

Oleuropein aglycone induces autophagy *in vivo* in a mouse model of A β deposition and in neuroblastoma cells: a mechanistic insight

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Mounting evidence supports the beneficial effects of the Mediterranean diet (MD) and the Asian diet in delaying ageing and in preventing age-related dysfunctions, cancer, diabetes and neurodegenerative diseases. The beneficial effects of the MD and Asian diets in reducing age-related dysfunctions, including Alzheimer's disease (AD), could be the consequence of the presence in specific foods of substantial amounts of specific polyphenols whose beneficial properties include the ability to interfere with amyloid aggregation. Oleuropein and its aglycone (OLE) are the major polyphenols in the leaves and drupes of *Oleaceae* and in the extra virgin olive oil (EVOO). Our previous data have highlighted the beneficial effects of OLE against protein/peptide aggregation *in vitro* and in TgCRND8 mice, a model of A β deposition. Young/middle aged TgCRND8 mice fed for 8 weeks with OLE (50 mg/kg of diet) displayed improved behavioural performance in the step-down passive avoidance and object recognition tests; immunofluorescence analysis of cerebral tissue in OLE-fed transgenic mice showed remarkably reduced β -amyloid levels and plaque deposits, OLE-fed mice brain display an astonishingly intense autophagic reaction, as shown by the increase of autophagosome markers expression and of lysosomal activity. The molecular and cellular mechanisms of autophagy induction by OLE were presently investigated in cultured SHSY-5Y neuroblastoma cells exposed to 50 μ M OLE. These cells showed increased autophagic vacuoles in association to a rise in cytosolic calcium coming from the SR stores, CaMKK activation and the ensuing AMPK activation by phosphorylation. These data paralleled those found in OLE-fed TgCRND8 mice, where we found mTOR inhibition and increased AMPK phosphorylation with decreased phosphorylation of p70S6K, an mTOR substrate. In conclusion, our data provide evidence that the mechanism of autophagy activation by OLE implies the activation of the Ca²⁺ - CaMKK - AMPK axis and inhibition of the mTOR signaling, confirming that polyphenols are useful to treat age-related diseases with autophagy dysfunction, including neurodegenerative diseases.

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