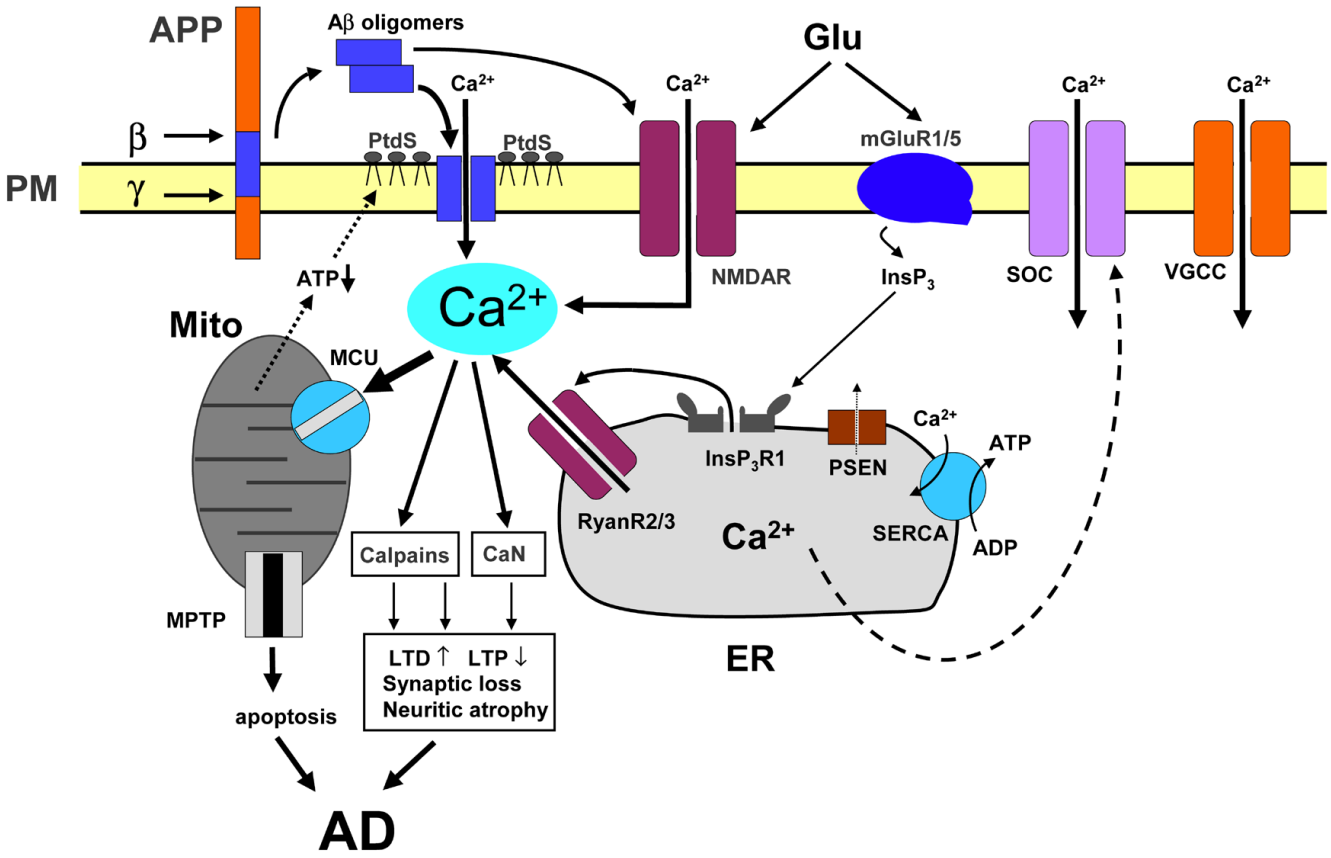

Figure 1. Calcium dysregulation in Alzheimer disease

Sequential cleavages of β-amyloid precursor protein (APP) by β-secretase (β) and β-secretase (β) generate amyloid β peptide (Aβ). Aβ forms oligomers, which can insert into the plasma membrane and form Ca^{2+}-permeable pores. The association of Aβ oligomers with the plasma membrane is facilitated by binding to surface phosphatidylserine (PtdS); age and Ca^{2+}-related mitochondrial impairment leads to ATP depletion and might trigger flipping of PtdS from the inner portion of the plasma membrane to the cell surface. Reduction in ATP levels and loss of membrane integrity causes membrane depolarization, which leads to facilitation of Ca^{2+} influx through NMDAR and VGCC. Aβ oligomers can also affect activity of NMDAR, AMPAR and VGCC directly. Glutamate stimulates activation of mGluR1/5 receptors, production of InsP3 and InsP3R -mediated Ca^{2+} release from the ER. Presenilins (PS) function as an ER Ca^{2+}-leak channels and many FAD mutations impair Ca^{2+}-leak-channel function of PS, resulting in excessive accumulation of Ca^{2+} in the ER. Increased ER Ca^{2+} levels result in enhanced Ca^{2+} release through InsP3 -gated InsP3R 1 and Ca^{2+}-gated RyanR(2/3). PS might also modulate activity of InsP3R, RyanR and SERCA pump directly. The activity of store-operated Ca^{2+} channels on the plasma membrane can be affected indirectly by PS mutations through the modulation of SERCA activity. Elevated cytosolic Ca^{2+} levels result in the activation of calcineurin (CaN) and calpains and lead to facilitation of LTD, inhibition of LTP, modification of neuronal cytoskeleton, synaptic loss and neuritic atrophy. Excessive Ca^{2+} is taken up by mitochondria through mitochondrial Ca^{2+} uniporter (MCU), eventually leading to opening of mitochondrial permeability-transition pore (mtPTP) and apoptosis.

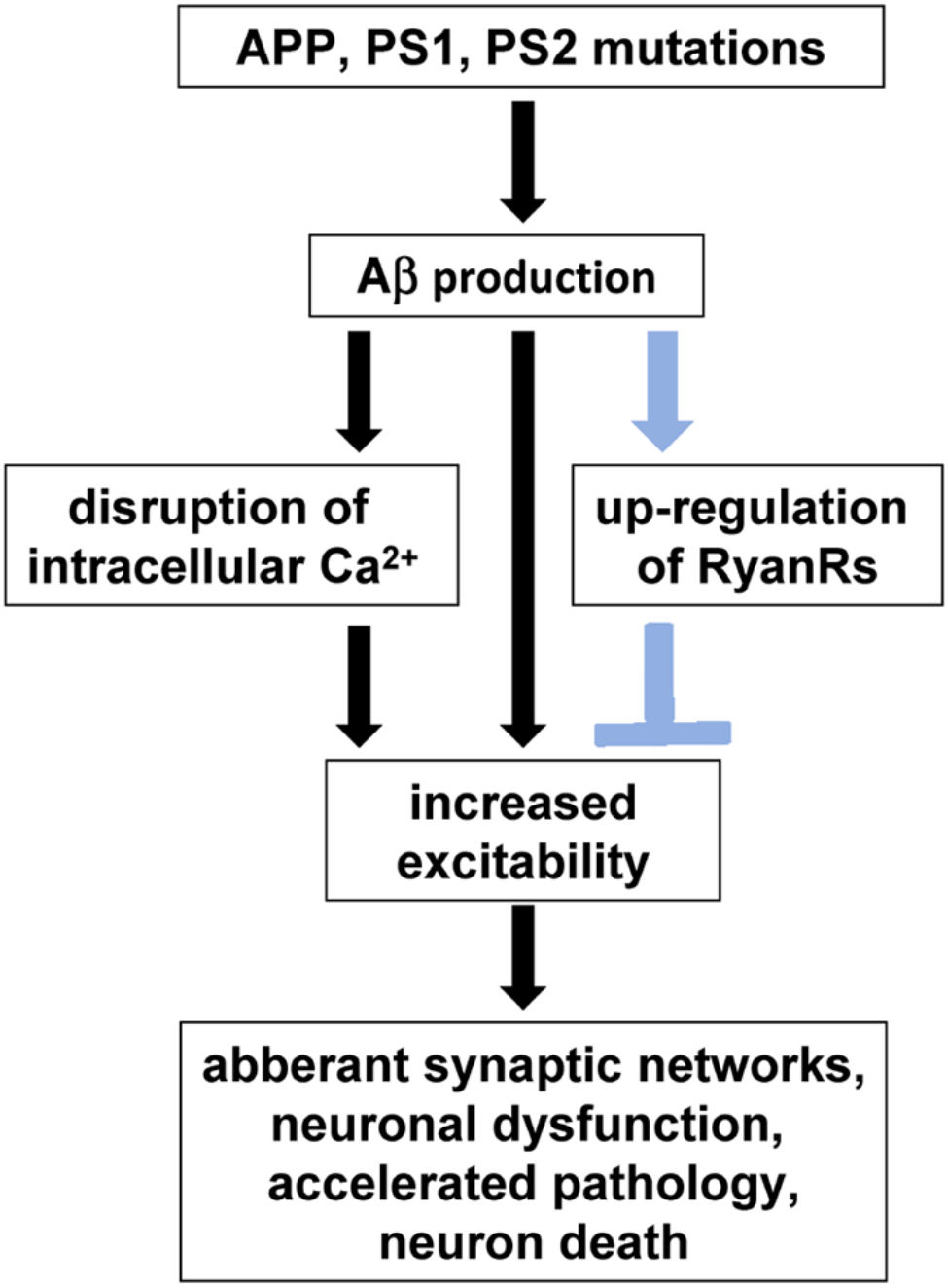

Figure 2. Pathways to neurodegeneration and neuroprotection in Alzheimer disease

Illustration of how changes to intracellular Ca^{2+} handling could lead to neurodegeneration (black arrows) or potentially neuroprotection (blue arrows). It is generally accepted that Aβ oligomers and sustained Ca^{2+} dysregulation contributes to neurodegeneration in AD. Recent studies have demonstrated that both contribute to increased neuronal excitability, which can trigger the aberrant remodelling of neuronal networks, neuronal dysfunction, Aβ production and cell death. New data suggests that particular types of Ca^{2+} dysregulation in AD could be compensatory, eg. the up-regulation of RyanRs, and are triggered in parallel to attenuate or delay neurodegenerative mechanisms.