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## Role of Neuroinflammation in Opioid Tolerance: Translational Evidence from Human-to-Rodent Studies.

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### Abstract

Opioid analgesics remain the most effective and widely used analgesics for the management of moderate to severe pain, including cancer pain and chronic non-cancer pain. However, the efficacy of long-term opioid analgesics is attenuated by tolerance and/or hyperalgesia after long-term use, preventing adequate pain relief under stable opioid dosages for chronic pain patients. Classical neuron-centered concepts about tolerance, such as internalization of opioid receptors, upregulation of N-methyl-D-aspartate receptor function, or downregulation of glutamate transporter activity, can only partially explain the phenomenon of tolerance. Recent evidence revealing glial activation and upregulation of inflammatory mediators in the rodent central nervous system has confirmed the pivotal role of neuroinflammation in neuropathic pain or opioid tolerance, or both. However, human evidence is still sparse. Based on our clinical practice, we conducted translational research by investigating the cerebrospinal fluid (CSF) cytokine and chemokine profiles of opioid-tolerant patients after research ethic committee approval. CSF samples from opioid-tolerant patients and opioid-naive subjects were compared. We found CXCL1, CXCL12, and leukemia inhibitory factor (LIF) were significantly upregulated among the opioid-tolerant patients and positively correlated with the opioid dosage. We translated these findings back to lab animal experiment; after induction of tolerance by morphine infusion, the spinal cord expression of CXCL1, CXCL12, and LIF were all upregulated. Although CXCL1 and CXCL12 infusion alone did not affect baseline tail-flick latency, morphine analgesic efficacy dropped significantly after intrathecal infusion of CXCL1 and CXCL12. After establishing tolerance by intrathecal continuous infusion of morphine, tolerance development was accelerated by co-administration of CXCL1 and CXCL12. In parallel, the effect was attenuated by co-administration of CXCL1- or CXCL12-neutralizing antibody or concordant receptor antagonists. On the contrary, although chronic morphine administration still induced

LIF upregulation in rat spinal cords, intrathecal injection of LIF potentiated the analgesic action of morphine and delayed the development of morphine tolerance. Upregulation of endogenously released LIF by long-term use of opioids might counterbalance the tolerance induction effects of other pro-inflammatory cytokines. CXCL1, CXCL12, and LIF are upregulated in both opioid-tolerant patients and rodents. The onset and extent of opioid tolerance were affected by modulating the intrathecal CXCL1/CXCR2, CXCL12/CXCR4, and LIF signaling and could be novel drug targets for the treatment of opioid tolerance.

**KEYWORDS:** Chemokine; Cytokine; Neuroinflammation; Opioid tolerance; Translational research

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