Neuroprotection against cerebral ischemic injury via VNUT-mediated pathway

Yuri Hirayama[1,2], Ha Pham Ngoc Le[2], Schuichi Koizumi[2], Naohiko Anzai[1]

[1]Dept. Pharmacol., Grad. Sch. Med., Chiba Univ., [2]Dept. Neuropharmacol., Interdisciplinary Grad. Sch. Med., Univ. Yamanashi

ATP is known to be increased in response to transient cerebral ischemia, but whether ATP increase is beneficial or harmful to ischemic injury is controversial, and a mechanism underlying the ATP increase is not clearly understood. Here, we show that the ATP exocytosis via microglial vesicular nucleotide transporter (VNUT) contributes to neuroprotection against cerebral ischemic injury. Using *in vivo* middle cerebral artery occlusion (MCAO) in mice, we found that extracellular ATP levels were increased and persisted at high levels until 3 days after MCAO in WT mice, but not in VNUT knockout mice. Cerebral ischemia increased expression of VNUT preferentially in microglia in the ischemic region and VNUT deficiency exacerbated cerebral infarction following MCAO, which indicated neuroprotective potential of microglial VNUT. In order to investigate the mechanism of VNUT upregulation, cytokine array was performed. We focused on IL-6, which was significantly increased at 1 day after MCAO, and found that when added to cultured microglia, IL-6 was able to induce microglial VNUT mRNA upregulation in *in vitro* experiment. Taken together, VNUT upregulated in response to ischemia via IL-6-mediated mechanism has a vital role for exocytosis of ATP from microglia and the events induce neuroprotection against ischemic injury.