Palmitoylethanolamide exerts neuroprotective effects in an *in vivo* model of Alzheimer's disease

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Alzheimer's disease (AD) is the most common late-onset, progressive, and age-dependent neurodegenerative disorder associated with dementia (Brookmeyer R., 2007). Deposit of β-amyloid (Aβ) and accumulation of hyperphosphorylated τ protein filaments in neurofibrillary tangles (NFTs) are considered peculiar hallmarks of AD (Ramirez-Bermudez J., 2012). Several studies shown that excess amount of Aβ causes neuronal multiple cytotoxic mechanisms, including increase of the intracellular Ca^{2+} level, oxidative stress, receptor-mediated activation of cell-death cascades, astrocyte activation, and Wnt pathway deregulation (Selkoe D.J. et al., 2008).

It has been demonstrated that the neurotrophin S100B, whose levels correlate with the degree of astrocyte activation, is able to disrupt the Wnt pathway through the involvement of Dickopff-1 (Dkk-1) (Esposito G. et al., 2008). In addition, it has been suggested that dysfunction of Wnt pathway could contribute to AD pathology (Inestrosa N.C. et al., 2010).

On the basis of these consideration, pharmacological manipulation of the Wnt cascade could be useful to achieve neuroprotection, also in AD. In this context, palmitoylethanolamide (PEA), an endogenous lipid compound, could be a promising agent. Indeed, it has been already demonstrated that this compound exerts marked antinflammatory actions and it is able to counteract astrocyte activation (Scuderi C. et al., 2011). PEA is the amide of ethanolamine and palmitic acid, abundant in the central nervous system and produced by glial cells (Cadas H. et al., 1996). PEA's beneficial properties seems to depend on the activation of the peroxisome proliferator-activated receptor-alpha (PPAR-α) (Scuderi C. et al., 2012; D'Agostino G. et al., 2012).

Here we describe the neuroprotective effects of systemic administration of PEA in adult male rats given intrahippocampal injection of $Aβ_{(1-42)}$. In order to investigate the molecular mechanisms responsible for the effects induced by PEA, we co-administered PEA with the GW6471, an antagonist of peroxisome proliferator-activated receptor-α (PPAR-α). Making use of the western blot and immunofluorescence techniques, we found that $Aβ_{(1-42)}$ injection results in severe changes of Wnt pathway. Interestingly PEA was able to restore the Aβ-induced alterations through PPAR-α involvement.

Considering the extreme safety and tolerability of PEA, already proven in humans, these findings offer new opportunities in the development of innovative AD treatment.

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