ANTI-AMYLOID OLIGOMER ACTIVITY OF HUMAN POLYPHENOL METABOLITES: NEW CANDIDATE ALZHEIMER'S-PREVENTING COMPOUNDS?

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Many neurodegenerative diseases, including Alzheimers' disease (AD), share the presence of amyloid aggregates, some of which, such as amyloid oligomers, are considered the most proximal neurotoxic species. Compounds specifically targeting amyloid oligomers are being actively sought and there is great interest for various natural polyphenols, especially flavonoids and flavan-3-ols, as potential AD-preventive agents. However, human metabolism of dietary plant flavonoid precursors through a combination of host and gut microbiota-assisted bioconversion complicates identification of the most relevant bioactive compounds. We addressed this issue by investigating the anti-proteotoxic activity of a comprehensive set of phenyl-gamma-valerolactone (PVL)-based, flavan-3-ol human metabolites, in different model systems of amyloid oligomer (AbO)-induced cell death. PVLs, and particularly the monohydroxylated 5-(4'-hydroxyphenyl)-gamma-valerolactone [(4'-OH)-PVL], proved capable of relieving AbO-induced cell death in yeast and mammalian cell model systems, and interfered with AbO but not amyloid fibril formation in vitro. Importantly, (4'-OH)-PVL exerted a protective effect on recognition memory and positively modulated neuroinflammation in an acute mouse model of AbO-induced memory impairment. As the main circulating metabolites of dietary flavan-3-ols, PVLs lend themselves as novel AbO-selective, candidate compounds for AD prevention worth of further investigation.