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   2020Y007

2. Title
   Regulation of Microglial Polarization to M1/M2 Phenotype by Nicotinic Receptors in Intracerebral Hemorrhage

3. Period
   2020-2022

4. Summary
   We previously revealed that long-term treatment with nicotine suppresses microglial activation, resulting in a protective effect against thrombin-induced shrinkage of the striatal tissue in organotypic slice cultures. Here, the effect of nicotine on impaired M1 and protective M2 microglial polarization was investigated using the BV-2 microglial cell line in the presence or absence of thrombin. Following nicotine treatment, α7 nicotinic acetylcholine receptor expression transiently increased and then gradually decreased until 14 days. Treatment with nicotine for 14 days slightly polarized M0 microglia to M2b and d subtypes. Co-exposure of thrombin and low concentration of interferon-γ recruited inducible NO synthase (iNOS)- and interleukin-1β-double-positive M1 microglia in a thrombin-concentration-dependent manner. Treatment with nicotine for 14 days significantly decreased the thrombin-induced increase of iNOS mRNA levels and conversely showed a tendency to increase arginase1 mRNA levels. Moreover, treatment with nicotine for 14 days suppressed thrombin-induced phosphorylation of p38 MAPK through the α7 receptor. Repeated intraperitoneal administration of α7 agonist PNU-282987 for 14 days selectively evoked the apoptosis of iNOS-positive M1 microglia at the perihematomal area and showed a neuroprotective effect in an *in vivo* intracerebral hemorrhage model. These findings revealed that long-term stimulation of α7 receptor causes suppression of thrombin-induced activation of p38 MAPK followed by apoptosis in neuropathic M1 microglia.