S57-4 Pathophysiological roles of TRP channels in glial cells

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Microglia, the resident innate immune cells in brain, have important roles in defense for the neural parenchyma, whereas chronic or uncontrolled activation of microglia can induce damage to neurons, therefore, regulation of microglial activation could be important in limiting secondary damage following neuroinflammation. Transient receptor potential (TRP) superfamily comprises a group of non-selective cation channels, some members of which are expressed in microglia; however their physiological roles remain to be elucidated. Here we will provide an overview of the physiological roles of TRP channels in the process of microglial activation, especially focusing on TRPV4 and TRPM2 channels. Using cultured microglia, we found that LPS, a potent stimulus for microglial activation, decreased the expression level of TRPV4 mRNA and Ca^{2+} responses induced by a TRPV4 selective agonist 4αPDD. Moreover, we observed that simultaneous application of 4α-PDD suppressed LPS-induced increases in the expression of galectin-3/MAC-2, a marker of activated microglia, the release of nitric oxide (NO) and TNF-α and its suppression was cancelled by TRPV4 antagonists or TRPV4 knockdown using siRNA. On the other hand, we found that LPS-induced NO release was attenuated in cultured microglia from TRPM2-KO mouse than in those from WT mouse, which may involve paracrine/autocrine augmentation of microglial activation by reactive oxygen species production. Taken together, microglial activation could be regulated in opposite direction by TRPV4 and TRPM2. We will mention their possibility of being targets for drugs in stressful conditions related to abnormal inflammatory responses in brain.