# Ginsenoside Rh2 promotes nonamyloidgenic cleavage of amyloid precursor protein via a cholesterol-dependent pathway

**J. Qiu[1]\*, W. Li[2]\*, S.H. Feng[3], M. Wang[3] and Z.Y. He[1]**

[1]Department of Neurology, First Hospital of China Medical University,
Shenyang, China
[2]Department of Neurology, General Hospital of Shenyang Military Command,
Shenyang, China
[3]Department of Neurology, 463rd Hospital of PLA, Shenyang, China

\*These authors contributed equally to this study.
Corresponding author: Z.Y. He
E-mail: zhiyihe4@gmail.com

**ABSTRACT.** Ginsenoside Rh2 (Rh2) is a ginseng derivative used in Chinese traditional medicine. We investigated whether Rh2 can help prevent Alzheimer's disease symptoms and examined underlying mechanisms. We injected Rh2 into tg2576 Alzheimer's disease model mice and looked for behavioral improvement and senile plaque reduction in brain slices. We measured amyloid precursor protein (APP) metabolism species changes, amyloid beta40 and 42 levels and β, γ secretase activity in primary hippocampal neurons. By living cell staining, we detected surface and endocytosed APP. We also measured cholesterol and lipid rafts in primary neurons. Rh2 treatment significantly improved learning and memory performance at 14 months of age; it also reduced brain senile plaques at this age. Based on *in vitro* experiments, we found that Rh2 treatment increased soluble APPα (sAPPα) levels, increased CTFα/β ratios, and reduced amyloid beta 40

and 42 concentrations. Surface APP levels dramatically increased. Based on living cell staining, we found that Rh2 inhibited APP endocytosis. Based on lipid removal and reload experiments, we found that Rh2 can modulate APP by reducing cholesterol and lipid raft levels. We concluded that Rh2 improves learning and memory function in Alzheimer's disease model mice, and that this improvement is accomplished by reducing amyloid beta secretion and APP endocytosis, which in turn is achieved by reducing cholesterol and lipid raft concentrations.