

## Olive Polyphenols: New Possible Tools against Type 2 Diabetes and Aging-Related Neurodegeneration

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Increasing evidence supports the idea that olive polyphenols are effective against several aging-associated diseases, including both systemic (type 2 diabetes, atherosclerosis, stroke, the metabolic syndrome, inflammatory diseases, cancer) and neurodegenerative (Alzheimer's and Parkinson diseases) pathologies, the latter still lacking an effective therapy [1-4]. The large literature in the field provides strong support to the benefits of the Mediterranean and Asian diets. In particular, increasing data are accumulating on the positive relation between type 2 diabetes and olive polyphenols, notably oleuropein (Ole) and its main metabolite, hydroxytyrosol (HT) [5]. On the other hand, more recently, a solid knowledge on a claimed protection by Ole, HT and oleocanthal, a third important olive polyphenol, against A $\beta$  plaque deposition in Alzheimer's disease (AD) as well as on the molecular basis of the latter, has been accumulating [6].

The concomitant anti-diabetic and anti-neurodegenerative power of olive polyphenols is not surprising, when one considers the raising awareness that diabetes (notably type 2 diabetes) and AD are two degenerative conditions closely related to each other, such that the risk of dementia is claimed to be increased by 1.9-fold in diabetic people [7]. Actually, insulin-resistance is a common feature of the two pathologies [8]. In addition, increased circulating insulin has at least two outcomes. The first consequence is the increased incretion of amylin (IAPP) by pancreatic cells which, besides in pancreatic  $\beta$  cells, displays its tendency to aggregate into amyloid assemblies also in the brain tissue; there, often they are found as a minor component in AD plaque deposits. In addition, recent data highlight cross-seeding between amylin and A $\beta$  aggregates, the main components of extracellular plaques in AD brain areas, leading to conclude that tiny amounts of amylin aggregates can seed extensive A $\beta$  aggregation [9]. The second consequence stems from the known substrate preferences of insulin degrading enzyme (IDE) and neprilysin, two proteases involved in degradation of both insulin, amylin and the A $\beta$  peptide [7,10,11]. Accordingly, increased insulin/amylin may hinder efficient degradation of A $\beta$ , resulting in raised levels of the latter, that, together with amylin seeding, can enhance A $\beta$  tendency to aggregate inside the brain [7].

In the past, the anti-diabetic and anti-neurodegeneration effects of olive polyphenols have been traced back to the potent antioxidant power of these compounds, particularly HT, the main Ole metabolite [12]. However, recent investigations have highlighted a more complex interference of these compounds with cell and tissue physiology. In fact, similarly to other plant polyphenols, olive polyphenols also possess remarkable anti-inflammatory power elicited both in peripheral tissues and in the central nervous system [13,14]; in addition, they are able to reprogram cell metabolism by modulating cell signaling pathways involved in the regulation of the mTORC and AMPK metabolic hubs. The resulting mTORC inhibition and AMPK activation, eventually favors the catabolic, instead

than the anabolic/proliferative, pathways [15,16]. One of the main outcomes of these modifications is the interference with the proteostasis balance, which results in a remarkable activation of autophagy, particularly macroautophagy [17]. The latter is a complex response to stress stimuli, such as nutrient deprivation, that helps the cells to clear, by lysosomal degradation, cellular components and undesired accumulating by-products for further use as building blocks; these materials also include intra- or extracellular protein aggregates of amyloid nature that stress and damage exposed cells [18]. On this aspect, it is of significance that brain autophagy is considerably decreased in neurodegenerative diseases, including AD [19].

Most of the biological effects of plant, notably olive, polyphenols result from their ability to modulate, in addition to proteostasis, the activity of transcription factors involved in the control of key cellular equilibria, such as the redox status. Several studies have reported that olive polyphenols modulate the activity of nrf-2, FOXO, TFEB or other transcription factor families that control the expression of genes whose products are involved in the redox, inflammatory or autophagic responses [20-23]. Even more importantly, these substances are starting to be described as important contributors to the epigenetic modifications involved in many of their activities. For example, we have recently reported that TgCRND8 mice, a murine model of Abeta plaque deposition, fed with a diet supplemented with Ole aglycone did not display the severe impairment of memory and cognitive performance displayed by normally fed littermates; rather, they cognitive behavior was undistinguishable from that recorded in w.t. mice. The strongly improved cognition, in these Ole-fed Tg mice, matched a remarkable reduction of neuroinflammation, A $\beta$  levels and A $\beta$  plaque load and consistency, together with improved neurogenesis and synaptic function (LTP) and an astonishing activation of the autophagic flux and autophagolysosome formation [24]. At least some of these effects were traced back to epigenetic modifications. In fact, Ole-fed Tg mice displayed increased histone acetylation, normally depressed in AD [25], which resulted from reduced levels of histone deacetylase 2 (HDAC2), normally upregulated in the AD brain [25] and, possibly, induced beclin-1/LC3 expression, whereas the expression of glutaminyl cyclase (QC) an enzyme abundantly expressed in brain cortex, hypothalamus and hippocampus was reduced. QC, whose mRNA is upregulated in the cortex and peripheral blood of AD patients [26] is involved in AD, where it is responsible for the generation of the pyroglutamylated A $\beta$ <sub>3-42</sub>. The latter, an A $\beta$  derivative more resistant to proteases and with strong tendency to aggregate, is possibly involved in the onset of plaque deposition [27]. Overall, increasing data are accumulating on the polyphenol-epigenetics relation particularly in cancer [28,29]; however, more knowledge on this theme is needed, mainly for what olive polyphenols are concerned, to complete the picture of the cellular effects of these molecules at the molecular level.

In conclusion, in addition to the population studies supporting the beneficial properties of olive oil [30,31], raising knowledge is focusing on its polyphenols, increasingly described as the main responsible for many virtues of the Mediterranean diet, including protection against type 2 diabetes, ageing and aging-related neurodegeneration. These studies are providing strong molecular support to the claimed effects of these substances. The resulting knowledge supports a positive modulation of the biochemical, physiological and epigenetic responses aimed at cell protection against the insult of various stressors responsible for cell impairment in several pathological conditions such as type 2 diabetes and AD. However, while Ole protection against type 2 diabetes has started to be supported not only mechanistically [32,33] but also by studies carried out in humans, yet to be confirmed in larger cohorts [34], Ole benefits against A $\beta$  aggregation and plaque deposition in AD, increasingly proven *in vitro*, as well as in cell and animal models, still awaits confirmation in humans by appropriate clinical trials.

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