Oleuropein aglycone hinders amyloid toxicity in the Aß-injected rat brain and in the TgCRND8 mice

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Alzheimer's disease (AD) is the most common form of dementia, pathologically characterized by increased accumulation of intracellular neurofibrillary tangles, and extracellular amyloid β1-42 (Aβ42) deposits. In the amyloid hypothesis Aß aggregates and initiates progressive neurodegeneration. Among lifestyle factors, several epidemiological data underscored a possible protective role of nutrition and the Mediterranean diet (MD) appears to be effective in attenuating AD-like pathology. Firstly, we investigated the neuroprotective and antinflammatory effects of an intracerebral injection of oleuropein aglycone (OLE), the main polyphenol present in the extra virgin olive oil, in rodents. To this aim the nucleus basalis magnocellularis (NBM) of adult male Wistar rats was injected with a 1.5 µl solution containing either Aß42 (50 µM) preincubated with OLE (450 µM) or OLE (450 µM) or Aß42 (50 µM) alone. Control rats were injected with 1.5 µl of phosphate buffer. Thirty days after injection the number of choline acetyltransferase (ChAT)-positive neurons, glia reaction and Aß peptide were immunohistochemically detected. The number of ChAT-positive neurons was significantly reduced (-33,33 %;$p < 0.05$) by the injection of Aß peptide. The co-injection of OLE completely restored to control levels the number of ChAT-positive neurons, markedly attenuated the Aß-induced astrocytes and microglia reaction, TNF-α immunoreactivity and the amount of A11 immunopositive Aß peptide.
Secondly, we studied the effects of 8 weeks dietary supplementation of OLE (50 mg/kg of diet), in the double transgenic TgCRND8 (Tg) mice of 3, 6 and 12 months. We found that dietary supplementation of OLE significantly reduced Aβ40 and Aß42 SDS and formic acid (FA) soluble fractions measured in the cortex of OLE-fed Tg mice of all ages as compared to age-matched untreated Tg mice. (SDS fractions: 3 months $p < 0.05$, 6 and 12 months $p<0.001$. FA fractions: 3 months $p < 0.05$, 6 months $p < 0.05$, 12 months $p < 0.001$). Pyroglutamate-modified Aß peptides at amino acid position 3 (Aß3pE-42), generated by the enzyme glutaminyl cyclase (QC), has been found as a major component of Aβ plaques in the hippocampus and cortex of AD patients. We report here that OLE-fed Tg mice of all ages show a marked reduction of Aß3pE-42 load, both as total plaque area and plaque number, in motor and pyriform cortices and hippocampus, as compared to untreated age-matched Tg mice (number of plaques at 12 months: motor cortex: -63%, $P<0.05$; pyriform cortex: -77%, $P<0.005$; hippocampus: -66%, $P<0.001$). In addition, an apparent reduction of QC immunoreactivity was detected in the cortex and CA1 area of the hippocampus in OLE-fed Tg mice.
Altogether these data further support the neuroprotective and anti-inflammatory activities of the polyphenol enriched in the extra virgin olive oil and suggest that dietary supplementation with OLE may prevent or delay the occurrence of AD.

This work was supported by Regione Toscana Salute 2009, Ente Cassa di Risparmio di Firenze 2010 and 2011 and Università di Firenze.