1. **No.**

   FP01912183

2. **Title**

   Therapeutic Strategy for Alzheimer's Disease Based on the Regulation of α7 Nicotinic ACh Receptor Functions in Brain Microglia

3. **Period**

   2016-2020

4. **Summary**

   Treatment of primary cultured microglia or BV2 cells with LPS significantly decreased the expression of α7-nAChR via the stimulation of toll-like receptor 4 (TLR4). In BV2 cells, the LPS-induced downregulation of α7-nAChR mRNA was mediated by histone deacetylase (HDAC) 2 and HDAC3. Treatment of BV2 cells with LPS decreased acetylation of H3K9. In addition, treatment of BV2 cells with LPS significantly reduced the level of acetylated histone H3 bound to the α7 nAChR promoter compared to levels of vehicle-treated cells. TMEM35A mRNA was not expressed in both primary cultured microglia and BV2 cells. Treatment of primary microglia with nicotine did not increase intracellular Ca2+concentraion. After overexpression of α7-nAChR in HEK293T cells and fractionation of intracellular organelles, the expression of α7-nAChR was mainly detected in the fraction of mitochondria and mitochondria-associated membrane.

   Intraperitoneal treatment of mice with LPS induced cognitive impairment. The LPS-induced cognitive impairment was significantly prevented by pretreatment with either a microglial inhibitor minocycline or an HDAC inhibitor suberoylanilide hydroxamic acid (SAHA). Intraperitoneal treatment of mice with LPS induced the activation of microglia in hippocampus, and this effect was significantly prevented by pretreatment with SAHA. The current study demonstrates that the TLR4-HDAC2/3 pathway is crucial in the regulation of α7-nAChR in microglia, and this may contribute to induction of cognitive dysfunction under neuroinflammatory condition. In addition, α7-nAChR may play unique roles through regulation of mitochondrial function in microglia.