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The protective role of proton-sensing TDAG8 in the brain injury in a mouse ischemia reperfusion model

Koichi Sato[1], Ayaka Tobo[1], Chihiro Mogi[1], Masayuki Tobo[1], Nobuhiro Yamane[2], Masahiko Tosaka[2], Hideaki Tomura[3], Dong-Soon Im[4] & Fumikazu Okajima[5]
[1]Laboratory of Signal Transduction, Institute for Molecular and Cellular Regulation, Gumma University, Maebashi, Japan
[2]Department of Neurosurgery, Gumma University Graduate School of Medicine, Maebashi, Japan
[3]Laboratory of Cell Signaling Regulation, Department of Life Sciences, School of Agriculture, Meiji university, Kawasaki, Japan
[4]College of Pharmacy, Kyung Hee University, Seoul, Republic of Korea
[5]Laboratory of Signal Transduction, Faculty of Pharmaceutical Sciences, Aomori University, Aomori, Japan

Abstract:

Extracellular acidification in the brain has been observed in ischemia; however, the physiological and pathophysiological implications of the pH reduction remain largely unknown. Here, we analyzed the roles of proton-sensing G protein-coupled receptors, including T-cell death-associated gene 8 (TDAG8), ovarian cancer G protein-coupled receptor 1 (OGR1), and G protein-coupled receptor 4 (GPR4) in a mouse ischemia reperfusion model. Cerebral infarction and dysfunctional behavior with transient middle cerebral artery occlusion (tMCAO) and subsequent reperfusion were exacerbated by the deficiency of TDAG8, whereas no significant effect was observed with the deficiency of OGR1 or GPR4. We confirmed that the pH of the predicted infarction region was 6.5. TDAG8 mRNA was observed in Iba1-positive microglia in the mouse brain. The tMCAO increased the mRNA expression of tumor necrosis factor-α in the ipsilateral cerebral hemisphere and evoked morphological changes in microglia in an evolving cerebral injury. These tMCAO-induced actions were significantly enhanced by the TDAG8 deficiency. Administration of minocycline, which is known to inhibit microglial activation, improved the cerebral infarction and dysfunctional behavior induced by tMCAO in the TDAG8-deficient mouse. Thus, acidic pH/TDAG8 protects against cerebral infarction caused by tMCAO, at least due to the mechanism involving the inhibition of microglial functions.

Keywords: Ischemia, extracellular acidification, TDAG8, mouse ischemia perfusion model, cerebral infarction, pH