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Rosmarinic acid potently inhibits amylin-induced neurotoxicity and amyloid formation

Paul Velander, Ling Wu, Anne Brown, Keith Ray, Rich Helm, David Bevan, Bin Xu
Virginia Tech, USA

Epidemiological studies show significant association between obesity-related type 2 diabetes (T2D) and risk for cerebrovascular disease and dementia (including neurodegenerative Alzheimer's disease, AD). Amylin is a 37-residue peptide hormone that is co-secreted with insulin from pancreatic beta cells. It is a highly amyloidogenic protein, similar to amyloid beta peptide Abeta 42 which is a well-known peptide factor involving in AD in the brain. Recent clinical studies reported that amylin plaques were deposited in the brain of diabetic patients, but not in age-matched health controls. Our cell-based studies demonstrated that amylin amyloid is highly toxic to human and mouse neuronal cell lines SH-SY5Y and Neuro2A. From a targeted screening of a collection of natural compounds used in complementary and alternative medicine, we identified that rosmarinic acid (RA) is a highly potent inhibitor against amylin amyloid formation (estimated to be one to two hundred nM in IC_{50}) and it rescues cell viability from amylin-induced cytotoxicity. Dissecting the two functional groups of rosmarinic acid, we found each group, caffeic acid and salvianic acid A respectively, have weaker-than-RA inhibitory and rescue functions, suggesting an additive or synergistic effect of the two functional groups. Our data suggests that the mechanism of RA mediated amylin amyloid inhibition may in part be due to site-specific binding to the amine groups in the peptide. Consistent with the experimental results, the inhibition effect by rosmarinic acid is demonstrated in computational molecular simulation analyses, providing an additional mechanism of non-covalent interactions between RA and the peptide as a way to block amylin oligomer and amyloid formation.

wvpaul1@vt.edu

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