

Oleuropein aglycone ameliorates cognitive impairment and neuropathology in a mouse model of A β deposition

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The claimed beneficial effects of the Mediterranean diet include prevention of several age-related dysfunctions including neurodegenerative diseases and Alzheimer-like pathology. These effects have been related to the protection against cognitive decline associated with aging and disease by a number of polyphenols found in red wine and extra virgin olive oil. The double transgenic TgCRND8 (Tg) mice, a model of amyloid- β (A β) deposition, (overexpressing the Swedish and Indiana mutations in the human amyloid precursor protein), aged 1.5, 4 and 10 months, and age-matched wild type control mice were used to examine *in vivo* the effects of 8 weeks dietary supplementation of Oleuropein aglycone (50 mg/kg of diet), the main polyphenol found in extra virgin olive oil. We found that dietary supplementation of Oleuropein aglycone significantly improves the cognitive performance in the 'step down' inhibitory avoidance task and in the object recognition test of young/middle-aged TgCRND8 mice respect to age-matched littermates fed with un-supplemented diet. Immunofluorescence analysis of cerebral tissue in Oleuropein aglycone-fed Tg mice showed a marked reduction of A β load both as total A β plaque area and plaque number in the cortex and hippocampus at all ages of the animals, as compared to untreated age-matched Tg mice (number of plaques: 3 months= cortex: - 80%, ***P<0.001; hippocampus: - 65%,**P<0.01; 6 months= cortex: - 70%, **P<0.01; hippocampus: - 60%,**P<0.01; 12 months= cortex: - 40%, **P<0.01; hippocampus: - 25%,*P<0.05). Most interestingly, Oleuropein aglycone treatment to Tg mice resulted in an intense bright and punctate immunoreactivity for the autophagic Beclin 1 and LC3-II markers and for the lysosome Catepsin B marker in the soma, perikarya and dendrites of neurons in different layers of somatosensory/parietal and entorhinal/piriform cortices, indicating that Oleuropein aglycone strongly induces autophagy and promotes autophagosome-lysosome fusion needed for cargo degradation. In addition, Oleuropein aglycone-fed Tg mice showed a reduced astrocytes reaction and reduced TNF- α immunoreactivity in the cortex and hippocampus, as compared to untreated Tg mice. This anti-inflammatory activity was not the result of the antioxidant power of Oleuropein aglycone, in fact, lipid peroxidation in the cortex of 3-month-old Tg mice was not significantly reduced by the treatment. Surprisingly, clusters of activated microglia were detected in the hippocampus and cortex of Oleuropein aglycone-fed Tg mice at the late stage of amyloid deposition, suggesting activated microglia involvement in plaque remodelling and phagocytosis. These results provide a strong evidence of protective and beneficial effects of Oleuropein aglycone on AD-like pathology and suggest that dietary supplementation with Oleuropein aglycone may prevent or delay the occurrence of Alzheimer's disease or, at least, may reduce the severity of its symptoms. This work was supported by Regione Toscana Salute 2009, Ente Cassa di Risparmio di Firenze 2010 e 2011 and Università di Firenze.