NEUROPROTECTIVE EFFECT OF CAFFEIC ACID PHENETHYL ESTER ON MICE MODEL OF ALZHEIMER'S DISEASE INVOLVES Nrf2/ARE SIGNALING PATHWAY

1)Morroni F. 2)Sita G. 3)Graziosi A. 4)Tarozzi A. 5)Hrelia P.

Alma Mater Studiorum - University of Bologna Pharmacy and BioTechnology

Alzheimer's disease (AD) is the most common form of dementia among older people. The cardinal neuropathological hallmark of AD is the accumulation of amyloid-β (A) into extracellular plaques that ultimately disrupt neuronal function and lead to neurodegeneration (Scheltens, 2016). Recent studies have implicated specific assembly subtypes of Aβ peptide, in particular soluble oligomers, as disease-relevant structures that may underlie memory loss in AD (Klein, 2013). Although soluble amyloid species are recognized triggers of the disease, no therapeutic approach is able to stop it. Caffeic acid phenethyl ester (CAPE) is one of the most extensively investigated active components of honeybees' propolis which possess many biological activities, including antibacterial, antiviral, antioxidant, anti-inflammatory, and anti-cancer effects (Murtaza, 2014). The protective potential of CAPE has been shown in different models of neurotoxicity (in vitro and in vivo) and it has been associated with immune-modulatory, antioxidant and anti-inflammatory properties (Barros Silva, 2013; dos Santos, 2014). The aim of the present study was to investigate the potential neuroprotective activity of CAPE in a murine model of AD. Abeta oligomers were injected intracerebroventricularly in C57BL/6 mice, and the treatment with CAPE (10 mg/kg) started 1 hour after the surgery for the next 10 days. At the end of the treatment, some animals were sacrificed while others performed behavioral test before the sacrifice. Behavioral analysis showed that CAPE ameliorated Abeta-induced memory impairment. Abeta injection determined a consistent increment of reactive oxygen species and glutathione levels and CAPE restored a physiological oxidative status. In addition, the expression of the nuclear transcriptional factor Nrf2 and heme oxygenase-1 were enhanced by CAPE treatment. Moreover, CAPE protected Abeta-induced apoptosis via blocking caspase-9 activation, and reversed Abeta injection-induced synaptic deficits. CAPE treatment was also associated with significant decreases in IBA1- and GFAP-positive cells in the hippocampus. These results highlighted an interesting neuroprotective activity of CAPE, which was able to restore a physiological oxidative status, interfere positively with Nrf2-pathway, decrease apoptosis and neuroinflammation and contribute to behavioral recovery. These findings suggested that CAPE could potentially be a promising neuroprotective agent against progressive neurodegenerative diseases such as AD.

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