Alzheimer’s Abeta1-42 Peptide Induces an Up-Regulation of NCX3 Activity That Contributes to Ca²⁺ Refilling into Endoplasmic Reticulum in Hippocampal Neurons

A. Pannaccione¹, C. D’Avanzo¹, A. Secondo¹, A. Esposito¹, P. Lippiello¹, R. Sirabella¹,², P. Molinaro¹, F. Boscia¹, G. Di Renzo¹, L. Annunziato¹,²

¹Division of Pharmacology Department of Neuroscience University of Naples “Federico II”, Italy, ²SDN, Naples, Italy

The 3 gene products of the Na⁺/Ca²⁺ exchanger (NCX) may play a pivotal role in several pathophysiological conditions in which Na⁺ and Ca²⁺ homeostasis is disrupted. In addition, Abeta₁₋₄₂ fragment, the peptide involved in Alzheimer Disease pathogenesis, causes an early increase in intracellular Ca²⁺ concentration. In the present study, 24 hours exposure of hippocampal neurons and NGF-differentiated PC-12 cells to Abeta₁₋₄₂ fragment induced dose-dependent up-regulation of NCX currents (I_NCX) in the reverse mode of operation monitored by patch- and current-clamp. Furthermore, this treatment caused the NCX-dependent intracellular Ca²⁺ refilling into Endoplasmic Reticulum (ER) measured by Fura-2AM single-cell video imaging. In neurons silenced with siRNA against NCX3 or obtained from ncx3⁻/⁻ mice, the increase in I_NCX or in ER Ca²⁺ refilling was prevented. In neurons silenced with siRNA against NCX3, Abeta₁₋₄₂ induced the activation caspase-12, a specific marker of ER stress. These results suggest that I_NCX up-regulation mainly mediated by NCX3 may play a crucial role in Ca²⁺ refilling into ER, thus helping neurons to prevent endoplasmic reticulum stress during Abeta₁₋₄₂ exposure.