Amyloid-β peptide fibrils induce nitro-oxidative stress in neuronal cells.

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Abstract

Different mechanisms including oxidative stress are proposed for amyloid-β peptide (Aβ) neurotoxicity, and here we contribute to demonstrate that nitro-oxidative stress is playing a key role. Yeasts are a well-known model for H2O2 toxicity. Interestingly, yeast cell wall prevents interaction of Aβ fibrils with membrane receptors or calcium channels and we found a significant viability reduction in yeasts when challenged with Aβ fibrils. Furthermore, iron and copper chelators, as well as the antioxidants glutathione and trolox, were neuroprotective on neuroblastoma cells and mouse hippocampal neurons challenged with Aβ fibrils. Glutathione prevents the oxidation, glycation and nitrotyrosination of cell proteins induced by Aβ. Trolox protected neurons in cell viability studies, maintaining the vesicular transport integrity and preventing the trigger of apoptotic mechanisms. Interestingly, we have also found that brain derived neuronal factor (BDNF) and neurotrophin-3 (NT-3) were able to protect mouse hippocampal and cortical neurons against H2O2 and Aβ fibrils. Considering that superoxide anion, produced by Aβ cell damage, and nitric oxide, whose production is altered in AD, react to form the highly reactive peroxynitrite anion, we studied the role of trolox to ameliorate the peroxynitrite cell damage. Finally, one of the major proteins to be nitrotyrosinated in AD, the triose phosphate isomerase (TPI) was assayed searching for a denitrase activity that could reverse intracellular nitrotyrosination. We have found that human neuroblastoma SH-SY5Y cells express a constitutive denitrase activity that partially denitrated nitro-TPI. Altogether, our results support a key role of nitro-oxidative stress in the neuronal damage induced by Aβ fibrils.