Inflammatory macrophages mediate neuropathic pain caused by type 2 diabetes mellitus

Norikazu Kiguchi, Fumihiro Saika, Daichi Kobayashi, Shinsuke Matsuzaki, Shiroh Kishioka

Department of Pharmacology, Wakayama Medical University, Japan

Type 2 diabetes mellitus (T2DM) is a common metabolic disease results in long-term complications associated with the dysfunction of nervous system, and more than 50% of patients eventually experience neuropathic pain. Given that peripheral neuroinflammation driven by inflammatory macrophages plays a pivotal role in the pathogenesis of neuropathic pain in rodent models of neuropathic pain following peripheral nerve injury, it is pivotal to determine whether inflammatory macrophages contribute to the pathogenesis of neuropathic pain caused by T2DM in mice.

C57BL/6J mice were fed high fat diet (HFD) or control diet ad libitum. In mice fed HFD, body weight rapidly increased, and hyperglycemia was observed on 4 weeks and persisted for at least 24 weeks during HFD feeding. The 50% paw withdrawal threshold evaluated by von Frey test was significantly decreased on 16 weeks in mice fed HFD, indicating mechanical allodynia. The mRNA expression levels of macrophage markers CD11b, CD68, and F4/80 were upregulated in the sciatic nerve (SCN) on 16 weeks in mice fed HFD compared to control mice, suggesting infiltration of macrophages in the SCN. Moreover, pro-inflammatory cytokines (IL-1β and TNFα) and chemokines (CC-chemokine ligand 3 (CCL3) and CCL4) were also upregulated in the SCN, being consistent with macrophage infiltration.

Because we previously found that α4β2 subtype of nicotinic acetylcholine receptor (nAChR) was able to suppress inflammatory macrophages, we examined the effects of TC-2559, an α4β2 nAChR agonist, on mechanical allodynia in mice fed HFD. Perineural administration of TC-2559 in the surrounding of SCN on 4 consecutive days from 16 weeks of HFD feeding attenuated mechanical allodynia. In addition, systemic administration of TC-2559 according to same schedule also improved mechanical allodynia in mice fed HFD, indicating that the developed allodynia associated with T2DM was relieved by TC-2559 treatments.

These results suggest that inflammatory macrophages underlie neuropathic pain induced by not only peripheral nerve injury but also T2DM. Further investigations are warranted to determine a fundamental role of inflammatory macrophages in diabetic neuropathic pain and to develop novel pharmacotherapy targeting to treat intractable neuropathic pain.