Role of NLRP3 Inflammasome in Cortical Spreading Depression-Induced Inflammatory Responses in Mice

Hsun-Ting Hsieh¹, Shih-Pin Chen^{2,3}, Shuu-Jiun Wang^{3,4,5}, Jiin-Cherng Yen¹

¹*Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan,* ²*Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan,* ³*Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan,* ⁴*Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan,* ⁵*Brain Research Center, National Yang-Ming University, Taipei, Taiwan*

Background:

Cortical spreading depression (CSD) is the pathophysiological basis of migraine aura and the trigger of migraine headache. It is known that CSD can induce caspase-1 activation leading to release of interleukin-1 β (IL-1 β) from neurons. However, the mechanism underlying CSD-induced neuronal caspase-1 activation remains unclear. The present study was aimed to investigate the role of NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome in CSD-induced neuroinflammation in cerebral cortex.

Methods:

C57BL/6 mice were used and anaesthetized with isoflurane. The skulls of mice were then drilled for 2 burr holes. The caudal hole was served for CSD induction, the rostral one was for CSD recording. CSD was recorded by a glass microelectrode with a diameter less than 1 μ m. KCl (300 mM) absorbed in a cotton ball was used to induce CSD.

Results:

The expression of NLRP3 protein in cerebral cortex was found to be increased by KCl-induced CSD in a time-dependent manner. Moreover, the protein level of caspase-1, an auto-cleaved product following inflammasome formation, was significantly increased in mice cortex following CSD generation induced by KCl for 2 hours. Similarly, CSD generation significantly enhanced the production of IL-1 β which was generated from an inactive precursor form subsequent to caspase-1 activation, in mice cortex. We further found that the increased protein levels of caspase-1 and IL-1 β were suppressed by pretreatment with MCC950, an inhibitor of NLRP3 inflammasome activation.

Conclusion:

CSD may increase caspase-1 and IL-1 β production via NLRP3 inflammasome activation in mice cortex.