Derivatives of calmodulin-like skin protein, named CLSP(1-61) and CLSPCOL, as anti-Alzheimer disease agents

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Calmodulin-like skin protein (CLSP), a secreted peptide, likely protect neurons from toxicity linked to Alzheimer disease (AD) via the heterotrimeric humanin receptor. We have addressed the issues regarding the clinical relevance of CLSP regulation in the AD pathogenesis and the potential of some CLSP derivatives named CLSP(1-61) and CLSPCOL as anti-AD agents by preclinical tests. By conducting an *in vitro* AD-related death assay, we have characterized endogenous CLSP interactors. By measuring the levels of CLSP interactors in AD-patient-derived samples, we have next examined whether the dysregulation of CLSP interactors contributes to the AD pathogenesis. Finally, by administering potent CLSP derivatives to AD models, we have tested their potentials as anti-AD therapeutic agents. Some CLSP-binding proteins including apolipoprotein E inhibited the CLSP-mediated neuroprotective effect. Oppositely, adiponectin enhances the CLSP activity and enabled CLSP to remain fully active even in the presence of overwhelming amounts of CLSP inhibitors, by binding to the humanin-homologous region of CLSP. We further show that both the level of adiponectin and the intraneuronal level of SH3BP5, a central intraneuronal signal transducer of the humanin/CLSP effect, were downregulated in AD patients. We designed CLSP (1-61) and CLSPCOL as anti-AD agents that are free from the suppression of CLSP inhibitors and tested their ant-AD efficacy. Adiponectin dominantly determines the CLSP activity. The downregulation of the AD-protective activity of CLSP, caused by the reduction of brain adiponectin, may contribute to the AD pathogenesis. CLSP-derived peptides, CLSP(1-61) and CLSPCOL, may be ideal disease-modifying anti-AD agents.