Nerve conduction blockade in the sciatic nerve prevents but does not reverse the activation of p38 mitogen-activated protein kinase in spinal microglia in the rat spared nerve injury model

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摘要

Abstract

BACKGROUND: Current evidence indicates that p38 mitogen-activated protein kinase activation in spinal microglia contributes to the development of neuropathic pain. However, how nerve injury activates p38 in spinal microglia is incompletely unknown. Nerve injury-induced ectopic spontaneous activity is essential for the generation of neuropathic pain. The authors examined whether peripheral neural activity is necessary for p38 activation in spinal microglia. METHODS: To examine whether spinal microglia activation depends on peripheral activity in the rat spared nerve injury (SNI) model, the authors blocked conduction in the sciatic nerve before or 2 days after SNI. The block was produced by applying bupivacaine-loaded microspheres above the nerve injury site. The p38 activation was examined by p38 phosphorylation using a phosphorylated p38 antibody, and neuropathic pain-related behavior was evaluated before and after intrathecal infusion of a p38 inhibitor. RESULTS: Three days after SNI, there was a marked p38 activation in the medial two thirds of the dorsal horn, where the injured tibial and peroneal nerves terminated and where isolectin B4 staining was lost. Phosphorylated p38 was only colocalized with the microglial surface marker OX-42, indicating a microglial localization of phosphorylated p38 in the SNI model. Bupivacaine microspheres produced persistent block (loss of sensory and motor function) of the sciatic nerve for the whole period of the study (3 days). This blockade prevented but did not reverse p38 activation in spinal microglia. Intrathecal infusion of the p38 inhibitor FR167653 prevented and reversed mechanical allodynia on post-SNI day 3. CONCLUSIONS: After nerve injury, activity in the peripheral nerve is required for the induction but not the maintenance of p38 activation in spinal microglia.