The Effects of Glycogen Synthase Kinase-3beta on Gspe Improves Adult Neurogenesis in APP/PS1 Mice

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Abstract: Objective Oxidative stress is a key factor in the pathogenesis of Alzheimer’s disease (AD), and antioxidant treatment of traditional has many shortcomings. Grape seed polyphenolic extract (GSPE)—a natural polyphenolic extract derived from grape seed is the most powerful antioxidants. Studise show that GSPE arrests memory deficits in Alzheimer’s animal model, but the mechanism is not certain. Previous studies demonstrated that activation of GSK-3 can cause memory deficits in Alzheimer’s disease. So we presumed that GSPE improves memory and promotes neurogenesis in APP/PS1 mice via down regulation activity of GSK-3. Methods: Observe the impacts of GSPE gavage on learning memory of APP/PS1 mice under different doses (100, 150 and 200 mg/kg/day) in order to determine the optimally effective concentration; Under an optimally effective concentration, investigate the impacts of GSPE on learning memory, neurogenesis levels and neuropathological changes of APP/PS1 mice; GSPE treatment APP/PS1 mice with up-regulated cerebral GSK-3 activities by giving GSK-3 agonist and GSK-3 mutant lentivirus, analyze the impacts of GSPE on learning memory, neurogenesis levels, neuropathological changes, synapsins, learning memory-related protein (c-Fos) expression and GSK-3 activities in transgenic mice; and investigate the effects of GSK-3 therein. Results: GSPE of 150mg/kg/day is an optimal concentration. GSPE improve the learning memory of APP/PS1 mice and enhance the LTP, neurogenesis, synapsins and learning memory-related protein levels while decrease GSK-3 activities. GSK-3 activities increased in APP/PS1 mice with up-regulated cerebral GSK-3 activities by giving GSK-3 agonist and GSK-3 mutant lentivirus, but GSPE administration cannot significantly improve the learning memory abilities, neurogenesis levels, synapsins and learning memory-related proteins in APP/PS1 mice. Conclusions: GSPE improve the behavioral disorder of APP/PS1 mice and enhance their cerebral neurogenesis. GSK-3 activity decline plays an important role in GSPE reversed cerebral neurogenesis of AD transgenic mice. Preliminarily elucidate the mechanism of GSK-3-c-Fos-synapse signal pathways in GSPE mediating neurogenesis of AD transgenic mice. This project will provide new experimental theory basis for GSPE in prevention of AD.

Keywords: Alzheimer’s disease; Neurogenesis; Grape seed polyphenolic extract; GSK-3; C-Fos

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