Neuroprotective properties of Caffeic acid phenethyl ester on Alzheimer's disease pathogenesis and cognition.

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Alzheimer's disease (AD) is the most common cause of dementia and the first neurodegenerative disease in our days. Early diagnosis of AD is critical and there is usually a time lag between the onset of symptoms and diagnosis, probably because of the compensative endogenous mechanisms. In this way, a good diagnosis is possible only after the death of a large number of neurons. Many evidences support the central role of β-amyloid peptide (Aβ) in the early stages and in the progression of AD. Indeed, recent studies have shown that Aβ aggregation in soluble oligomers or fibrils is accountable of synaptic dysfunctions and neuronal death in patients. The central hypothesis is that Aβ is responsible for the iperactivation and dysregulation of inflammatory responses through glial cells, causing the progressive cognitive deterioration in AD.
To date, there are not therapeutic strategies able to restore neuronal functionality in AD. For this reason appears evident how important is the concept of neuroprotection. A valid neuroprotective strategy, aimed to arrest or slow down damage evolution, should act in the time window between the lesion occurred and the propagation of the irreversible injury. Neuroinflammation, oxidative stress and apoptotic process may be considered functional targets to this end. Bioactive multifunctional compounds represent a wide class of molecules with a well-documented biological activity that may be crucial in the restorative and preventive treatment of neurodegenerative conditions. Caffeic acid phenetyl ester (CAPE), located in propolis, has already shown anti-inflammatory, immunomodulatory, and antioxidant properties; that are all involved in the evolution of AD.
Taking into account these considerations, the aim of the present study is to investigate the potential neuroprotective activity of CAPE in an experimental murine model of AD, through an integrative approach of biomolecular and behavioral analysis. The goal is to outline innovative strategies to prevent and control neuroinflammation, neurodegeneration and cognitive involvement bounded to AD. To this end, we injected $A\beta_{1-42}$ oligomers intracerebroloventricularly (i.c.v.) in C57BL/6 mice, and the treatment with CAPE (10 mg/kg) started 1 hour after the surgery for the next 3 or 10 days. After 10 days a portion of animals were sacrificed while other animals performed behavioral test (Morris Water Maze, MWM) before the sacrifice. Behavioral analysis showed that the lesion induced by the injection of $A\beta_{1-42}$ reduced significantly cognitive skills in our mouse model. On the other hand, animals treated with CAPE showed a positive recovery underlying the efficacy of the molecule of our interest to counteract $A\beta_{1-42}$ action. We analyzed the redox cell status through the evaluation of the reactive oxygen species (ROS) formation. Our data showed that $A\beta_{1-42}$ determined a consistent increment in ROS formation and CAPE was able to restore a physiological oxidative cellular status. We also evaluated glutathione (GSH) levels, one of the main endogenous antioxidant system. Our results have showed 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. 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. In conclusion, our data highlighted an interesting neuroprotective activity of CAPE, which was able to restore a physiological oxidative status, interfere positively with Nrf2-pathway, and contribute to behavioral recovery.