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CCR5 is an important pathological regulator in the development and maintenance of neuropathic pain

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Abstract

Neuropathic pain is a reflection of aberrant functioning of pathologically altered nervous systems, which is often caused by peripheral nerve injury and represented by one hallmark called tactile allodynia (pain hypersensitivity to innocuous stimuli). The mechanism underlying development of tactile allodynia remains largely unknown. Recent studies have revealed that several molecules of chemokine family is involved in the pathogenesis of neuropathic pain. However, chemokine family and also chemokine receptor family consist of large number of molecules, and there are sophisticated signal crosstalk between each ligand and receptor set. Here we found that single intrathecal administration of recombinant CC chemokine ligand 3 (CCL3) produce two phase tactile allodynia. In the first phase, the paw withdrawal threshold (PWT) to mechanical stimulation decreased over first 30 minutes and the recovery persisted for 5 hours. However the PWT decreased again from 24 hours to 10 days in the second phase. The first phase clearly suppressed by a C-C chemokine receptor type 1 (CCR1) antagonist pretreatment but second phase was not affected. The second phase was dose-dependently suppressed by a C-C chemokine receptor type 5 (CCR5) antagonist that treated simultaneously with CCL3. Thus CCL3 has dual effect for pain induction; acute and transient effect and slowly developing long lasting effect. In the model of neuropathic pain that caused by surgically injured peripheral nerve, the level of CCL3 and CCR5 mRNA but not CCR1 mRNA was significantly increased in ipsilateral spinal cord after nerve injury. This increase was observed from day1 to day14 after nerve injury. Intrathecal injection of the CCR5 antagonist and CCL3 neutralizing antibody successfully suppressed the development of neuropathic pain. Furthermore, we found the CCR5 antagonist can reverse the established neuropathic pain. These results suggest that one of the chemokine signaling triggered by CCL3 has crucial role in the mechanism of neuropathic pain. Thus, CCR5 might be a effective therapeutic target for pain induced after nerve injury.