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EPAC2-DEFICIENCY LEADS TO MORE SEVERE NEUROLOGICAL DEFICIT AND LARGER INFARCT WITH HIGHER GLIAL REACTIVITY AFTER TRANSIENT MIDDLE CEREBRAL OCCLUSION

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Introduction: Exchange proteins activated by cAMP (Epac1 and Epac2) belong to a family of cAMP-regulated guanine nucleotide exchange factors (cAMPGEFs) for the small GTPases, Rap1 and Rap2[1]. Epac1 was thought to be important in maintenance of tight and adhesion junctions between endothelial cells[2] , suggesting that Epac may play an important role in blood brain barrier (BBB) function.

Objective: Previously, it was shown that Epac2 mRNA is expressed in the brain[3]. Here, the protein expression of Epac2 was determined and compared to that of Epac1. In addition, the role of Epac2 was determined in the BBB and brain function after ischemia/reperfusion injury.

Method: Six regions of brain from Epac2 wild type ($Epac2^{+/+}$) mice was dissected, and proteins were extracted in order to determine the expression of Epac1 and Epac2 under normal and ischemic condition by Western blot analysis. $Epac2^{+/+}$ and homozygous Epac2 knockout ($Epac2^{-/-}$) [4] mice were exposed to 2 hrs of middle cerebral artery occlusion followed by 22 hrs of reperfusion (tMCAO). Then, the neurological score was determined. The infarct and edema in ipsilateral side was determined by TTC stained brain section. After tMCAO, contralateral and ipsilateral hemispheres of brains were collected for histological and biochemical analyses, including Western blot analysis, RT-PCR, and immunocytochemistry.

Results: Under normal condition, Epac1 and Epac2 are widely expressed in the various regions of brain of $Epac2^{+/+}$ mice, including olfactory bulb, cerebellum, brainstem, cortex, midbrain and hippocampus. We have confirmed that Epac2 is absent in the brain of $Epac2^{-/-}$ mice. Interestingly, there was no compensation by Epac1 in brain of $Epac2^{-/-}$ mice, which showed no obvious abnormality in brain. However, $Epac2^{-/-}$ knockout mice showed significantly more severe neurological deficits, larger infarct volume and edema compared to those of $Epac2^{+/+}$ mice after tMCAO. The ipsilateral hemisphere of $Epac2^{-/-}$ brain also showed higher GFAP expression.

Conclusion: Taken together, Epac2 may not contribute to brain function under normal condition. However, Epac2 may protect the brain from ischemia/reperfusion injury. Currently, the detailed mechanisms of protective role of Epac2 in I/R brain injury is being further investigated.

References:

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