THE BH4 DOMAIN OF BCL-XL COUNTERACTS BETA AMYLOID PEPTIDE TOXICITY ON CAPILLARY ENDOTHELIUM

RAFFAELLA SOLITO, SANDRA DONNINI, SILVIA CANTARA, ANTONIO GIACHETTI, AND MARINA ZICHE

Section of Pharmacology, Department of Molecular Biology, University of Siena

Oxidative stress is one of the factor contributing to blood brain barrier degeneration. This phenomenon is observed during pathological conditions such as Alzheimer's disease or cerebral amyloid angiopathy in which brain hemorrhages are very frequent. Both diseases are characterized by beta amyloid peptide deposition either in neurons or in vessels. Oxidative stress leads to impairment of mitochondrial functions and apoptotic cell death subsequent to caspases activation. In this study oxidative stress conditions, as evidenced by the oxidation of intracellular H2DCFDA, were produced on cultured capillary endothelium by administration of Aβ peptides in the micromolar range. This treatment reduced endothelial cell survival by increasing caspase 3 activation. BH4 domain of Bcl-xl administrated to endothelial cells as the conjugated form with TAT peptide, reverts Aβ-induced apoptotic cell death by activating a survival program which is Akt/endothelial nitric oxide synthase dependent. Taken together these results suggest the possibility to characterize TAT-BH4 as a new pharmacological agent capable to restore endothelial viability and consequently BBB function thus contributing to the treatment of Alzheimer's disease.

This work was supported by Telethon Foundation (Project #GGP06148) and Monte dei Paschi Siena Foundation (MPS).