A peptide JNK inhibitor blocks mechanical allodynia after spinal nerve ligation: respective roles of JNK activation in primary sensory neurons and spinal astrocytes for neuropathic pain development and maintenance

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摘要

Abstract

Optimal management of neuropathic pain is a major clinical challenge. We investigated the involvement of c-Jun N-terminal kinase (JNK) in neuropathic pain produced by spinal nerve ligation (SNL) (L5). SNL induced a slow (>3 d) and persistent (>21 d) activation of JNK, in particular JNK1, in GFAP-expressing astrocytes in the spinal cord. In contrast, p38 mitogen-activated protein kinase activation was found in spinal microglia after SNL, which had fallen to near basal level by 21 d. Intrathecal infusion of a JNK peptide inhibitor, D-JNKI-1, did not affect normal pain responses but potently prevented and reversed SNL-induced mechanical allodynia, a major symptom of neuropathic pain. Intrathecal D-JNKI-1 also suppressed SNL-induced phosphorylation of the JNK substrate, c-Jun, in spinal astrocytes. However, SNL-induced upregulation of GFAP was not attenuated by spinal D-JNKI-1 infusion. Furthermore, SNL induced a rapid (<12 h) but transient activation of JNK in the L5 (injured) but not L4 (intact) DRG. JNK activation in the DRG was mainly found in small-sized C-fiber neurons. Infusion of D-JNKI-1 into the L5 DRG prevented but did not reverse SNL-induced mechanical allodynia. Finally, intrathecal administration of an astroglial toxin, L--aminoadipate, reversed mechanical allodynia. Our data suggest that JNK activation in the DRG and spinal

cord play distinct roles in regulating the development and maintenance of neuropathic pain, respectively, and that spinal astrocytes contribute importantly to the persistence of mechanical allodynia. Targeting the JNK pathway in spinal astroglia may present a new and efficient way to treat neuropathic pain symptoms.