

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

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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), cholinergic 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 A β fragment (1-42), which compacts into amyloid plaques, while the cleavage by γ secretase of APP, within the A β segment forms sAPP and prevents the formation of A β (Zetterberg et al. 2010 *Exp Gerontol* 45, 23-29). Among the proteases which have A β -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 γ 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 synthesized in our lab and administered in a chronic treatment during intracerebroventricular infusion of A β (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 A β (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