Evaluation of the possible therapeutic potential of palmitoylethanolamide in a transgenic animal model of Alzheimer's disease: focus on neuroinflammation and synaptic dysfunction

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Neuroinflammation and synaptic dysfunction in Alzheimer's disease (AD) have been previously considered as epiphenomena with inflammation and altered neurotransmission occurring when damaged neurons provoke an activation response of glia and changes in neuron biology. Accumulating evidence, however, is now challenging this earlier view and points to a causal role of these events in AD, thus suggesting that compounds targeting these processes might be effective therapeutic agents in AD. In this context, anti-inflammatory and neuroprotective functions in animal AD models have been particularly attributed to the endocannabinoids belonging to the acylethanolamide family, like anandamide, oleoylethanolamide and palmitoylethanolamide (PEA). In the central nervous system, PEA is produced by neurons, microglia and astrocytes, and exerts a local anti-injury function through a down-modulation of mast cells and by protecting neurons from excitotoxicity. Recently, PEA has been defined as a cannabinoid receptor-inactive endocannabinoid-related molecule, with different mechanisms of action such as the activation of a cell surface receptor (CB2-like or GPR55), the activation of a nuclear receptor of the peroxisome proliferator-activated receptor (PPAR) family and the action as "entourage" compound enhancing endocannabinoid activity at their receptors and/or inhibiting endocannabinoid.

The general aim of the proposed study was to validate PEA as a clinical candidate for AD therapy. To this aim, we verified whether chronic (3 months) PEA treatment (100 mg/kg/day, added to food) prevents/slows the age-dependent progression of the pathology in a transgenic animal model of AD [the triple-transgenic murine model of AD (3xTg-AD), which harbors 3 mutant human genes (AβPPSwe, PS1M146V, tauP301L)]. In a first phase of the study we evaluated plasma and brain tissue levels of PEA after its oral administration. In particular, we evaluated two brain regions (i.e. hippocampus and prefrontal cortex) that are involved in cognitive functions and are particularly affected in AD pathology. We have now demonstrated that orally administered PEA is able to increase PEA brain levels, especially in the hippocampus. Furthermore, the chronic treatment with PEA in presymptomatic animals (2-3 months of age) showed some protective effects against synaptic dysfunction and neuroinflammation. Although preliminary, these data suggest the potential of PEA in modifying AD progression, at least in the present animal model of the pathology.

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