

## Oleuropein aglycone protects against pyroglutamylated-3 amyloid- $\beta$ toxicity: biochemical, epigenetic and functional correlates

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### A B S T R A C T

Amyloid- $\beta$  ( $A\beta$ ) fragments, oligomeric  $A\beta$  aggregates, and pyroglutamylated- $A\beta$  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  $A\beta_{42}$  deposits in the brain of young and middle-aged TgCRND8 mice. Here, we extended our study to aged TgCRND8 mice showing increased pE3- $A\beta$  in the brain deposits. We report that oleuropein aglycone is active against glutamylcyclase-catalyzed pE3- $A\beta$  generation reducing enzyme expression and interferes both with  $A\beta_{42}$  and pE3- $A\beta$  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.