CHRONIC INHIBITION OF FATTY ACID AMIDE HYDROLASE AMELIORATES THE ALZHEIMER-LIKE PHENOTYPE IN 3×TG-AD MICE

Tommaso Cassano[1], Silvio Calcagnini[2], Gaurav Bedse[2], Michele Lavecchia[2], Alessandra Caruso[2], Sergio Scaccianoce[2], Marialuisa de Ceglia[2], Cristina Anna Gallelli[2], Marzia Friuli[2], Adele Romano[2], Silvana Gaetani[2]

[1]Deptartment of Clinical and Experimental Medicine - University of Foggia, Foggia - Italy
[2]Department of Physiology and Pharmacology, Sapienza - University of Rome, Rome - Italy

Objectives: Acylethanolamides can exert neuroprotective/anti-inflammatory effects in Alzheimer's disease (AD). The inhibition of the enzyme fatty acid amide hydrolase (FAAH) can increase the endogenous tone of acylethanolamides, such as anandamide. This increase is able to produce selective anxiolytic-like and anti-depressant-like effects in rodents.
We tested the hypothesis that a chronic treatment with the selective FAAH inhibitor PF-3845 could exert beneficial effects on the onset or on the progression of the neurofunctional alterations developing in the triple transgenic mouse model of AD (3×Tg-AD). These alterations appear at 6 months of age and include amyloid plaques and neurofibrillary tangles, synaptic plasticity impairments, accelerated age-related cognitive decline and depressive-like behaviour.

Methods: Both young ("presymptomatic", at 4 months of age) and old ("symptomatic", at 10 months of age) 3×Tg-AD mice were treated with PF-3845 (10 mg/kg) for two months (administered subcutaneously every other day). At the end of the treatment we tested our hypothesis following an integrated approach, involving behavioural, biochemical and immunohistochemical analyses.

Results: PF-3845 was able to improve spatial and recognition memory, and to ameliorate the depressive- and anhedonia-like symptoms in both young and old 3×Tg-AD mice. Moreover, it reduced beta-amyloid and tau pathology in the hippocampus and frontal cortex of old mice and increased the hippocampal expression BDNF.

Conclusions: PF-3845 treatment was efficacious not only in preventing the onset of the neurofunctional alterations, but also in partially restoring such alterations in old symptomatic mice, thus suggesting that FAAH might represent a promising target for the development of novel anti-Alzheimer's therapies.