Caffeic acid phenethyl ester treatment counteracts efficiently β-Amyloid toxicity in an *in vivo* model of Alzheimer's disease: a time course evaluation

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Alzheimer's disease (AD) is considered the most frequent neurodegenerative disease age-related and the main cause of dementia in elderly patients worldwide. AD is characterized by the progressive loss of cognitive capacities; firstly the short term memory ability and then all intellectual functions are involved. The principal morphological abnormalities that could be observed in the evolution of AD are the formation of neuritics plaques of β-amyloid (Aβ) protein and the intracellular neurofibrillary agglomerates of tau protein hyperphosporylated, beyond microgliosis, dystrophic neuritis and neuronal and synaptic death. AD etiology is still unknown; the most common pathogenetic hypothesis involved the activation of amyloid cascade, where the crucial event could be an imbalance between the degradation and production of Aβ peptide. Polyphenols are natural compounds that have already shown interesting and promising neuroprotective properties, especially through their antioxidant activity, and in AD, an anti-amyloidogenic property. The caffeic acid phenetyl ester (CAPE), located in propolis, have shown anti-inflammatory, immunomodulatory, antiproliferative, antioxidant and antimicrobial properties; that are all involved in the evolution of AD. The aim of the present study is to investigate the potential neuroprotective functions of CAPE in an experimental murine model of AD. We injected $A\beta_{1-42}$ oligomers intracerebroloventricularly in C57BL/6 mice, and the treatment with CAPE (10 mg/kg) started 1 hour after the surgery for the next 10 days. After 10 days a portion of animals were sacrificed while others animals performed behavioral test (Morris Water Maze, MWM) before the sacrifice. Behavioral analysis shows that the lesion induced by the injection of $A\beta_{1-42}$ oligomers reduces significantly cognitive skills in our mouse models. On the other hand, animals treated with CAPE after the damage induced show a positive recovery underlying the efficacy of the molecule of our interest to counteract $A\beta_{1-42}$ oligomers action. We analyzed the redox cell status through the evaluation of the reactive oxygen species (ROS) formation. Our data show that $A\beta_{1-42}$ oligomers injection determines a consistent increment in ROS formation and CAPE is able to restore a physiological oxidative cellular status. We also evaluated glutathione (GSH) levels, one of the main endogenous antioxidant system. Our results have shown the ability of CAPE to modify the GSH content slowing down its levels at basal values. In addition, we investigated the expression of the nuclear transcriptional factor Nrf2, able to control the transcription of several cellular systems of detoxification and defense. In our experimental model, we observed a significant increment of Nrf2 activation in animals lesioned and then treated with CAPE, showing a probable implication of this pathway in its mechanism of neuroprotection. Finally we investigated synaptic activity and Aβ protein immunoreactivity by immunohistochemistry. Our results have shown increased synaptophysin reactivity in Aβ/CAPE group compared to Aβ/vehicle group and a decrease of Aβ protein deposition in the same group. In conclusion, our data show an interesting neuroprotective activity of CAPE. It is not only able to restore a physiological oxidative status and to interfere positively with Nrf2-pathway, but also to contribute to the improvement of synaptic functions and behavioral recovery.