pPKC ε mediated metalloproteinase 2 and 9 levels upon ibuprofen and lipoic acid coniugate (codrug 1) treatment in an Alzheimer disease rat brain model

Susi Zara¹, Monica Rapino², Marianna De Colli³, Laura Serafina Cerasa¹, Amelia Cataldi³

¹ Dipartimento di Scienze del Farmaco, Università “G. d’Annunzio” Chieti-Pescara, Italia
² Istituto di Genetica Molecolare, CNR, Unità di Chieti, Italia
³ Dipartimento di Medicina e Scienze dell’Invecchiamento, Università “G. d’Annunzio” Chieti-Pescara, Italia

Alzheimer’s Disease (AD) begins with loss of recent memory and is associated to pathological and histological hallmarks such as β amyloid plaques, neural tangles (NFT), cholinergetic deficit, extensive neuronal loss and synaptic changes in the cerebral cortex and hippocampus. The amyloid cascade hypothesis implies the activity of β, γ secretases which mediate the cleavage of Amyloid Precursor Protein (APP), the formation of amyloidogenic Aβ fragment (1-42), which compacts into amyloid plaques, while the cleavage by ? secretase of APP, within the Aβ segment forms sAPP and prevents the formation of Aβ (Zetterberg et al. 2010 Exp Gerontol 45, 23-29). Among the proteases which have Aβ-degrading activity, Metalloproteinase (MMP) 2, disclosing β secretase-like activity, is included, while MMP9 seems to contribute to neuronal death (Yan et al. 2006 J Biol Chem 281, 24566-74). In addition, intracellular signalling protein Protein Kinase C (PKC) can control ? secretase, preventing the formation of β amyloid, and prolonging the life span of AD (de Barry et al. 2010 Exp Gerontol 45, 64-69). A lipophilic molecular combination (codrug 1), obtained by joining an antioxidant molecule, lipoic acid, with an anti-inflammatory compound, ibuprofen (IBU) has been synthetized in our lab and administered in a chronic treatment during intracerebroventricular infusion of Aβ (1-40) peptide in rat brains as a model of AD (Sozio et al. 2010 Arch Pharm 343,133-42).

Here we show the effects exerted by codrug 1 on PKC ε-mediated MMP2 and MMP9 levels regulation in Aβ (1-40) infused rat cerebral cortex. Interestingly codrug 1, lowering Metalloproteinases expression via PKC ε down-modulation, seems to control Alzheimer’s disease induced cerebral amyloid deposits, neuronal death and, lastly, behavioural deterioration. Moreover the cognitive test evidences that codrug 1 treatment decreases the number of reference memory errors and the time spent to perform the test suggesting this compound as an useful therapeutical tool against AD.

Keywords: Alzheimer’s disease, metalloproteinases, PKCs, ibuprofen, lipoic acid, codrug 1