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Review

When, where and how? Focus on neuronal calcium dysfunctions in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD), since its characterization as a precise form of dementia with its own pathological hallmarks, has captured scientists' attention because of its complexity. The last 30 years have been filled with discoveries regarding the elusive aetiology of this disease and, thanks to advances in molecular biology and live imaging techniques, we now know that an important role is played by calcium (Ca^{2+}). Ca^{2+}, as ubiquitous second messenger, regulates a vast variety of cellular processes, from neuronal excitation and communication, to muscle fibre contraction and hormone secretion, with its action spanning a temporal scale that goes from microseconds to hours. It is therefore very challenging to conceive a single hypothesis that can integrate the numerous findings on this issue with those coming from the classical fields of AD research such as amyloid-beta (Aβ) and tau pathology. In this contribution, we will focus our attention on the Ca^{2+} hypothesis of AD, dissecting it, as much as possible, in its subcellular localization, where the Ca^{2+} signal meets its specificity. We will also follow the temporal evolution of the Ca^{2+} hypothesis, providing some of the most updated discoveries. Whenever possible, we will link the findings regarding Ca^{2+} dysfunction to the other players involved in AD pathogenesis, hoping to provide a crossover body of evidence, useful to amplify the knowledge that will lead towards the discovery of an effective therapy.

Contents

1. Introduction

When the Ca^{2+} hypothesis of AD arose during the late '80s and early '90s, it was somehow disconnected from the amyloid cascade hypothesis that was already moving its first steps [1,2]. When, later in the decade, studies linking Aβ accumulation and

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deposition to Ca^{2+} dysregulation begun to appear the amyloid and the Ca^{2+} hypotheses became linked [3]. It was soon clear that not only amyloid plaques but also soluble Aβ aggregates, and specifically Aβ oligomers (Aβo), were exerting significant toxicity, either endogenously produced or exogenously administered to cells and primary neurons in culture [4–6] (Fig. 1). The Ca^{2+} hypothesis of AD, by positing intracellular Ca^{2+} dysregulation as the direct consequence of Aβ toxicity, offered one of the richest grounds for researchers in the field. It obscured the fact, however, that Ca^{2+} dysregulation at the onset of AD can occur independently of Aβ accumulation and toxicity [7]. AD is now considered as a multiple hits disease where amyloid and tau dysfunctions are aggravated by oxidative stress, intracellular Ca^{2+} imbalance and metabolic disturbance. A large body of evidence strongly points towards Ca^{2+} as a possible unifying element underlying AD pathophysiology. According to the amyloid cascade hypothesis, Aβ toxicity precedes tau pathology but exactly how Aβ and tau cooperate in synaptic dysfunction is still a controversial issue [8]. Studies with AD patients as well as with amyloid precursor protein (APP) and/or tau mouse models have shown that tau defects affect the lateral entorhinal cortex at an early stage but require Aβ to reach other cortical sites [9].

In this contribution, we will mainly focus on the relationship between cellular Ca^{2+} handling and AD, paying special attention to the crosstalk with Aβ. Given the large amount of data collected, the often contrasting hypotheses and the vast array of cellular players more directly involved in Ca^{2+} homeostasis, the review will be divided in thematic paragraphs, based on the "anatomy" of the Ca^{2+} signal (Fig. 2).

2. Plasma membrane channels

It was initially suggested that Aβ peptides are capable of forming plasma membrane channels [10]; indeed, remarkable increases in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) were reported upon challenging cultured cells with either Aβ40 or Aβ42 [11] [12,13]. The "ion channel hypothesis" for Aβ toxicity, as proposed by Arispe's group, was mainly supported by *in vitro* studies demonstrating the formation of cation selective channels, whose permeation is inhibited by metals such as Zn^{2+} and Cu^{2+} and by particular peptides designed to line the pore-forming region [14,15]. The ion channel hypothesis got further support from Demuro's studies showing that, in oocytes, Aβ injection causes cytosolic Ca^{2+} rises due to Ca^{2+} entry across Aβ channels formed in the plasma membrane as well as Ca^{2+} release via stimulation of the Gq/PLC pathway [16]. This hypothesis contrasts with *in vivo* data showing that exogenously applied Aβ enhance the overall plasma membrane permeability to anions and cations rather than forming a Ca^{2+}-selective pathway [17]. Since the first observations describing the increase in the $[Ca^{2+}]_{cyt}$ of cells directly harvested from AD patients [18], many groups had focused their attention on this phenomenon changing the paradigm from the channel-forming to the channel-modulating hypothesis. This intense effort led to a plethora of hypothetical candidates capable of mediating cellular Ca^{2+} overload by Aβ since neuronal cells have a vast array of Ca^{2+}-permeable plasma membrane channels at their disposal. As suggested players implicated in the pathogenesis of AD, and possibly mediating Aβ toxicity, we will here consider the voltage-operated Ca^{2+} channels (VOCCs), the nicotinic acetylcholine receptors (nAChRs), the ionotropic glutamate receptors [*N*-Methyl-D-aspartate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs)], the Ca^{2+} homeostasis modulator 1 (CALHM1), as well as the store-operated Ca^{2+} channels (SOCCs). For a thorough investigation on this issue, also including the plethora of Aβ binding

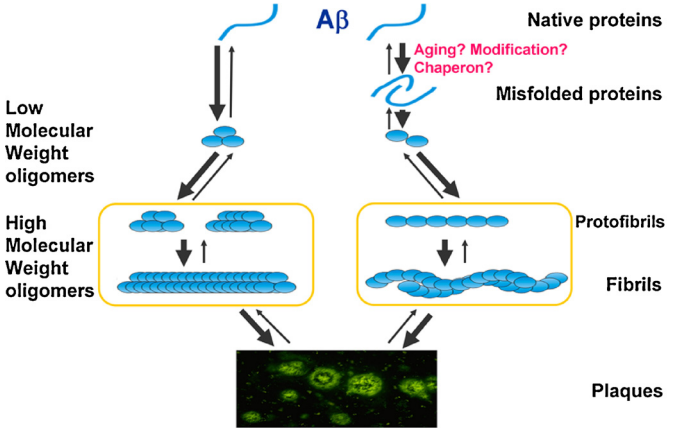

Fig. 1. Aβ aggregation pathways. Aβ42 can aggregate following different pathways that lead to different, albeit coexisting, products. The left side shows a trimer-based aggregation process resulting in soluble aggregates of Low and High Molecular Weight (Aβo) that are responsible for a vast array of cellular effects . The right side shows the pathway leading to the formation of insoluble fibrils. Both pathway eventually can lead to plaques. Modified from [135].

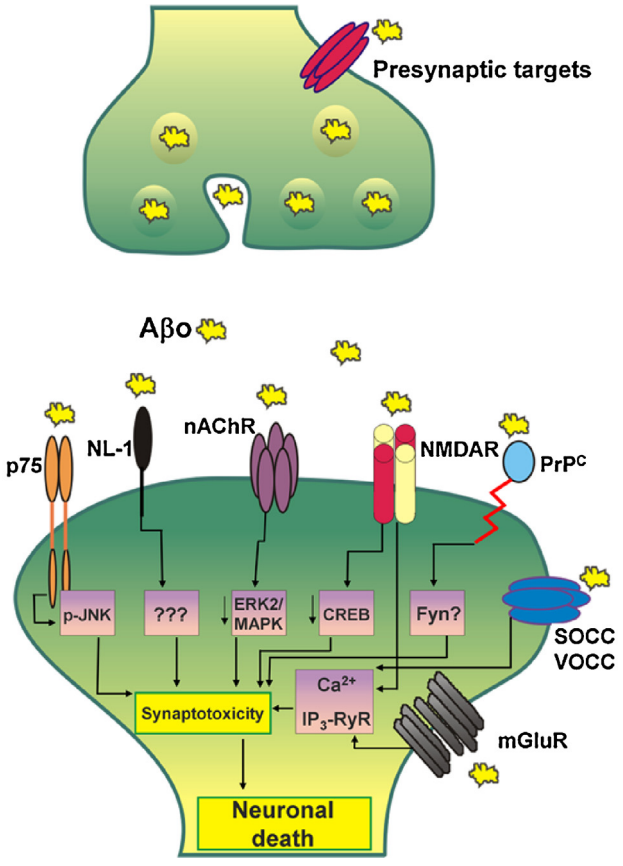

Fig. 2. Synaptic Aβo targets. Aβo impair the functionality of several targets localized at the synaptic level. We have here reviewed some of the major pathways involving Ca^{2+} dynamics, among which: metabotropic glutamate receptor (mGluR), store-operated Ca^{2+} channel (SOCC), cellular prion protein (PrP^C), *N*-methyl-D-aspartate ionotropic glutamate receptor (NMDAR), nicotinic acetylcholine receptor (α7-nAChR), voltage-operated Ca^{2+} channel (VOCC). Other targets less directly involved on Ca^{2+} homeostasis such as the neuroligin-1 (NL-1) adhesion molecule and the low affinity Nerve Growth Factor receptor (p75), have not been included but see Refs. [136]. Only receptors located at the postsynaptic site are here highlighted; however, also targets at the presynaptic site should be considered to fully explain Aβo toxicity. Modified from [136].