Oleuropein aglycone protects against pyroglutamylated-3 amyloid-β toxicity: biochemical, epigenetic and functional correlates

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ABSTRACT

Amyloid-β (Aβ) fragments, oligomeric Aβ aggregates, and pyroglutamylated-Aβ peptides, as well as epigenetic mechanisms and autophagy dysfunction all appear to contribute in various ways to Alzheimer’s disease progression. We previously showed that dietary supplementation of oleuropein aglycone, a natural phenol abundant in the extra virgin olive oil, can be protective by reducing Aβ42 deposits in the brain of young and middle-aged TgCRND8 mice. Here, we extended our study to aged TgCRND8 mice showing increased pE3-Aβ in the brain deposits. We report that oleuropein aglycone is active against glutaminylcylcase-catalyzed pE3-Aβ generation reducing enzyme expression and interferes both with Aβ42 and pE3-Aβ aggregation. Moreover, the phenol astonishingly activates neuronal autophagy even in mice at advanced stage of pathology, where it increases histone 3 and 4 acetylation, which matches both a decrease of histone deacetylase 2 expression and a significant improvement of synaptic function. The occurrence of these functional, epigenetic, and histopathologic beneficial effects even at a late stage of the pathology suggests that the phenol could be beneficial at the therapeutic, in addition to the prevention, level.