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ORIGINAL PAPER

Dysregulation of Calcium Homeostasis in Alzheimer's Disease

David H. Small

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Abstract The accumulation of oligomeric species of β-amyloid protein in the brain is considered to be a key factor that causes Alzheimer's disease (AD). However, despite many years of research, the mechanism of neurotoxicity in AD remains obscure. Recent evidence strongly supports the theory that Ca^{2+} dysregulation is involved in AD. Amyloid proteins have been found to induce Ca^{2+} influx into neurons, and studies on transgenic mice suggest that this Ca^{2+} influx may alter neuronal excitability. The identification of a risk factor gene for AD that may be involved in the regulation of Ca^{2+} homeostasis and recent findings which suggest that presenilins may be involved in the regulation of intracellular Ca^{2+} stores provide converging lines of evidence that support the idea that Ca^{2+} dysregulation is a key step in the pathogenesis of AD.

Keywords Amyloid · Calcium · Toxicity · Alzheimer's disease · Dementia

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Pathologically, AD is characterized by the deposition of protein, extracellularly as amyloid plaques, and intracellularly as neurofibrillary tangles [1]. While neurofibrillary tangles are commonly found in a number of neurodegenerative diseases, amyloid plaques are only a hallmark of AD. For this reason, the deposition of amyloid has generally been considered to be more closely associated with the primary pathogenic mechanism of AD [2].

Amyloid plaques are principally composed of the β-amyloid protein (Aβ) protein, a 4-kDa polypeptide which is derived by proteolytic cleavage from the β-amyloid precursor protein (APP) [3]. APP is cleaved on the N-terminal side of the Aβ sequence by an aspartyl protease termed β-secretase or BACE1 (an acronym for β-site APP cleaving enzyme-1; Fig. 1). This cleavage results in production of an APP C-terminal fragment (C99) which is then further cleaved by γ-secretase (a complex of proteins containing presenilin1 or 2, aph-1, pen-2 and nicastrin) to produce Aβ and an APP intracellular domain fragment (AICD) which may have functions related to intracellular signalling [4]. Recent studies clearly show that it is the build-up of soluble oligomeric forms of Aβ that triggers neurodegeneration in AD [5]. For example, all familial AD mutations increase either the total amount or the proportion of aggregating Aβ species [6].

Dysregulation of Ca^{2+} in Alzheimer's Disease

It has been known for more than 20 years that Ca^{2+} levels are increased in ageing neurons [7, 8]. On the basis of this observation, it has been suggested that dysregulation of Ca^{2+} may underlie the neurodegeneration that occurs in AD [9]. Ca^{2+} is a key regulator of synaptic plasticity [10] and therefore it is easy to see how dysregulation of Ca^{2+} could lead to cognitive abnormalities. In addition, Ca^{2+} plays a central role in excitotoxicity. For example, the activation of Ca^{2+}-dependent proteases (caspases, calpains) is probably an important step in the breakdown of cytoskeletal proteins in apoptosis (Fig. 2) [11].

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D. H. Small (✉)
Menzies Research Institute, University of Tasmania,
Private Bag 24, Hobart, TAS 7001, Australia
e-mail: d.h.small@menzies.utas.edu.au

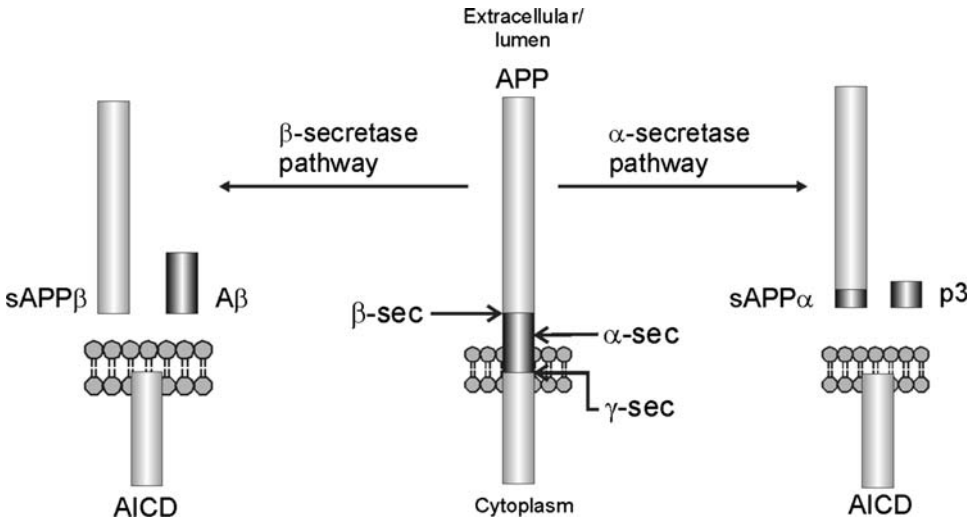

Fig. 1 Proteolytic processing of the amyloid precursor protein (APP). APP can be cleaved by the α-secretase (*α-sec*) and γ-secretase (*γ-sec*) to produce two secreted fragments (sAPPα and p3) and an APP intracellular domain (*AICD*) fragment. Alternatively, APP can be cleaved first by the *β*-secretase (*β-sec*) followed by γ-sec to produce sAPP*β*, A*β* and AICD

A*β* Disrupts Ca^{2+}

The possibility that A*β* may disrupt Ca^{2+} in neurons has been given a strong boost by recent in vivo imaging studies of transgenic mice with extensive amyloid deposits. These studies using a genetically encoded Ca^{2+} indicator show that Ca^{2+} levels are elevated in dystrophic neurites in the region of amyloid deposits [12]. Thus there is strong recent experimental support for the idea originally proposed by Landfield, Kachaturian and others [7–9]. It seems likely that some of this disruption may be due to a direct effect of A*β*. Studies by Mattson et al. [13] first showed that A*β* increases the level of cytoplasmic Ca^{2+}, thereby rendering neurons more susceptible to glutamate-induced neurotoxicity. A number of more recent studies have shown that this increase in cytoplasmic Ca^{2+} is principally due to an influx of extracellular Ca^{2+} across the cell membrane [14, 15].

The mechanism by which Ca^{2+} influx is stimulated by A*β* remains obscure. Several mechanisms have been proposed. Mark et al. [14] suggested that A*β* may impair membrane ATPase activity, thereby causing Ca^{2+} destabilisation, while other studies have suggested that this influx may be induced in association with lipid peroxidation [15]. A third hypothesis proposed by Arispe et al. [16, 17] suggests that A*β* may bind to the plasma membrane to form artificial membrane pores. This idea has recently been supported by the work of several groups. Electrophysiological and atomic force microscopy studies by Lal et al. [18–21] have shown that A*β* oligomers can form small annular structures on lipid membranes which resemble membrane pores. Indeed, similar structures have also been seen by Lansbury et al. using another neurotoxic protein α-synuclein [22]. Studies by Glabe and coworkers [23–25] also support the notion that A*β* peptides can disrupt lipid membranes. However, in these studies the investigators suggest that A*β* may cause weakening or thinning of the plasma membrane. Despite the large number of studies suggesting that A*β* may directly disrupt lipid membranes, most of the evidence for the membrane pore hypothesis comes from in vitro studies using purified A*β* and artificial lipid membranes. To date, no direct evidence for the formation of membrane pores by A*β* has been obtained from cell culture or in vivo studies.

In contrast to the artificial pore hypothesis, there is abundant evidence both from cell culture and in vivo studies to indicate that A*β* can trigger Ca^{2+} influx through endogenous membrane ion channels. Several studies indicate that A*β* may trigger the opening of NMDA receptors. Domingues et al. [26] observed that A*β* toxicity was blocked by a non-specific NMDA receptor antagonists in cultures of HEK293 cells expressing NMDA receptors. Snyder et al. [27] have proposed that effects of A*β* on NMDA receptors may be mediated by a direct action on α7 nicotinic acetylcholine receptors (α7nAChR), as several studies report that A*β* may bind directly to α7nAChRs. However, this possibility has been disputed by Small et al. [28], who could not find any evidence for a direct interaction between A*β* and the α7nAChR. Ye et al. [29] reported that A*β* can open a nonselective cation channel and Good et al. [30] found that A*β* can block a fast-inactivating potassium current, leading to membrane depolarization and the influx of Ca^{2+} through voltage-gated channels. Studies using other amyloidogenic proteins support the notion that oligomers stimulate Ca^{2+} influx via voltage-gated Ca^{2+} channels. Silei et al. [31] showed that prion protein can stimulate the opening of L-type channels and our own studies [32] show that amyloidogenic transthyretin can induce Ca^{2+} influx through both L- and N-type channels.

Studies from our group [33] have shown that incubation of neuronally differentiated P19 cells with A*β* can increase the level of acetylcholinesterase (AChE) in the cells

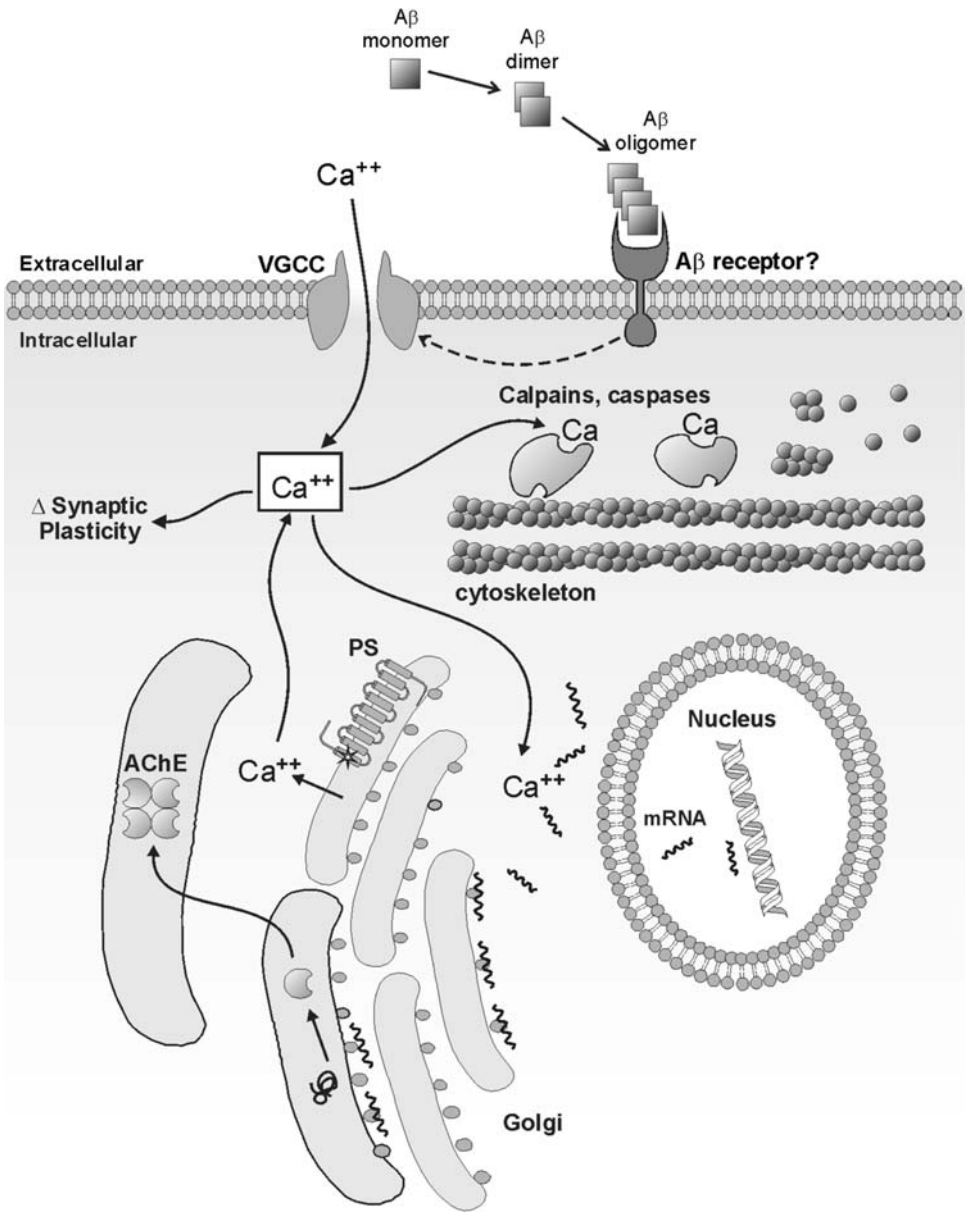

Fig. 2 The central role of Ca^{2+} in the pathogenesis of Alzheimer's disease. Figure shows several hypothetical mechanisms which may destabilise Ca^{2+} in neurons. Association of Aβ oligomers with an as yet unidentified cell surface receptor can stimulate the opening of voltage-gated Ca^{2+} channels (*VGCC*). Ca^{2+} may leak from intracellular stores in association with disease-causing mutations in presenilins (*PS*). Increased cytosolic Ca^{2+} can disrupt events associated with synaptic plasticity, activate calpains and caspases which can degrade cytoskeletal proteins, and contribute to other events such as an increase in acetylcholinesterase (*AChE*) levels, possibly through the stabilisation of AChE mRNA

(Fig. 2). This increase is dependent on Ca^{2+} influx via L-type voltage-gated channels [33]. Entry of Ca^{2+} through L-type channels had previously been shown to increase AChE mRNA in muscle cells via a mechanism involving an increase in mRNA stability [34]. Thus, a similar mechanism may operate in neurons. Aβ causes the selective increase in a minor amphililic glycoform of acetylcholinesterase [35]. Interestingly, this minor form of acetylcholinesterase is elevated in AD brain and CSF as well as in two transgenic mouse models of Aβ overproduction and in rats injected intracranially with Aβ [36–38]. The results of all of these experiments suggest that Aβ oligomers act to stimulate L-type voltage-gated Ca^{2+} channels early in the pathogenesis of AD.

Genetic Factors that Influence Ca^{2+} Homeostasis

Recent studies indicate that genetic factors could also play a role in the dysregulation of Ca^{2+} homeostasis in AD. It is now well established that mutations in the genes encoding presenilins-1 or 2 cause familial AD (FAD) [39]. In the case of the presenilin-1 gene, more than 100 FAD mutations have now been identified, and, at the time of writing, 6 FAD mutations have been identified in the presenilin-2 gene. It seems very likely that all FAD mutations cause AD via a similar mechanism, i.e., by increasing the relative proportion of Aβ species that aggregate readily. For example, many presenilin mutations increase the amount of Aβ1-42, which aggregates more readily than Aβ1-40 [39].

Presenilins are an important component of the γ-secretase processing complex. Indeed, knockout of the presenilin gene has been shown to abolish γ-secretase cleavage of APP [40]. Over the last few years, evidence has slowly accumulated that presenilins may form part of the catalytic subunit of the γ-secretase. Intramembranous proteolysis of APP may occur through a catalytic mechanism involving two aspartyl residues located within a pore-forming transmembrane region of the protein [41].

Despite intensive investigation, the mechanism by which presenilins cause γ-secretase cleavage remains unclear. Recent studies have complicated a straightforward interpretation of presenilin's function. Presenilin mutations have been found to increase release of intracellular Ca^{2+} from ryanodine or inositol 1,4,5-trisphosphate (IP_3) channels [42, 43]. Landman et al. [44] showed that presenilin mutations can influence phosphoinositol metabolism, thereby altering cation flux through transient receptor potential M7 channels, and very recently, Cheung et al. [45] found that presenilins can regulate Ca^{2+} channel gating via the IP_3 receptor.

At first sight, the effect of presenilin mutations on intracellular Ca^{2+} stores seems to be unrelated to γ-secretase cleavage. However, it is possible that there is a link between γ-secretase activity and intracellular Ca^{2+} stores. Green et al. [46] found that presenilin mutant-induced enhancement of Aβ secretion was abolished in IP_3 receptor knockout cells. The finding suggests that γ-secretase cleavage must be downstream of IP_3 signalling, but how this occurs is still very unclear. The finding that presenilin influences IP_3 signalling and Ca^{2+} release and that IP_3 is required for Aβ production raises some doubts as to whether our models of presenilin's action are correct.

Interest in the Ca^{2+} dysregulation hypothesis of AD has also been promoted by the finding that a polymorphism in a gene involved in the regulation of Ca^{2+} homeostasis (Ca^{2+} homeostasis modulator-1 or CALHM1) may increase the risk of AD (allele-specific odds ratio = 1.44) [47]. Significantly, expression of a polymorphic variant of this gene (P86L), that is linked to increased risk of AD, has been found to reduce Ca^{2+} levels and to increase Aβ production in transfected cells. Based on its sequence similarity to the ion selectivity filter of the NMDA receptor, it has been suggested that this gene may encode a glycoprotein that is a Ca^{2+} channel component [47].

Mechanism of Disease Progression

The clinical features of AD pursue an inexorable downward course [48]. Initially, patients exhibit relatively mild cognitive impairment. However, as the disease progresses, patients exhibit more severe amnesia accompanied by apathy and stupor. At later stages of the disease, patients become bedridden. The neuropathology of AD typically reflects the clinical course [49]. Amyloid plaques and neurofibrillary tangles are seen in the hippocampus and neocortex, and as the disease progresses they increase in number, although the correlation between the number of amyloid plaques and the clinical symptoms is relatively poor [50]. A closer examination shows that the disease seems to spread on the basis of neuronal connectivity, initially affecting neurons associated with memory processing. Tangle-bearing neurons are often first seen in the trans-entorhinal cortex [49]. The neurodegeneration can spread to the hippocampus via the CA3 and CA1 neurons and from there to the association cortex.

The specific pattern of neuronal vulnerability may be explained by a process known as synaptic scaling [51], a relatively slow form of synaptic plasticity which controls the amount of excitatory input at synapses, and thereby helps to preserve the normal function of neural networks in the brain [52]. When the excitatory input from one neuron decreases, possibly as a result of Aβ induced neurotoxicity, other neurons respond by increasing the release of excitatory neurotransmitter. The increase in neurotransmitter release probably involves an increase in cytoplasmic Ca^{2+}, which may, in turn, render healthy neurons more vulnerable to Aβ toxicity [51]. In this manner, neurodegeneration may spread via neuronal connectivity. Both tumour necrosis factor-α (TNFα) and brain-derived neurotrophic factor (BDNF) have been implicated in synaptic scaling in the cortex [52, 53]. These factors can have opposite effects on neuronal excitability, with TNFα increasing the firing of cortical neurons [53] and BDNF decreasing the firing [52]. Consistent with the idea that neuronal excitability may be increased in the AD brain, the level of excitatory TNFα has been reported to be increased [54] and the level of BDNF has been reported to decrease in the AD brain [55].

Summary and Conclusions

There is now ample evidence to indicate that Ca^{2+} homeostasis is dysregulated in the AD brain. Converging lines of evidence suggest that several disease-associated genes can influence Ca^{2+} signalling. While not all of the Aβ-induced neurotoxicity may be directly associated with an increase in cytosolic Ca^{2+}, it is clear that the central role of Ca^{2+} in synaptic plasticity and excitotoxicity make Ca^{2+} a key suspect in the mechanism of neurodegeneration. It is possible that Ca^{2+} dysregulation may be target for drug development in AD. To date, little work has been done in this area. A retrospective analysis of the use of calcium antagonists is encouraging [56], however, to date only one clinical study has been performed (on an L-type VGCC

inhibitor called MEM-1003, an analogue of nimodipine). Although results of this study have not been published, the study was of limited duration (12 weeks). Therefore, calcium antagonists may be worth testing in more long-term clinical trials.

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