Activation of toll-like receptor 4 induces downregulation of sigma-1 receptor in microglia

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Background: Inflammatory responses could be involved in induction of neurodegenerative diseases. Microglia are known to act as the main immune cell in the central nervous system, and contribute to regulate inflammatory reactions in the brain. The activation of sigma 1 receptor (Sig1R) in microglia is neuroprotective, while microglial Sig1R expression is reduced in the brains of patients with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. The current study has investigated mechanisms underlying downregulation of microglial Sig1R expression by activation of toll-like receptor 4 (TLR4), which plays an important role in inflammatory responses.
Method: Primary cultured microglia were prepared from the cortex of neonatal Wistar rats. Expression levels of mRNA or protein were measured by the real-time PCR or Western blot, respectively.
Results: TLR4 activation by ☒lipopolysaccharide(LPS), an agonist of TLR4, significantly reduced the expression level of microglial Sig1R in dose and time dependent manner. Inhibition of p38 mitogen-activated protein kinases (p38 MAPK) and histone deacetylase (HDAC) restored decrease of Sig1R mRNA levels. Among HDACs, HDAC6 was specifically involved in the LPS-induced downregulation of Sig1R.
Conclusions: The current study indicates that the expression level of Sig1R in microglia is regulated via p38 MAPK and HDAC6 under inflammatory conditions.