Cytotoxicity of intracellular Aβ42 amyloid oligomers involves Ca^{2+} release from the ER by stimulated production of inositol trisphosphate

Angelo Demuro [1] and Ian Parker [1, 2]

Key words: Alzheimer's disease – calciumopathy

Oligomeric forms of Aβ peptides associated with Alzheimer`s disease (AD) disrupt cellular Ca^{2+} regulation by liberating Ca^{2+} into the cytosol from both extracellular and intracellular sources. We elucidated the actions of intracellular Aβ42 by imaging Ca^{2+} responses to injections of Aβ oligomers into *Xenopus* oocytes. Two types of signal were observed: (i) local, 'channel-like' transients dependent on extracellular Ca^{2+} influx, which resembled signals from amlyoid pores formed by extracellular application of oligomers; (ii) local transients and global Ca^{2+} waves, resembling Ca^{2+} puffs and waves mediated by inositol trisphosphate (IP_3). The latter responses were suppressed by antagonists of the IP_3 receptor (caffeine and heparin), by pretreatment with the Gi/o-protein inhibitor pertussis toxin, and by pre-treatment with lithium to deplete membrane inositol lipids. We show that G-protein-mediated stimulation of IP_3 production and consequent liberation of Ca^{2+} from the endoplasmic reticulum by intracellular Aβ oligomers is cytotoxic, potentially representing a novel pathological mechanism in AD which may be further exacerbated by AD-linked mutations in presenilins to promote opening of IP_3 receptor/channels.