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Glial Calcium Signalling in Alzheimer's Disease

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Abstract The most accredited (and fashionable) hypothesis of the pathogenesis of Alzheimer Disease (AD) sees accumulation of β-amyloid protein in the brain (in both soluble and insoluble forms) as a leading mechanism of neurotoxicity. How β-amyloid triggers the neurodegenerative disorder is at present unclear, but growing evidence suggests that a deregulation of Ca^{2+} homeostasis and deficient Ca^{2+} signalling may represent a fundamental pathogenic factor. Given that symptoms of AD are most likely linked to synaptic dysfunction (at the early stages) followed by neuronal loss (at later and terminal phases of the disease), the effects of β-amyloid have been mainly studied in neurones. Yet, it must be acknowledged that neuroglial cells, including astrocytes, contribute to pathological progression of most (if not all) neurological diseases. Here, we review the literature pertaining to changes in Ca^{2+} signalling in astrocytes exposed to exogenous β-amyloid or in astrocytes from transgenic Alzheimer disease animals models, characterized by endogenous β-amyloidosis. Accumulated experimental data indicate deregulation of Ca^{2+} homeostasis and signalling in astrocytes in AD, which should be given full pathogenetic consideration. Further studies are warranted to comprehend the role of deficient astroglial Ca^{2+} signalling in the disease progression.

Keywords Alzheimer's disease · Astrocyte · Calcium signalling · Glutamate receptors · $InsP_3$ receptors · Neuroglia

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1 Introduction

Neuroglial cells, astrocytes, oligodendrocytes, NG2 cells, and microglia contribute to pathological progression of most (if not all) neurological diseases. The role of glia is either primary (e.g., in Alexander disease or in hepatic encephalopathy) or secondary (e.g., in stroke); with neuroglial reactions being fundamental for defining progression and outcome of neurological disorders (Giaume et al. 2007; Verkhratsky et al. 2013). Nonetheless, neurodegenerative diseases are considered primarily from the neurono-centric angle, which is somewhat surprising because the pathological potential of neuroglia in neurodegenerative pathology was recognized already at the beginning of the twentieth century (Alzheimer 1910). Contribution of neuroglial cells in the progression of various neurodegenerative diseases is multifaceted; all types of glia are affected and their pathological remodelling is disease-specific (Pekny et al. 2014; Sofroniew 2014; Verkhratsky et al. 2013). In Alzheimer's disease (AD), which represents a progressive neurodegenerative pathology with a characteristic histological profile of senile plaques and neuronal tangles (Alzheimer 1907; Braak et al. 1998), astrocytes undergo both atrophy and reactive gliosis (Verkhratsky et al. 2010), oligodendrocytes show generalized atrophy with significant white matter lesions (Rodriguez and Verkhratsky 2011) and microglia shows increased density and activated phenotypes in association with functional paralysis (Krabbe et al. 2013; Rodriguez et al. 2013).

The β-amyloid hypothesis of AD regards accumulation of β-amyloid protein (in both soluble and insoluble forms) as a leading mechanism of neurotoxicity. Although considerable evidence has been accumulated regarding the effects of β-amyloid on neurones (Bezprozvanny and Mattson 2008; Popugaeva and Bezprozvanny 2014; Stutzmann 2007; Stutzmann and Mattson 2011), its action on glial cells has been investigated to a much lesser extent. How β-amyloid leads to neurodegeneration is at present controversial, although the possibility that it leads to a chronic deregulation of cellular calcium homeostasis has been gaining credibility in recent years. Indeed, it has been postulated that AD might represent a "chronic calciumopathy" (Stutzmann 2007). Here we shall overview the glial side

of this hypothesis and narrate the fundamental role of deregulation of glial Ca^{2+} homeostasis and signalling in β-amyloid-associated cellular pathology.

2 Calcium Signalling in Neuropathology

Tight control over intracellular Ca^{2+} concentrations, that in the cytosol of all living cells does not exceed 50 to 100 nM, reflects an early evolutionary choice of phosphate (i.e., ATP) as a universal energy saving molecule; indeed reactions involving phosphate ultimately require low Ca^{2+} (Burnstock and Verkhratsky 2012; Case et al. 2007). Molecular cascades responsible for Ca^{2+} homeostasis are evolutionally conserved, many of them being present in prokaryotes and in the most ancient eukaryotes (Plattner and Verkhratsky 2013). The steep concentration gradient for Ca^{2+} aimed at the cytosol is successfully employed for signalling, with dynamic intracellular Ca^{2+} changes being arguably the most ubiquitous and versatile signalling system universally expressed through all life forms (Berridge et al. 2000; Carafoli et al. 2001). Deregulation of Ca^{2+} homeostasis represents a similarly universal mechanism of cellular pathology, because its failure inevitably triggers cell malfunction and often deregulated Ca^{2+}-handling appears as the main mediator of necrotic or programmed (apoptosis, autophagy, anoikis, etc.) cell death (Carafoli 2004; Orrenius et al. 2003; Zhivotovsky and Orrenius 2011).

Molecular cascades controlling Ca^{2+} homeostasis and signalling are represented by Ca^{2+} channels (that mediate transmembrane Ca^{2+} diffusion), Ca^{2+} exchangers, ATP-dependent Ca^{2+} transporters, Ca^{2+}-binding proteins, and Ca^{2+}-dependent enzymes (e.g., kinases, phosphatases, etc). (Petersen et al. 1994). The combination of different types of proteins involved in Ca^{2+} homeostasis determines cell-specific Ca^{2+} toolkits (Berridge et al. 2000). These toolkits define specific cellular responses to external stimuli. Furthermore, these toolkits have a high degree of plasticity so that the Ca^{2+} signalling machinery can rapidly adapt to environmental challenges. The universal role of Ca^{2+} for cell signalling and metabolism defines the pathological potential of the Ca^{2+} homeostatic machinery.

In neuropathology, slow and relatively minor modifications of Ca^{2+} homeostatic/signalling toolkits may contribute to pathological progression through impacting, for example, on synaptic transmission, neuronal metabolism, and ultimately on neuronal survival. These aberrant, abnormal or asthenic calcium signals have been implicated in a wide variety of neurological and neuropsychological disorders including ischemia, malignant hyperthermia, major depression, autistic spectrum disorders, epilepsy, migraine, and neurodegeneration (Gargus 2009; Kullmann 2010; Stutzmann 2007; Stutzmann and Mattson 2011). Deregulation of Ca^{2+} homeostasis in chronic disorders, including AD, is most likely determined by subtle alterations developing over decades and accumulating to reveal detectable footprints of the disequilibrium, which ultimately contribute to the appearance of specific symptoms (Stutzmann 2007).

In non-excitable neuroglial cells, Ca^{2+} signals are considered to be one of the main substrates for cellular excitability, as stimulation of glia with various neurotransmitters, neuromodulators, and neurohormones almost invariably triggers cytoplasmic Ca^{2+} responses, which in turn regulate and control glial physiological processes (Verkhratsky et al. 1998, 2012). In pathology the aberrant Ca^{2+} signalling can play a leading role in modifying glia-dependent neuroprotection, glial reactivity as well as glia-derived neurotoxicity (Nedergaard et al. 2010). For example, glial calcium signals and calcium waves contribute to survival of neurones in stroke penumbra (Takano et al. 2009), purinoreceptor-mediated Ca^{2+} signals regulate microglial motility and activation (Kettenmann et al. 2011), whereas $InsP_3$-receptors ($InsP_3Rs$) induced Ca^{2+} release is fundamental for initiation of reactive astrogliosis (Kanemaru et al. 2013)

3 Amyloid Hypothesis of Alzheimer's Disease

The amyloid hypothesis of AD postulates that an abnormal production and accumulation of toxic β-amyloid peptides, which derive from the amyloid precursor protein (APP) through cleavage by β-secretase and γ-secretase, underlies neuronal death and atrophy of the brain with consequent dementia. The amyloid protein associated with AD was initially purified from vascular amyloid deposits (Glenner and Wong 1984b); with the very same amyloid protein being identified in the brains of patients affected by Down's syndrome (Glenner and Wong 1984a). Subsequently, β-amyloid was detected in the senile plaques of AD patients and numerous experiments have demonstrated neurotoxicity of fibrillar β-amyloid (Forloni et al. 1993; Mattson et al. 1992) as well as of its various soluble forms and specific fragments (Brouillette et al. 2012; Mucke and Selkoe 2012; Ono et al. 2009).

The consolidation of the amyloid hypothesis of AD was further assisted by the identification of pathological genes associated with autosome-dominant early onset family AD (which accounts for $<1\%$ of all cases of AD). Indeed, these familiar forms are associated with mutations in genes encoding the amyloid precursor protein (APP), presenilin 1 or 2 (PS1, PS2), which are all components of the enzymatic complex responsible for APP processing directly associated with generation of β-amyloid (Selkoe 2001). The AD hypothesis, however, remains the matter of much dispute, and numerous clinical trials targeting either β-amyloid production or aimed at β-amyloid clearance have signally failed (Castellani et al. 2009; Castellani and Smith 2011; Chakroborty and Stutzmann 2013; Lemere and Masliah 2010). Similarly unclear remains the physiological role for β-amyloid, which may be involved in the regulation of synaptic activity (Kamenetz et al. 2003) and in neuroprotection (Pearson and Peers 2006). Removal of β-amyloid from mixed neuronal cultures either by inhibiting APP cleavage or by immune-depletion induces death of neurones but does not affect neuroglia; addition of $\beta\text{-amyloid}_{1-40}$ into these cultures was neuroprotective in concentrations between 10 pM and 1 nM (Plant et al. 2003).

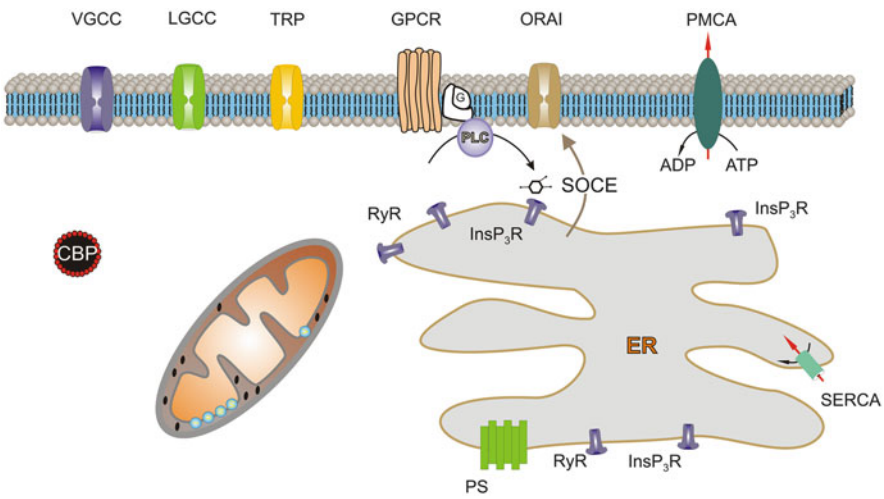

Fig. 1 Molecular cascades which may contribute to deregulated Ca^{2+} homeostasis and Ca^{2+} signalling in the context of AD. Deregulation of Ca^{2+} homeostasis signalling in AD may involve increased Ca^{2+} influx through plasmalemmal voltage- or ligand-gated channels as well as through TRP and ORAI channels. These channels can be modified through interactions with β-amyloid peptide, which, in addition, may form Ca^{2+}-permeable ionophores in the plasmalemma, albeit in high concentrations. Exposure to b-amyloid also increases expression of RyRs and augments Ca^{2+} release mediated by GPCR-$InsP_3$Rs cascade. Mutant presenelins localized in the ER membrane also can increase Ca^{2+} release and thus contribute to excitotoxicity

4 Deregulated Ca^{2+} Signalling in Experimental AD

The abnormalities in Ca^{2+} homeostasis and aberrant neuronal Ca^{2+} signalling are generally believed to be pathologically relevant for the development of AD (Fig. 1), contributing to synaptic dysfunction and loss in synaptic connectivity, increased β-amyloid production, cognitive deficiency, and ultimately resulting in neuronal loss (Bezprozvanny 2013; Bezprozvanny and Mattson 2008; LaFerla 2002; Stutzmann 2007). The very first calcium hypothesis of ageing and AD was proposed by Zaven Khachaturian, who based his ideas on the experiments of Phillip Landfield (Khachaturian 1987; Landfield 1987). This hypothesis proposed that deregulation of Ca^{2+} homeostasis (with a chronic increase in cytosolic Ca^{2+} and the consequent excitotoxic cell death) was the key factor in both normal ageing and AD, the main differences being the speed of Ca^{2+} homeostatic failure – slow in ageing and faster in disease (Toescu et al. 2004; Verkhratsky and Toescu 1998). As it were, the Ca^{2+} deregulation in ageing appeared to be extremely mild and physiological ageing was proven to proceed without substantial loss of neural cells (Pakkenberg et al. 2003; Toescu and Verkhratsky 2007; Verkhratsky et al. 2004). In neurodegenerative AD pathology however, more substantial changes in Ca^{2+} homeostasis have been revealed and their pathological potential considered.

Exposure to β-amyloid has been shown to affect Ca^{2+} homeostasis and Ca^{2+} signalling in neurones. The mechanisms that underlie these events remain a matter of debate. A direct action on the permeability of the plasma membrane to Ca^{2+} has been proposed (Mark et al. 1997). Moreover, β-amyloid peptides (albeit in high concentrations) can act as membrane ionophores permeable to Ca^{2+} ions and thus establish a pathological pathway for Ca^{2+} influx (Arispe et al. 1993; Lashuel et al. 2002). Alternatively, β-amyloid can interact and modify plasmalemmal Ca^{2+} channels and Ca^{2+}-permeable ionotropic receptors (e.g., NMDA or acetylcholine receptors) increasing therefore Ca^{2+} influx and hence cellular Ca^{2+} overload (Demuro et al. 2010). In addition β-amyloid was reported to increase expression of ryanodine receptors (RyR) and increase their open probability thereby increasing Ca^{2+} induced Ca^{2+} release in skeletal muscle (Shtifman et al. 2010). Similarly, exposure to β-amyloid increases $InsP_3$-induced Ca^{2+} release in neurones by directly interacting with the $InsP_3$ receptor or by affecting mGluR5 metabotropic glutamate receptors (Stutzmann and Mattson 2011).

The link between genetic abnormal AD-related background and perturbations in cellular Ca^{2+} homeostasis is provided by presenilins. Neurones isolated from transgenic animals expressing AD-associated mutant PS1 gene show increased susceptibility to Ca^{2+}-mediated excitotoxicity, the latter being initiated by excessive Ca^{2+} release from the endoplasmic reticulum (Guo et al. 1999; Keller et al. 1998). Increase in Ca^{2+} release can reflect direct interactions between mutant PS and $InsP_3R$ resulting in an increased $InsP_3R$ open probability, appearance of channel opening bursts and an increase in the channel sensitivity to $InsP_3$ (Cheung et al. 2008, 2010; Goussakov et al. 2010). These effects can be further exacerbated by increases in Ca^{2+}-induced (i.e., RyR-mediated) Ca^{2+} release. Expression of RyRs was found to be elevated in PC12 expressing the PS1 mutant gene as well as in neurones from PS1 mutant knock-in mice (Chan et al. 2000). An increase in RyR-mediated Ca^{2+} signalling was also observed in cultured neurones (Smith et al. 2005; Zhang et al. 2010), and in slices from 3xTg-AD mice (bearing mutated genes for APP, PS1, and tau) and from TAS/TPM AD mice (expressing mutant APP and PS1 genes). In these last experiments, RyR-mediated Ca^{2+} release was substantially elevated in dendrites, dendritic spines, and somata of both AD strains when compared with non-transgenic controls (Goussakov et al. 2010; Stutzmann et al. 2006). Importantly, aberrant Ca^{2+} release was observed in AD mice of all ages, being already present in very young animals, being therefore potentially an early marker for pathology.

Last, PS1 has been proposed to mediate, at least in part, the Ca^{2+} leak from the ER, the precise nature of which remains somewhat enigmatic (Hammadi et al. 2013; Lang et al. 2011). Indeed, it has been shown that mutations of PS1 affect the Ca^{2+}-leak from the endoplasmic reticulum thereby leading to an overload and an altered Ca^{2+} homeostasis and signalling (Nelson et al. 2007; Tu et al. 2006); this hypothesis remains however a matter of controversy and debate (Shilling et al. 2012).

5 Astroglia in Neurodegeneration and AD

Neurodegenerative diseases are chronic disorders that ultimately result in the death of neurones, atrophy of the brain, and profound functional and cognitive deficits. The progression and symptoms of neurodegenerative disorders are highly polymorphic, and yet their outcome is inevitably fatal and curative strategies are purely symptomatic. While, undoubtedly, the symptoms of neurodegenerative disorders reflect neuronal dysfunction (e.g., synaptic failure and loss of synaptic connectivity) or neuronal death, the underlying cause of the disorder might reside (at least in part) in other brain cells, which possibility has not been pursued avidly in contemporary studies of most neurodegenerative disorders.

The contribution of astroglia to neurodegenerative disorders is multifaceted and complex. In toxic encephalopathies such as brain poisoning with heavy metals (mercury, lead, or aluminium) or with ammonia (hepatic encephalopathy or Reye's syndrome) loss of astroglia-dependent glutamate clearance and K^+ buffering with subsequent excitotoxicity and brain oedema represents a key pathogenic step (Brusilow et al. 2010; Butterworth 2010; De Keyser et al. 2008; Struys-Ponsar et al. 2000; Verkhratsky et al. 2013; Yin et al. 2007). Similarly, profound loss of astroglial glutamate transporters is the triggering factor in Wernicke–Korsakoff encephalopathy (Hazell 2009; Hazell et al. 2009).

Astrocyte degeneration was recently identified as an early and possibly leading factor defining death of motoneurones and hence pathological progression of amyotrophic lateral sclerosis (ALS). Glial atrophy and emergence of apoptotic and degenerative astrocytes preceded neuronal damage and clinical symptoms (Rossi et al. 2008; Rossi and Volterra 2009; Valori et al. 2014). Specific expression of the mutant human superoxide dismutase (hSOD1) gene (associated with familiar form of ALS) in astrocytes led to an increased vulnerability to glutamate, to activation of microglia and neurotoxicity; whereas silencing of this gene specifically in astrocytes delayed ALS progression (Yamanaka et al. 2008). The pathogenesis of ALS is also linked to down-regulation of astroglial glutamate transporters with ensuing excitotoxicity; transgenic deletion of GLT-1/EAAT2 glutamate transporter in mice caused death of motor neurones, thus reproducing a key pathological feature of the disease (Staats and Van Den Bosch 2009). Astrodegeneration and astroglial death were also described for other types of neurodegenerative dementia such as fronto-temporal dementia, Pick's disease, fronto-temporal lobar degeneration, thalamic dementia, and HIV-associated dementia (Broe et al. 2004; Kersaitis et al. 2004; Potts and Leech 2005). In Huntington disease (HD), the expression of pathological huntingtin with a large polyQ repeat in astrocytes increased neurotoxicity and the susceptibility to glutamate-induced seizures, which may reflect a down-regulation of glutamate uptake (Bradford et al. 2010).

In Alzheimer's disease, atrophic changes in astroglia have been reported in several mouse models including 3xTG-AD and PDAPP-J20 mice carrying the Swedish and Indiana APP human mutations (Beauquis et al. 2013;

Kulijewicz-Nawrot et al. 2012; Olabarria et al. 2010, 2011; Yeh et al. 2011). This atrophy, manifested in the decrease in GFAP-, glutamine synthetase-, and/or s100-β-immunoreactive astroglial profiles preceded plaque formation and showed strong region-dependence. Atrophic changes appeared very early (at 1 month of age) in the entorhinal cortex, around 6 months of age in the prefrontal cortex and ~12 months of age in the hippocampus.

Astrodegeneration and astroglial atrophy in neurodegeneration is also complemented by reactive astrogliosis, which usually develops at later stages of the pathology reflecting most likely appearance of disease-specific lesions (such as loss of motoneurones in ALS or β-amyloid depositions in AD). Astrogliosis in neurodegenerative diseases is of a relatively mild variety with no signs of glial scar formation (Rodriguez and Verkhratsky 2011; Verkhratsky et al. 2010). Incidentally, in experimental AD, reactive astrogliosis in response to β-amyloid depositions is region dependent: it is prominent in the hippocampus and absent in the entorhinal and prefrontal cortex (Kulijewicz-Nawrot et al. 2012; Olabarria et al. 2010; Yeh et al. 2011), possibly being associated with the higher vulnerability of the two portions of the brain to AD pathology.

6 β-Amyloid and Astroglial Calcium Signalling

The majority of studies investigating the effects of β-amyloid have been performed in vitro, in cultured primary astrocytes. There is very little homogeneity between the models used, as the source of astrocytes differs with regard to the brain area investigated, to the quality of cultures (mixed neurone/astrocyte or purely astrocytic), and to the extent to which microglia was removed from the cultures. To add to the complexity, there is heterogeneity in the concentrations of β-amyloid, the species of β-amyloid (monomers, oligomers, fibrils), the length of the β-amyloid peptide (1–42, 1–40, or 25–35), the conformity of the preparation of these species, and the duration of exposure to β-amyloid. Moreover, the majority of groups working in this area are focusing on different outcomes. The reasons for the paucity and heterogeneity of studies on the effects of β-amyloid on cultured astrocytes may reflect a bias towards a neurono-centric hypothesis of AD, which makes attempts to study astrocytes somewhat perfunctory. It should be acknowledged that the issues raised above are not unique to investigations of astrocytes; they similarly mirror studies on neurones. Nonetheless, the abundance of reports describing neuronal behaviors in the presence of β-amyloid makes the heterogeneity less apparent when attempting to generate unifying concepts.

6.1 Does β-Amyloid Exposure Induce Calcium Signals in Astrocytes?

Exposure to exogenous oligomeric β-amyloid has been reported to induce a variety of effects in astrocytes, including fast $[Ca^{2+}]_i$ transients (Alberdi et al. 2013; Chow et al. 2010; Jalonen et al. 1997; Stix and Reiser 1998) and Ca^{2+} oscillations (Abramov et al. 2003, 2004). These observations, however, are not uniform because several similarly designed studies failed to observe any acute effects of β-amyloid on astroglial $[Ca^{2+}]_i$ (Casley et al. 2009; Lim et al. 2013; Toivari et al. 2011). The key difference in experimental designs seems to be associated with β-amyloid concentrations. Micromolar concentrations trigger acute Ca^{2+} responses, whereas lower concentrations (<1 μM) yield either no or less reproducible effects. While this is generally true, a recent article suggested that low (200 pM) concentrations of β-amyloid can modulate the α7nAChRs receptor thereby altering the frequency and amplitude of spontaneous or evoked Ca^{2+} waves (Lee et al. 2014). It should be noted that β-amyloid concentrations may vary both in physiological conditions and in AD (which, for example, might reflect the distance to the plaque (Koffie et al. 2009)) and therefore the fact that only high concentrations induce reproducible effects should not be dismissed outright as irrelevant. Other mechanisms of β-amyloid-induced $[Ca^{2+}]_i$ transients may involve various Ca^{2+}-entry pathways (Abramov et al. 2003, 2004; Chow et al. 2010) as well as Ca^{2+}-release from intracellular stores (Alberdi et al. 2013; Chow et al. 2010; Stix and Reiser 1998). There are emerging data indicating that β-amyloid can also modify astroglial responses to neurotransmitters. Exposure of cultured cortical astrocytes to low (200 pM) concentrations of $\beta\text{-amyloid}_{25\text{-}35}$ did not cause acute Ca^{2+} responses, but significantly potentiated serotonin- and glutamate-induced $[Ca^{2+}]_i$ transients (Toivari et al. 2011). This report has not been followed up but it would be of interest to postulate that β-amyloid per se induces Ca^{2+}-responses only at high concentrations but modulates action of other signalling molecules at lower concentrations.

The effect of sub-acute (up to 12 h) β-amyloid exposure has been reported to induce a rise in basal calcium levels in hippocampal (Lim et al. 2013) and cortical (Haughey and Mattson 2003) primary astrocytes. The rise was modest (basal calcium concentrations were doubled) and was confined to cell subpopulations. Furthermore, this sub-acute treatment in cortical astrocytes also increased frequency and amplitude of mechanically induced intercellular Ca^{2+}-waves (Haughey and Mattson 2003). An increase in time-delayed intercellular spontaneous waves between astrocytes in cultured cortical rat astrocytes has also been noted following exposure to 5 μM $\beta\text{-amyloid}_{1\text{–}42}$ (Chow et al. 2010). A modest increase in basal $[Ca^{2+}]_i$ in the presence of β-amyloid could be sufficient to trigger signalling cascades that might have long-term repercussions on astrocyte function (see below). Yet, it should be acknowledged that in other studies (which, however, employed somewhat different conditions) these changes have not been observed (Jalonen et al. 1997) or, surprisingly, a decrease in basal calcium has been detected (Meske et al. 1998). Longer exposures (24–72 h) of astrocytes to 100 nM β-amyloid

have shown an increase in mGluR5 signalling and in store-operated calcium entry (Casley et al. 2009; Lim et al. 2013) in hippocampal and cortical astrocytes.

Several transgenic mouse models of AD that carry various combinations of relevant mutated human genes have been developed in the last decade (Gotz and Ittner 2008; Gotz et al. 2004; Oddo et al. 2003). These model animals mimic, to various degrees, histopathological features and some clinical symptoms of AD, although they do not faithfully reproduce the pathology, especially when it concerns the sporadic form of the disease. Most of the studies performed on these models focus on neuronal function, although several attempts to study astroglia have also been reported.

An obvious strategy to investigate changes in calcium signalling is capitalizing on primary cultures from these mice, with the generic limitations associated with the in vitro settings. In particular, these primary cultures are prepared from newborn animals, when the disease is not yet apparent although the genetic defects are evidently already present. In hippocampal astroglial cultures from 3xTg-AD transgenic animals, a significant increase in ATP- and DHPG-induced $[Ca^{2+}]_i$ transients and an increase in store-operated Ca^{2+} entry when compared to wild-type controls were observed (Grolla et al. 2013b; Ronco et al. 2014). These effects could also be induced in wild-type astrocytes by incubation with β-amyloid for 72 h. Similar treatment with β-amyloid of hippocampal astroglial cultures prepared from 3xTG-AD failed to modify $[Ca^{2+}]_i$ dynamics, suggesting that the two experimental protocols (exogenous β-amyloid application vs. transgenic animals) share the same molecular pathways (Grolla et al. 2013b). Remodelling of the Ca^{2+} signalling toolkit was region specific and was completely absent in astroglial cultures prepared from entorhinal cortex from the same animals (Grolla et al. 2013b). Incidentally, the entorhinal astrocytes failed to mount astrogliotic response to β-amyloid depositions in the 3xTg-AD mice in vivo (Yeh et al. 2011). The $InsP_3$-dependent Ca^{2+} signalling is critical for astrogliosis initiation (Kanemaru et al. 2013), and absence of β-amyloid effects on $InsP_3$-dependent toolkit in astroglial cells from entorhinal cortex may be associated with their astrogliotic deficiency. An increase in basal $[Ca^{2+}]_i$ levels and enhanced thapsigargin-induced Ca^{2+} transients (reflecting depletion of the ER due to an unopposed Ca^{2+} leak) were also found in astrocytes from Trisomy 16 mice, an animal model of Down syndrome that shares certain pathological features with AD (Bambrick et al. 1997). A lack of effect on store-operated Ca^{2+}-entry was reported on cortical astrocyte cultures prepared from Tg5469 animals (which overproduce human APP). In contrast, in cortical astrocytes cultured from mice with genetic deletion of APP the store-operated Ca^{2+}-entry was decreased (Linde et al. 2011). Although the conditions and protocols used in experiments on cultured astrocytes obtained from genetically modified mice are difficult to compare, it seems that some form of Ca^{2+} deregulation in glial cells is evident in most, if not in all, models. This conclusion is supported by experiments on brain slices. For example, in acute brain slices prepared from Tg2576 mice (in which a pathologically mutant form of APP, APPK670/671L is overexpressed), astrocytic Ca^{2+} spikes display a significantly

higher frequency compared to wild-type animals (Pirttimaki et al. 2013; Riera et al. 2011).

Monitoring cellular Ca^{2+} signals in the intact animals is challenging and only sporadic attempts in the context of AD have been made hitherto. Yet, these studies strongly support a deregulation of Ca^{2+} signalling in astroglia in AD-type pathology. For example, basal astrocyte calcium was almost doubled (compared to WT controls) in cells from APP/PS1 mice studied with two-photon microscopy through a chronic cranial window (Kuchibhotla et al. 2009). This increase in resting $[Ca^{2+}]_i$ was paralleled with an appearance of spontaneous Ca^{2+} activity, synchronous hyperactivity, and long-range aberrant Ca^{2+} waves in astroglial syncytia (Kuchibhotla et al. 2009). This aberrant activity was independent of neurones, as it could not be blocked by tetrodotoxin and was evident only at advanced disease stages when plaques were already present. At the earlier stages of pathology, studied in the APP_{Swe} mice (which carries another mutant human APP gene) when they were 2–4 months old, i.e. prior to accumulation of extracellular amyloid deposits a higher frequency of spontaneous Ca^{2+} oscillations was observed when compared to non-transgenic controls (Takano et al. 2007). In the 3xTG-AD mice, this aberrant behavior was evident only in selected sub-populations of astrocytes while no changes were observed in the Dutch/Iowa mice (Takano et al. 2007). Interestingly, the same authors showed that intravenous administration of β-amyloid (0.4 mg/Kg) was associated with an increase in astrocyte Ca^{2+} oscillations in wild-type animals and in Dutch/Iowa mice (Takano et al. 2007).

6.2 *Effects of β-Amyloid on the Astroglial Calcium Toolkit*

When analyzing gene expression in human AD brains using microarray assays, changes in genes associated with the Ca^{2+} signalling toolkit have been among the most consistently reported (Cooper-Knock et al. 2012). These results highlight that a general deregulation of Ca^{2+} homeostasis develops in AD pathology and further supports the Ca^{2+} hypothesis of AD, although these experiments do not discriminate between neuronal and glial changes. Recently, by using laser-capture microdissection, astrocytes from the temporal cortex of patients with different Braak stages were compared. In total 32 genes of the Ca^{2+} signalling pathway (as classified by Kyoto Encyclopaedia of Genes and Genomes, KEGG), including a number of CaMKII isoforms, plasma membrane Ca^{2+}-ATPases, RyRs, and $InsP_3Rs$, were found to be decreased at more advanced stages of the disease (Braak 5-6) compared to earlier stages (Braak 1-2) (Simpson et al. 2011). Obviously, as no control brains were available, it is not possible to ascertain whether earlier stages presented changes in the Ca^{2+} signalling toolkit. Immunohistochemistry is more informative and selective changes have also been observed using this approach in astrocytes from AD brains. For example, the MRC Cognitive Function and Ageing Study Group has recently reported that calpain-10, a Ca^{2+}-dependent protease, is significantly up-regulated in astrocytes but not in neurones from the

temporal cortex of AD brains (Garwood et al. 2013); increase in expression of calpain-10 correlated with the density of neuritic plaques, neurofibrillary tangles, and Braak stage of the disease. Calpain-10 is by no means the only protein of the Ca^{2+} toolkit with altered expression in AD brains, as an increase in mGluR5 (Casley et al. 2009; Grolla et al. 2013a), calcineurin (Norris et al. 2005), calsenelin (Jin et al. 2005), NFκB (Grolla et al. 2013a), and NFAT3 (Abdul et al. 2009). A decrease in EAAT2 (Abdul et al. 2009) has also been reported.

6.3 *Cultured Astrocytes Provide Clues that the Ca^{2+} Signalling Toolkit is Altered Upon Exposure to β-Amyloid*

Chronic (24–72 h) treatment of rat cultured cortical and hippocampal astrocytes with low concentrations (0.1–100 nM) of β-amyloid$_{1–42}$ oligomers induces an up-regulation of nicotinic acetylcholine receptors of α7nAChR, α4nAChR, and β2nAChR types at the transcriptional level (Xiu et al. 2005). The relevance of these data is strengthened by the findings that the α7nAChR subunit is also up-regulated in astrocytes in post-mortem AD human tissue, as revealed by PCR and immunohistochemistry (Hellstrom-Lindahl et al. 1999; Teaktong et al. 2003; Yu et al. 2005). Transcriptional effects of β-amyloid on Ca^{2+}-regulating genes in astrocytes also include mGluR5 and $InsP_3$ receptors (Casley et al. 2009; Grolla et al. 2013a; Lim et al. 2013). This most likely explains the increased Ca^{2+} responses to DHPG, a specific mGluR5 agonist, observed in β-amyloid-treated astrocytes (Grolla et al. 2013a, b). Furthermore, an up-regulation of mGluR5 in plaque-associated astrocytes has been shown in AD model mice expressing mutant PS1 (Shrivastava et al. 2013), as well as in post-mortem AD human brains (Lim et al. 2013). Finally, expression of mRNA for transient receptor potential (TRP) and Orai channels (associated with receptor- and store-operated Ca^{2+} entry) also appears to be modulated by β-amyloid treatment of astrocyte cell cultures (Ronco et al. 2014).

It is universally acknowledged that calcineurin, a Ca^{2+}-dependent phosphatase, is activated by small long-lasting increases in $[Ca^{2+}]_i$ (Dolmetsch et al. 1997; Klee et al. 1998). Overexpression of CaN in plaque-associated astrocytes has been shown in AD model mice (Norris et al. 2005) as well as in AD human brains (Lim et al. 2013). It is therefore not surprising that inhibition of this enzyme, either by pharmacological or molecular means, is able to counteract the up-regulation of $InsP_3R$ and mGluR5 induced by β-amyloid (Lim et al. 2013; Norris et al. 2005). This transcriptional regulation was suggested to proceed via the transcription factor NFAT (Abdul et al. 2009). Targeting of astrocytes in APP/PS1 AD model mice with adeno-associated virus vector which induced expression of the peptide VIVIT that interferes with calcineurin/NFAT signalling pathway improved synaptic plasticity and cognitive function as well as reduced β-amyloid load (Furman et al. 2012). Furthermore, up-regulation of mGluR5 and $InsP_3R$ type 2 expression

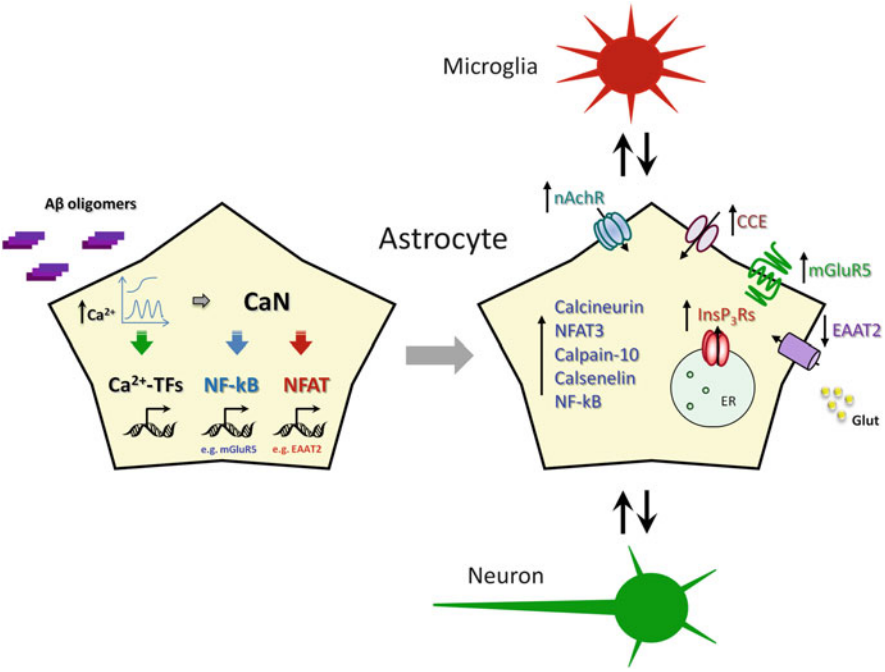

Fig. 2 Ca^{2+}-hypothesis of AD seen from the astrocyte angle. β-amyloid triggers small cytosolic calcium rises or aberrant oscillations in cultured astrocytes and in astrocytes in vivo. These in turn are sufficient to activate Ca^{2+}-dependent enzymes and Ca^{2+}-dependent transcription factors (Ca^{2+}-TF). So far, activation of the CaN-NFAT and CaN-NFκB pathways have been demonstrated, but other pathways may also be involved. Activation of Ca^{2+}-dependent gene expression leads to re-programming of the Ca^{2+}-toolkit. Again, a number of changes have been seen in cell culture, animal models, or in various brain preparations, but others could also occur. Changes may be specific to particular brain areas. Last, it is likely that, at the same time, similar changes (more or less important, we cannot establish at this moment) occur in microglia and in neurones and the interplay between all cell types with deregulated Ca^{2+}-signalling eventually leads to synaptic failure and neuronal cell death

induced by β-amyloid is suppressed by both calcineurin and by NFκB inhibition, suggesting that NFAT may not be the only Ca^{2+}-dependent transcription factor involved (Lim et al. 2013).

7 Future Perspectives

The data currently available suggest that β-amyloid affects calcium signalling in astrocytes by remodelling the Ca^{2+}-signalling toolkit. Furthermore, data from intact animals using the cranial window technique and data from post-mortem tissues corroborate that these two events indeed occur in AD. At present, calcineurin would be an ideal link between the Ca^{2+}-signals and genetic reprogramming (see Fig. 2 for

a hypothetical model), but other signalling pathways are almost certainly involved and should be considered. Importantly, remodelling of Ca^{2+} signalling toolkit by β-amyloid is profoundly different from that induced by pro-inflammatory agents such as LPS, IL-1β or TNF-α (Ronco et al. 2014), indicating thus that β-amyloid induces specific changes in astrocytes in AD.

Many critical questions, however, need to be addressed, which might have repercussions in the field and could impact on possible therapeutic strategies.

First, how does β-amyloid trigger Ca^{2+}-elevations in the different animal models of the disease? The possible mechanisms are only partially described in neurones (Supnet and Bezprozvanny 2010) and therefore it would be important to understand if the same pathways are operative in glia. In neurones, a number of receptors at the postsynaptic membrane have been proposed to interact with Aβ including receptors for glutamate and PrP(C) (see Dinamarca et al. 2012 and Um et al. 2013 for details and references). It would be imaginative to speculate that a receptor also exists in astroglia by which β-amyloid leads to Ca^{2+}-rises.

Second, does β-amyloid-dependent Ca^{2+}-deregulation in astrocytes occur as a consequence of neuronal dysfunction, does it precede neuronal dysfunction and is therefore the mysterious early event or does it develop simultaneously and independently? Given that the concentrations of β-amyloid affecting neurones and glia in vitro are in the same range, it is difficult to imagine that the changes in astrocyte signalling are "late" events in the disease. Furthermore, at least in the 3xTg AD animal model, we have observed Ca^{2+} deregulation in cultures from neonatal pups (Grolla et al. 2013a, b), suggesting, again, that astrocytes are among the first to be affected. While astrogliosis is a general hallmark of late-stage AD, it is likely that the subtle changes on Ca^{2+}-signalling are unrelated to this and that astrocytes undergo different changes at the earlier stages of the disease; as indeed the atrophy observed in the pre-plaque phase of AD pathology in animal models would suggest (Olabarria et al. 2010; Verkhratsky et al. 2010).

Third, and likely the most important question of them all, is whether β-amyloid-induced astrocyte Ca^{2+}-deregulation is at all relevant to initiation and progression of AD. To this end, it is almost certain that the symptomatology of mild cognitive impairment and of developed AD reflects synaptic deficits and neuronal loss and therefore, if a role of astrocytes is to be found, it is in their ability to protect and maintain the neuronal networks, or else mediate neurotoxicity.

Fourth, what is the correlation between changes induced by β-amyloid in neurones, in microglia, and in astrocytes? At present, most of the literature focuses on a single cell type, and this may not give us a full picture of what happens in a brain where, simultaneously, microglia, astrocytes, and neurones respond to environmental challenges in a concerted and mutually interdependent manner.

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References

Abdul HM, Sama MA, Furman JL, Mathis DM, Beckett TL, Weidner AM, Patel ES, Baig I, Murphy MP, LeVine H 3rd, Kraner SD, Norris CM (2009) Cognitive decline in Alzheimer's disease is associated with selective changes in calcineurin/NFAT signaling. J Neurosci 29:12957–12969

Abramov AY, Canevari L, Duchen MR (2003) Changes in intracellular calcium and glutathione in astrocytes as the primary mechanism of amyloid neurotoxicity. J Neurosci 23:5088–5095

Abramov AY, Canevari L, Duchen MR (2004) Calcium signals induced by amyloid β peptide and their consequences in neurons and astrocytes in culture. Biochim Biophys Acta 1742:81–87

Alberdi E, Wyssenbach A, Alberdi M, Sanchez-Gomez MV, Cavaliere F, Rodriguez JJ, Verkhratsky A, Matute C (2013) Ca^{2+}-dependent endoplasmic reticulum stress correlates with astrogliosis in oligomeric amyloid β-treated astrocytes and in a model of Alzheimer's disease. Aging Cell 12:292–302

Alzheimer A (1907) Über eine eigenartige Erkrankung der Hirnrinde. Allg Z Psychiat Psych Gericht Med 64:146–148

Alzheimer A (1910) Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe. In: Nissl F, Alzheimer A (eds) Histologische und histopathologische Arbeiten über die Grosshirnrinde mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, vol 1–3. Gustav Fischer, Jena, pp 401–562

Arispe N, Rojas E, Pollard HB (1993) Alzheimer disease amyloid beta protein forms calcium channels in bilayer membranes: blockade by tromethamine and aluminum. Proc Natl Acad Sci U S A 90:567–571

Bambrick LL, Golovina VA, Blaustein MP, Yarowsky PJ, Krueger BK (1997) Abnormal calcium homeostasis in astrocytes from the trisomy 16 mouse. Glia 19:352–358

Beauquis J, Pavia P, Pomilio C, Vinuesa A, Podlutskaya N, Galvan V, Saravia F (2013) Environmental enrichment prevents astroglial pathological changes in the hippocampus of APP transgenic mice, model of Alzheimer's disease. Exp Neurol 239:28–37

Berridge MJ, Lipp P, Bootman MD (2000) The versatility and universality of calcium signalling. Nat Rev Mol Cell Biol 1:11–21

Bezprozvanny I (2013) Presenilins and calcium signaling-systems biology to the rescue. Sci Signal 6:pe24

Bezprozvanny I, Mattson MP (2008) Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. Trends Neurosci 31:454–463

Braak H, de Vos RA, Jansen EN, Bratzke H, Braak E (1998) Neuropathological hallmarks of Alzheimer's and Parkinson's diseases. Prog Brain Res 117:267–285

Bradford J, Shin JY, Roberts M, Wang CE, Sheng G, Li S, Li XJ (2010) Mutant huntingtin in glial cells exacerbates neurological symptoms of Huntington disease mice. J Biol Chem 285:10653–10661

Broe M, Kril J, Halliday GM (2004) Astrocytic degeneration relates to the severity of disease in frontotemporal dementia. Brain 127:2214–2220

Brouillette J, Caillierez R, Zommer N, Alves-Pires C, Benilova I, Blum D, De Strooper B, Buee L (2012) Neurotoxicity and memory deficits induced by soluble low-molecular-weight amyloid-β1–42 oligomers are revealed in vivo by using a novel animal model. J Neurosci 32:7852–7861

Brusilow SW, Koehler RC, Traystman RJ, Cooper AJ (2010) Astrocyte glutamine synthetase: importance in hyperammonemic syndromes and potential target for therapy. Neurotherapeutics 7:452–470

Burnstock G, Verkhratsky A (2012) Purinergic signalling and the nervous system. Springer, Heidelberg, p 715

Butterworth RF (2010) Altered glial-neuronal crosstalk: cornerstone in the pathogenesis of hepatic encephalopathy. Neurochem Int 57:383–388

Carafoli E (2004) The ambivalent nature of the calcium signal. J Endocrinol Invest 27:134–136

Carafoli E, Santella L, Branca D, Brini M (2001) Generation, control, and processing of cellular calcium signals. Crit Rev Biochem Mol Biol 36:107–260

Case RM, Eisner D, Gurney A, Jones O, Muallem S, Verkhratsky A (2007) Evolution of calcium homeostasis: from birth of the first cell to an omnipresent signalling system. Cell Calcium 42:345–350

Casley CS, Lakics V, Lee HG, Broad LM, Day TA, Cluett T, Smith MA, O'Neill MJ, Kingston AE (2009) Up-regulation of astrocyte metabotropic glutamate receptor 5 by amyloid-β peptide. Brain Res 1260:65–75

Castellani RJ, Smith MA (2011) Compounding artefacts with uncertainty, and an amyloid cascade hypothesis that is 'too big to fail'. J Pathol 224:147–152

Castellani RJ, Lee HG, Siedlak SL, Nunomura A, Hayashi T, Nakamura M, Zhu X, Perry G, Smith MA (2009) Reexamining Alzheimer's disease: evidence for a protective role for amyloid-beta protein precursor and amyloid-beta. J Alzheimers Dis 18:447–452

Chakroborty S, Stutzmann GE (2013) Calcium channelopathies and Alzheimer's disease: Insight into therapeutic success and failures. Eur J Pharmacol. doi:10.1016/j.ejphar.2013.11.012

Chan SL, Mayne M, Holden CP, Geiger JD, Mattson MP (2000) Presenilin-1 mutations increase levels of ryanodine receptors and calcium release in PC12 cells and cortical neurons. J Biol Chem 275:18195–18200

Cheung KH, Shineman D, Muller M, Cardenas C, Mei L, Yang J, Tomita T, Iwatsubo T, Lee VM, Foskett JK (2008) Mechanism of Ca^{2+} disruption in Alzheimer's disease by presenilin regulation of $InsP_3$ receptor channel gating. Neuron 58:871–883

Cheung KH, Mei L, Mak DO, Hayashi I, Iwatsubo T, Kang DE, Foskett JK (2010) Gain-of-function enhancement of IP3 receptor modal gating by familial Alzheimer's disease-linked presenilin mutants in human cells and mouse neurons. Sci Signal 3:ra22

Chow SK, Yu D, Macdonald CL, Buibas M, Silva GA (2010) Amyloid b-peptide directly induces spontaneous calcium transients, delayed intercellular calcium waves and gliosis in rat cortical astrocytes. ASN Neuro 2:e00026

Cooper-Knock J, Kirby J, Ferraiuolo L, Heath PR, Rattray M, Shaw PJ (2012) Gene expression profiling in human neurodegenerative disease. Nat Rev Neurol 8:518–530

De Keyser J, Mostert JP, Koch MW (2008) Dysfunctional astrocytes as key players in the pathogenesis of central nervous system disorders. J Neurol Sci 267:3–16

Demuro A, Parker I, Stutzmann GE (2010) Calcium signaling and amyloid toxicity in Alzheimer disease. J Biol Chem 285:12463–12468

Dinamarca MC, Rios JA, Inestrosa NC (2012) Postsynaptic receptors for amyloid-β oligomers as mediators of neuronal damage in Alzheimer's disease. Front Physiol 3:464

Dolmetsch RE, Lewis RS, Goodnow CC, Healy JI (1997) Differential activation of transcription factors induced by Ca^{2+} response amplitude and duration. Nature 386:855–858

Forloni G, Chiesa R, Smiroldo S, Verga L, Salmona M, Tagliavini F, Angeretti N (1993) Apoptosis mediated neurotoxicity induced by chronic application of beta amyloid fragment 25–35. Neuroreport 4:523–526

Furman JL, Sama DM, Gant JC, Beckett TL, Murphy MP, Bachstetter AD, Van Eldik LJ, Norris CM (2012) Targeting astrocytes ameliorates neurologic changes in a mouse model of Alzheimer's disease. J Neurosci 32:16129–16140

Gargus JJ (2009) Genetic calcium signaling abnormalities in the central nervous system: seizures, migraine, and autism. Ann N Y Acad Sci 1151:133–156

Garwood C, Faizullabhoy A, Wharton SB, Ince PG, Heath PR, Shaw PJ, Baxter L, Gelsthorpe C, Forster G, Matthews FE, Brayne C, Simpson JE, Function MRCC; Ageing Neuropathology Study G (2013) Calcium dysregulation in relation to Alzheimer-type pathology in the ageing brain. Neuropathol Appl Neurobiol 39:788–799

Giaume C, Kirchhoff F, Matute C, Reichenbach A, Verkhratsky A (2007) Glia: the fulcrum of brain diseases. Cell Death Differ 14:1324–1335

Glenner GG, Wong CW (1984a) Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. Biochem Biophys Res Commun 122:1131–1135

Glenner GG, Wong CW (1984b) Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys Res Commun 120:885–890

Gotz J, Ittner LM (2008) Animal models of Alzheimer's disease and frontotemporal dementia. Nat Rev Neurosci 9:532–544

Gotz J, Streffer JR, David D, Schild A, Hoerndli F, Pennanen L, Kurosinski P, Chen F (2004) Transgenic animal models of Alzheimer's disease and related disorders: histopathology, behavior and therapy. Mol Psychiatry 9:664–683

Goussakov I, Miller MB, Stutzmann GE (2010) NMDA-mediated Ca^{2+} influx drives aberrant ryanodine receptor activation in dendrites of young Alzheimer's disease mice. J Neurosci 30:12128–12137

Grolla AA, Fakhfouri G, Balzaretti G, Marcello E, Gardoni F, Canonico PL, DiLuca M, Genazzani AA, Lim D (2013a) Ab leads to Ca^{2+} signaling alterations and transcriptional changes in glial cells. Neurobiol Aging 34:511–522

Grolla AA, Sim JA, Lim D, Rodriguez JJ, Genazzani AA, Verkhratsky A (2013b) Amyloid-β and Alzheimer's disease type pathology differentially affects the calcium signalling toolkit in astrocytes from different brain regions. Cell Death Dis 4:e623

Guo Q, Sebastian L, Sopher BL, Miller MW, Ware CB, Martin GM, Mattson MP (1999) Increased vulnerability of hippocampal neurons from presenilin-1 mutant knock-in mice to amyloid beta-peptide toxicity: central roles of superoxide production and caspase activation. J Neurochem 72:1019–1029

Hammadi M, Oulidi A, Gackiere F, Katsogiannou M, Slomianny C, Roudbaraki M, Dewailly E, Delcourt P, Lepage G, Lotteau S, Ducreux S, Prevarskaya N, Van Coppenolle F (2013) Modulation of ER stress and apoptosis by endoplasmic reticulum calcium leak via translocon during unfolded protein response: involvement of GRP78. FASEB J 27:1600–1609

Haughey NJ, Mattson MP (2003) Alzheimer's amyloid β-peptide enhances ATP/gap junction-mediated calcium-wave propagation in astrocytes. Neuromolecular Med 3:173–180

Hazell AS (2009) Astrocytes are a major target in thiamine deficiency and Wernicke's encephalopathy. Neurochem Int 55:129–135

Hazell AS, Sheedy D, Oanea R, Aghourian M, Sun S, Jung JY, Wang D, Wang C (2009) Loss of astrocytic glutamate transporters in Wernicke encephalopathy. Glia 58:148–156

Hellstrom-Lindahl E, Mousavi M, Zhang X, Ravid R, Nordberg A (1999) Regional distribution of nicotinic receptor subunit mRNAs in human brain: comparison between Alzheimer and normal brain. Brain Res Mol Brain Res 66:94–103

Jalonen TO, Charniga CJ, Wielt DB (1997) β-Amyloid peptide-induced morphological changes coincide with increased K^+ and Cl^- channel activity in rat cortical astrocytes. Brain Res 746:85–97

Jin JK, Choi JK, Wasco W, Buxbaum JD, Kozlowski PB, Carp RI, Kim YS, Choi EK (2005) Expression of calsenilin in neurons and astrocytes in the Alzheimer's disease brain. Neuroreport 16:451–455

Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, Malinow R (2003) APP processing and synaptic function. Neuron 37:925–937

Kanemaru K, Kubota J, Sekiya H, Hirose K, Okubo Y, Iino M (2013) Calcium-dependent N-cadherin up-regulation mediates reactive astrogliosis and neuroprotection after brain injury. Proc Natl Acad Sci U S A 110:11612–11617

Keller JN, Guo Q, Holtsberg FW, Bruce-Keller AJ, Mattson MP (1998) Increased sensitivity to mitochondrial toxin-induced apoptosis in neural cells expressing mutant presenilin-1 is linked to perturbed calcium homeostasis and enhanced oxyradical production. J Neurosci 18:4439–4450

Kersaitis C, Halliday GM, Kril JJ (2004) Regional and cellular pathology in frontotemporal dementia: relationship to stage of disease in cases with and without Pick bodies. Acta Neuropathol 108:515–523

Kettenmann H, Hanisch UK, Noda M, Verkhratsky A (2011) Physiology of microglia. Physiol Rev 91:461–553

Khachaturian ZS (1987) Hypothesis on the regulation of cytosol calcium concentration and the aging brain. Neurobiol Aging 8:345–346

Klee CB, Ren H, Wang X (1998) Regulation of the calmodulin-stimulated protein phosphatase, calcineurin. J Biol Chem 273:13367–13370

Koffie RM, Meyer-Luehmann M, Hashimoto T, Adams KW, Mielke ML, Garcia-Alloza M, Micheva KD, Smith SJ, Kim ML, Lee VM, Hyman BT, Spires-Jones TL (2009) Oligomeric amyloid β associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Proc Natl Acad Sci U S A 106:4012–4017

Krabbe G, Halle A, Matyash V, Rinnenthal JL, Eom GD, Bernhardt U, Miller KR, Prokop S, Kettenmann H, Heppner FL (2013) Functional impairment of microglia coincides with β-amyloid deposition in mice with Alzheimer-like pathology. PLoS One 8:e60921

Kuchibhotla KV, Lattarulo CR, Hyman BT, Bacskai BJ (2009) Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. Science 323:1211–1215

Kulijewicz-Nawrot M, Verkhratsky A, Chvatal A, Sykova E, Rodriguez JJ (2012) Astrocytic cytoskeletal atrophy in the medial prefrontal cortex of a triple transgenic mouse model of Alzheimer's disease. J Anat 221:252–262

Kullmann DM (2010) Neurological channelopathies. Annu Rev Neurosci 33:151–172

LaFerla FM (2002) Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease. Nat Rev Neurosci 3:862–872

Landfield PW (1987) 'Increased calcium-current' hypothesis of brain aging. Neurobiol Aging 8:346–347

Lang S, Erdmann F, Jung M, Wagner R, Cavalie A, Zimmermann R (2011) Sec61 complexes form ubiquitous ER Ca^{2+} leak channels. Channels (Austin) 5:228–235

Lashuel HA, Hartley D, Petre BM, Walz T, Lansbury PT Jr (2002) Neurodegenerative disease: amyloid pores from pathogenic mutations. Nature 418:291

Lee L, Kosuri P, Arancio O (2014) Picomolar amyloid-β peptides enhance spontaneous astrocyte calcium transients. J Alzheimers Dis 38:49–62

Lemere CA, Masliah E (2010) Can Alzheimer disease be prevented by amyloid-β immunotherapy? Nat Rev Neurol 6:108–119

Lim D, Iyer A, Ronco V, Grolla AA, Canonico PL, Aronica E, Genazzani AA (2013) Amyloid beta deregulates astroglial mGluR5-mediated calcium signaling via calcineurin and Nf-κB. Glia 61:1134–1145

Linde CI, Baryshnikov SG, Mazzocco-Spezzia A, Golovina VA (2011) Dysregulation of Ca^{2+} signaling in astrocytes from mice lacking amyloid precursor protein. Am J Physiol Cell Physiol 300:C1502–C1512

Mark RJ, Lovell MA, Markesbery WR, Uchida K, Mattson MP (1997) A role for 4-hydroxynonenal, an aldehydic product of lipid peroxidation, in disruption of ion homeostasis and neuronal death induced by amyloid β-peptide. J Neurochem 68:255–264

Mattson MP, Cheng B, Davis D, Bryant K, Lieberburg I, Rydel RE (1992) β-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. J Neurosci 12:376–389

Meske V, Hamker U, Albert F, Ohm TG (1998) The effects of β/A4-amyloid and its fragments on calcium homeostasis, glial fibrillary acidic protein and S100b staining, morphology and survival of cultured hippocampal astrocytes. Neuroscience 85:1151–1160

Mucke L, Selkoe DJ (2012) Neurotoxicity of amyloid β-protein: synaptic and network dysfunction. Cold Spring Harb Perspect Med 2:a006338

Nedergaard M, Rodriguez JJ, Verkhratsky A (2010) Glial calcium and diseases of the nervous system. Cell Calcium 47:140–149

Nelson O, Tu H, Lei T, Bentahir M, de Strooper B, Bezprozvanny I (2007) Familial Alzheimer disease-linked mutations specifically disrupt Ca^{2+} leak function of presenilin 1. J Clin Invest 117:1230–1239

Norris CM, Kadish I, Blalock EM, Chen KC, Thibault V, Porter NM, Landfield PW, Kraner SD (2005) Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. J Neurosci 25:4649–4658

Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction. Neuron 39:409–421

Olabarria M, Noristani HN, Verkhratsky A, Rodriguez JJ (2010) Concomitant astroglial atrophy and astrogliosis in a triple transgenic animal model of Alzheimer's disease. Glia 58:831–838

Olabarria M, Noristani HN, Verkhratsky A, Rodriguez JJ (2011) Age-dependent decrease in glutamine synthetase expression in the hippocampal astroglia of the triple transgenic Alzheimer's disease mouse model: mechanism for deficient glutamatergic transmission? Mol Neurodegener 6:55

Ono K, Condron MM, Teplow DB (2009) Structure-neurotoxicity relationships of amyloid β-protein oligomers. Proc Natl Acad Sci U S A 106:14745–14750

Orrenius S, Zhivotovsky B, Nicotera P (2003) Regulation of cell death: the calcium-apoptosis link. Nat Rev Mol Cell Biol 4:552–565

Pakkenberg B, Pelvig D, Marner L, Bundgaard MJ, Gundersen HJ, Nyengaard JR, Regeur L (2003) Aging and the human neocortex. Exp Gerontol 38:95–99

Pearson HA, Peers C (2006) Physiological roles for amyloid beta peptides. J Physiol 575:5–10

Pekny M, Wilhelmsson U, Pekna M (2014) The dual role of astrocyte activation and reactive gliosis. Neurosci Lett 565C:30–38

Petersen OH, Petersen CC, Kasai H (1994) Calcium and hormone action. Annu Rev Physiol 56:297–319

Pirttimaki TM, Codadu NK, Awni A, Pratik P, Nagel DA, Hill EJ, Dineley KT, Parri HR (2013) α7 Nicotinic receptor-mediated astrocytic gliotransmitter release: Ab effects in a preclinical Alzheimer's mouse model. PLoS One 8:e81828

Plant LD, Boyle JP, Smith IF, Peers C, Pearson HA (2003) The production of amyloid β peptide is a critical requirement for the viability of central neurons. J Neurosci 23:5531–5535

Plattner H, Verkhratsky A (2013) Ca^{2+} signalling early in evolution–all but primitive. J Cell Sci 126:2141–2150

Popugaeva E, Bezprozvanny I (2014) Can the calcium hypothesis explain synaptic loss in Alzheimer's disease? Neurodegener Dis 13:139–141

Potts R, Leech RW (2005) Thalamic dementia: an example of primary astroglial dystrophy of Seitelberger. Clin Neuropathol 24:271–275

Riera J, Hatanaka R, Uchida T, Ozaki T, Kawashima R (2011) Quantifying the uncertainty of spontaneous Ca^{2+} oscillations in astrocytes: particulars of Alzheimer's disease. Biophys J 101:554–564

Rodriguez JJ, Verkhratsky A (2011) Neuroglial roots of neurodegenerative diseases? Mol Neurobiol 43:87–96

Rodriguez JJ, Noristani HN, Verkhratsky A (2013) Microglial response to Alzheimer's disease is differentially modulated by voluntary wheel running and enriched environments. Brain Struct Funct. doi:10.1007/s00429-013-0693-5

Ronco V, Grolla AA, Glasnov TN, Canonico PL, Verkhratsky A, Genazzani AA, Lim D (2014) Differential deregulation of astrocytic calcium signalling by amyloid-β, TNFα, IL-1β and LPS. Cell Calcium 55:219–229

Rossi D, Volterra A (2009) Astrocytic dysfunction: insights on the role in neurodegeneration. Brain Res Bull 80:224–232

Rossi D, Brambilla L, Valori CF, Roncoroni C, Crugnola A, Yokota T, Bredesen DE, Volterra A (2008) Focal degeneration of astrocytes in amyotrophic lateral sclerosis. Cell Death Differ 15:1691–1700

Selkoe DJ (2001) Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 81:741–766

Shilling D, Mak DO, Kang DE, Foskett JK (2012) Lack of evidence for presenilins as endoplasmic reticulum Ca^{2+} leak channels. J Biol Chem 287:10933–10944

Shrivastava AN, Kowalewski JM, Renner M, Bousset L, Koulakoff A, Melki R, Giaume C, Triller A (2013) β-amyloid and ATP-induced diffusional trapping of astrocyte and neuronal metabotropic glutamate type-5 receptors. Glia 61:1673–1686

Shtifman A, Ward CW, Laver DR, Bannister ML, Lopez JR, Kitazawa M, LaFerla FM, Ikemoto N, Querfurth HW (2010) Amyloid-beta protein impairs Ca^{2+} release and contractility in skeletal muscle. Neurobiol Aging 31:2080–2090

Simpson JE, Ince PG, Shaw PJ, Heath PR, Raman R, Garwood CJ, Gelsthorpe C, Baxter L, Forster G, Matthews FE, Brayne C, Wharton SB, Function MRCC; Ageing Neuropathology Study G (2011) Microarray analysis of the astrocyte transcriptome in the aging brain: relationship to Alzheimer's pathology and APOE genotype. Neurobiol Aging 32:1795–1807

Smith IF, Hitt B, Green KN, Oddo S, LaFerla FM (2005) Enhanced caffeine-induced Ca^{2+} release in the 3xTg-AD mouse model of Alzheimer's disease. J Neurochem 94:1711–1718

Sofroniew MV (2014) Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. Neuroscientist 20:160–172

Staats KA, Van Den Bosch L (2009) Astrocytes in amyotrophic lateral sclerosis: direct effects on motor neuron survival. J Biol Phys 35:337–346

Stix B, Reiser G (1998) b-Amyloid peptide 25–35 regulates basal and hormone-stimulated Ca^{2+} levels in cultured rat astrocytes. Neurosci Lett 243:121–124

Struys-Ponsar C, Guillard O, van den Bosch de Aguilar P (2000) Effects of aluminum exposure on glutamate metabolism: a possible explanation for its toxicity. Exp Neurol 163:157–164

Stutzmann GE (2007) The pathogenesis of Alzheimers disease is it a lifelong "calciumopathy"? Neuroscientist 13:546–559

Stutzmann GE, Mattson MP (2011) Endoplasmic reticulum Ca^{2+} handling in excitable cells in health and disease. Pharmacol Rev 63:700–727

Stutzmann GE, Smith I, Caccamo A, Oddo S, Laferla FM, Parker I (2006) Enhanced ryanodine receptor recruitment contributes to Ca^{2+} disruptions in young, adult, and aged Alzheimer's disease mice. J Neurosci 26:5180–5189

Supnet C, Bezprozvanny I (2010) The dysregulation of intracellular calcium in Alzheimer disease. Cell Calcium 47:183–189

Takano T, Han X, Deane R, Zlokovic B, Nedergaard M (2007) Two-photon imaging of astrocytic Ca^{2+} signaling and the microvasculature in experimental mice models of Alzheimer's disease. Ann N Y Acad Sci 1097:40–50

Takano T, Oberheim N, Cotrina ML, Nedergaard M (2009) Astrocytes and ischemic injury. Stroke 40:S8–S12

Teaktong T, Graham A, Court J, Perry R, Jaros E, Johnson M, Hall R, Perry E (2003) Alzheimer's disease is associated with a selective increase in α7 nicotinic acetylcholine receptor immunoreactivity in astrocytes. Glia 41:207–211

Toescu EC, Verkhratsky A (2007) The importance of being subtle: small changes in calcium homeostasis control cognitive decline in normal aging. Aging Cell 6:267–273

Toescu EC, Verkhratsky A, Landfield PW (2004) Ca^{2+} regulation and gene expression in normal brain aging. Trends Neurosci 27:614–620

Toivari E, Manninen T, Nahata AK, Jalonen TO, Linne ML (2011) Effects of transmitters and amyloid-β peptide on calcium signals in rat cortical astrocytes: Fura-2AM measurements and stochastic model simulations. PLoS One 6:e17914

Tu H, Nelson O, Bezprozvanny A, Wang Z, Lee SF, Hao YH, Serneels L, De Strooper B, Yu G, Bezprozvanny I (2006) Presenilins form ER Ca^{2+} leak channels, a function disrupted by familial Alzheimer's disease-linked mutations. Cell 126:981–993

Um JW, Kaufman AC, Kostylev M, Heiss JK, Stagi M, Takahashi H, Kerrisk ME, Vortmeyer A, Wisniewski T, Koleske AJ, Gunther EC, Nygaard HB, Strittmatter SM (2013) Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer aβ oligomer bound to cellular prion protein. Neuron 79:887–902

Valori CF, Brambilla L, Martorana F, Rossi D (2014) The multifaceted role of glial cells in amyotrophic lateral sclerosis. Cell Mol Life Sci 71:287–297

Verkhratsky A, Toescu EC (1998) Calcium and neuronal ageing. Trends Neurosci 21:2–7
Verkhratsky A, Orkand RK, Kettenmann H (1998) Glial calcium: homeostasis and signaling function. Physiol Rev 78:99–141
Verkhratsky A, Mattson MP, Toescu EC (2004) Aging in the mind. Trends Neurosci 27:577–578
Verkhratsky A, Olabarria M, Noristani HN, Yeh CY, Rodriguez JJ (2010) Astrocytes in Alzheimer's disease. Neurotherapeutics 7:399–412
Verkhratsky A, Rodriguez JJ, Parpura V (2012) Calcium signalling in astroglia. Mol Cell Endocrinol 353:45–56
Verkhratsky A, Rodriguez JJ, Parpura V (2013) Astroglia in neurological diseases. Future Neurol 8:149–158
Xiu J, Nordberg A, Zhang JT, Guan ZZ (2005) Expression of nicotinic receptors on primary cultures of rat astrocytes and up-regulation of the α7, α4 and β2 subunits in response to nanomolar concentrations of the b-amyloid peptide$_{1-42}$. Neurochem Int 47:281–290
Yamanaka K, Chun SJ, Boillee S, Fujimori-Tonou N, Yamashita H, Gutmann DH, Takahashi R, Misawa H, Cleveland DW (2008) Astrocytes as determinants of disease progression in inherited amyotrophic lateral sclerosis. Nat Neurosci 11:251–253
Yeh CY, Vadhwana B, Verkhratsky A, Rodriguez JJ (2011) Early astrocytic atrophy in the entorhinal cortex of a triple transgenic animal model of Alzheimer's disease. ASN Neuro 3:271–279
Yin Z, Milatovic D, Aschner JL, Syversen T, Rocha JB, Souza DO, Sidoryk M, Albrecht J, Aschner M (2007) Methylmercury induces oxidative injury, alterations in permeability and glutamine transport in cultured astrocytes. Brain Res 1131:1–10
Yu WF, Guan ZZ, Bogdanovic N, Nordberg A (2005) High selective expression of a7 nicotinic receptors on astrocytes in the brains of patients with sporadic Alzheimer's disease and patients carrying Swedish APP 670/671 mutation: a possible association with neuritic plaques. Exp Neurol 192:215–225
Zhang H, Sun S, Herreman A, De Strooper B, Bezprozvanny I (2010) Role of presenilins in neuronal calcium homeostasis. J Neurosci 30:8566–8580
Zhivotovsky B, Orrenius S (2011) Calcium and cell death mechanisms: a perspective from the cell death community. Cell Calcium 50:211–221

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