4-O-METHYLHONOKIOL ATTENUATED MEMORY IMPAIRMENT OF PRESENILIN 2 MUTANT MICE THROUGH REDUCTION OF OXIDATIVE DAMAGES, AND INACTIVATION OF ASTROCYTES AND ERK PATHWAY

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Presenilin 2 (PS2) mutation increases Aβ generation and neuronal cell death in the brains of AD patients. In the previously study, we showed that increased oxidative damages and activation of extracellular signal-regulated kinase (ERK) were associated with Aβ generation and neuronal cell death in the neuronal cells expressing mutant PS2. In this study, we showed that oral treatment of 4-O-methylhonokiol, a novel compound isolated from Magnolia officinalis for 3 months (1.0 mg/kg) prevented PS2 mutation-induced memory impairment and neuronal cell death accompanied with reduction of Aβ₁₋₄₂ accumulation. We also found that 4-O-methylhonokiol inhibited PS2 mutation-induced activation of ERK and β-secretase, and oxidative protein and lipid damages, but recovered glutathione level in cortex and hippocampus of PS2 mutant mice. Additionally, 4-O-methylhonokiol prevented PS2 mutation-induced activation of astrocytes as well as production of TNF-α, IL-1β, reactive oxygen species (ROS) and nitric oxide (NO) in the neurons. Generation of TNF-α, IL-1β, ROS, NO and ERK activation in the cultured astrocytes treated with lipopolysaccharides (1 µg/ml) were also prevented by 4-O-methylhonokiol in a dose dependent manner. These results suggest that the improving effects of 4-O-methylhonokiol on memory function may be associated with the suppression of the activation of ERK and astrocytes as well as the reduction of the oxidative damages. Thus, 4-O-methylhonokiol may be useful in the prevention and treatment of AD.