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4-O-methylhonokiol attenuated memory impairment through reduction of oxidative damage, and amyloid-β generation and accumulation in mouse models of Alzheimer's disease

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Accumulations of amyloid-β (Aβ) and oxidative damage are critical pathological mechanisms in the development of Alzheimer's disease (AD). We found that 4-O- methylhonokiol, a compound extracted from Magnolia officinalis, improved memory dysfunction in Aβ-injected and presenilin 2 mutant mice through the reduction of oxidative stress and accumulated Aβ. To investigate mechanisms of the reduced Aβ accumulation, we examined generation, degradation, efflux and aggregation of Aβ in Swedish AβPP AD model (AβPPsw) mice pre-treated with 4-O-methylhonokiol (1.0 mg/kg) for 3 months. 4-O-methylhonokiol treatment recovered memory impairment and prevented neuronal cell death. This memory improving activity was associated with 4-O-methylhonokiol-induced reduction of $A\beta_{1-42}$ accumulation in the brains of AβPPsw mice. According to the reduction of $A\beta_{1-42}$ accumulation, 4-O-methylhonkiol modulated oxidative damage sensitive enzymes. 4-O-methylhonkiol decreased expression and activity of brain beta-site AβPP cleaving enzyme (BACE1), but increased clearance of Aβ in the brain through an increase of expressions and activities of Aβ degradation enzymes; insulin degrading enzyme and neprilysin. 4-O-methylhonkiol also increased expression of Aβ transport molecule, low density lipoprotein receptor-related protein-1 in the brain and liver. 4-O-methylhonkiol decreased carbonyl protein and lipid peroxidation, but increased glutathione levels in the brains of AβPPsw mice suggesting that oxidative damage of protein and lipid is critical in the impairment of those enzyme activities. 4-O-methylhonokiol treatment also prevented neuronal cell death in the AβPPsw mousee brain through inactivation of caspase-3 and BAX. These results suggest that 4-O-methylhonokiol might prevent the development and progression of AD by reducing Aβ accumulation through an increase of clearance and decrease of Aβ generation via antioxidant mechanisms.

Biography

Jin Tae Hong completed his B.S. and M.S. from Chungbuk National University College of Pharmacy and Ph.D. from Kentucky University Graduate Center for Toxicology. From 1990 to 2001, He was Senior Researcher, Korea Food and Drug Administration (KFDA). He is currently a professor at Chungbuk National University. He has been serving as an advisory board member of KFDA, a member of Society of Toxicology and American association for Cancer Research in U.S.A. He is also a vice president of Korean Society of Toxicogenomics and Toxico- proteomics, and a chief of research planning of The Pharmaceutical Society, Korea.