Effects of Palmitoylethanolamide against β-amyloid induced toxicity in cortical primary astrocyte-neuron co-cultures from Wild-Type and 3xTg-AD mice.

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Alzheimer's disease (AD) is the most common cause of dementia. It is a chronic, age-dependent and irreversible pathology [1].

Besides the classical neuropathological features of AD, namely cerebral senile plaques containing extracellular deposits of β-amyloid peptide (Aβ), and intraneuronal neurofibrillary tangles (NFTs), neuroinflammatory processes have been identified as a component of the disease. Neuroinflammation is detectable at the earliest stages of AD and the inflammatory reactions of microglia and astroglia are intimately associated with the pathogenesis and progression of AD [2].

Astrocytes become activated and release cytokines and many other factors that mediate inflammatory responses, reactive gliosis can become a self-perpetuating process which, at the end, exacerbates the injury and represents a non-physiological state in which astrocytes lose their helpful properties. Thus, a therapeutic approach aimed both to neuroprotection and to neuroinflammation reduction may be effective in AD [3].

The endocannabinoid system is implicated in AD progression since it is involved in modulation of neuroinflammation, oxidative stress, mitochondrial dysfunction and excitotoxicity [4]. In particular, a neuroprotective role has been suggested for the molecules belonging to the class of endogenous fatty acid amides. Among these, the palmitoylethanolamide (PEA) has attracted attention as an important anti-inflammatory, analgesic and neuroprotective mediator acting at several molecular targets in both central and peripheral nervous system [5].

The aim of this study was to determine the possible neuroprotective effects of PEA against $A\beta_{42}$-induced damages in astrocyte-neuron co-culture preparations obtained from the triple-transgenic murine model of AD (3xTg-AD) and their wild-type littermates (non-Tg) mice.

To this purpose, the astrocytes were exposed (24 hours) to $A\beta_{42}$ (0.5 μM) and, when necessary, PEA (0.1 μM) was applied in pretreatment (1 hour) before $A\beta_{42}$ and maintained in contact with the cells during the peptide exposure. After the peptide removal, a monolayer of neurons was plated above the treated astrocytes.

In astrocyte-neuron co-cultures from non-Tg mice, a significant reduction in neuronal viability, an increase in number of apoptotic nuclei and an alteration in neuronal morphology were observed. These effects were counteracted by pretreatment with PEA.

Surprisingly, any deleterious effects of $A\beta_{42}$ were observed in astrocyte-neuron co-cultures from 3xTg-AD mice. Furthermore, PEA either alone or in combination with the peptide, did not affect any parameters in this preparation.

Taken together, these results demonstrate that 1) astrocytes play a key role in the development and progression of $A\beta_{42}$-induced neurotoxicity in non-Tg, but not in 3xTg-AD mice and 2) PEA displayed promising protective properties against $A\beta_{42}$-induced damages in astrocyte-neuron co-cultures from non-Tg mice.

REFERENCES.

[1] Steardo L Jr, Bronzuoli MR, Iacomino A, Esposito G, Steardo L, Scuderi C. (2015). **Does neuroinflammation turn on the flame in Alzheimer's disease? Focus on astrocytes.** Front Neurosci. 9:259.

[2] Bedse G, Romano A, Lavecchia AM, Cassano T, Gaetani S. (2015). **The role of endocannabinoid signaling in the molecular mechanisms of neurodegeneration in Alzheimer's disease.** J Alzheimers Dis. 43:1115-36.

[3] Colangelo AM, Alberghina L, Papa M. (2014). **Astrogliosis as a therapeutic target for neurodegenerative diseases.** Neurosci Lett. 565:59-64.

[4] Aso E, Ferrer I. (2014). **Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic.** Front Pharmacol. 5:37.

[5] Petrosino S, Iuvone T, Di Marzo V. (2010). **N-palmitoyl-ethanolamine: Biochemistry and new therapeutic opportunities.** Biochimie. 92:724-7. Review.