NEUROPROTECTIVE SIGNALING PATHWAY VIA NICOTINIC RECEPTORS

T. Kume\textsuperscript{1} and A. Akaike\textsuperscript{1,2}
\textsuperscript{1}Graduate School of Pharmaceutical Sciences, Kyoto University, Japan and \textsuperscript{2}Graduate School of Pharmaceutical Sciences, Nagoya University

**Introduction.** Our previous data showed that treatment of nicotine or donepezil prevented glutamate-induced cytotoxicity via nicotinic receptors (nAChRs) using primary culture of rat cortical neurons. The present study was performed to investigate the detailed mechanisms of nAChR-mediated neuroprotection, especially involvement of glycogen synthase kinase-3β (GSK3β) as a downstream of PI3K-Akt pathway.

**Methods.** Neuronal death was determined by LDH release assay in rat primary culture of cerebral cortex. Phosphorylation of GSK3β and the expression level of β-catenin were measured by western blot analysis.

**Results and Conclusion.** Donepezil induced the Ser9-phosphorylation of GSK3β in rat cultured cortical neurons. LY294002, an inhibitor of PI3K, prevented that phosphorylation of GSK3β. Glutamate induced the Tyr216-phosphorylation of GSK3β. Donepezil prevented glutamate-induced phosphorylation of Tyr216. Bcl-2 was upregulated by donepezil treatment, but not by SB216763, an inhibitor of GSK3β treatment. On the other hand, the expression level of β-catenin was increased by both donepezil and SB216763. These results suggested that inactivation of GSK3β as the downstream signaling of PI3K-Akt pathway play a crucial role in the nAChR-mediated neuroprotection.