

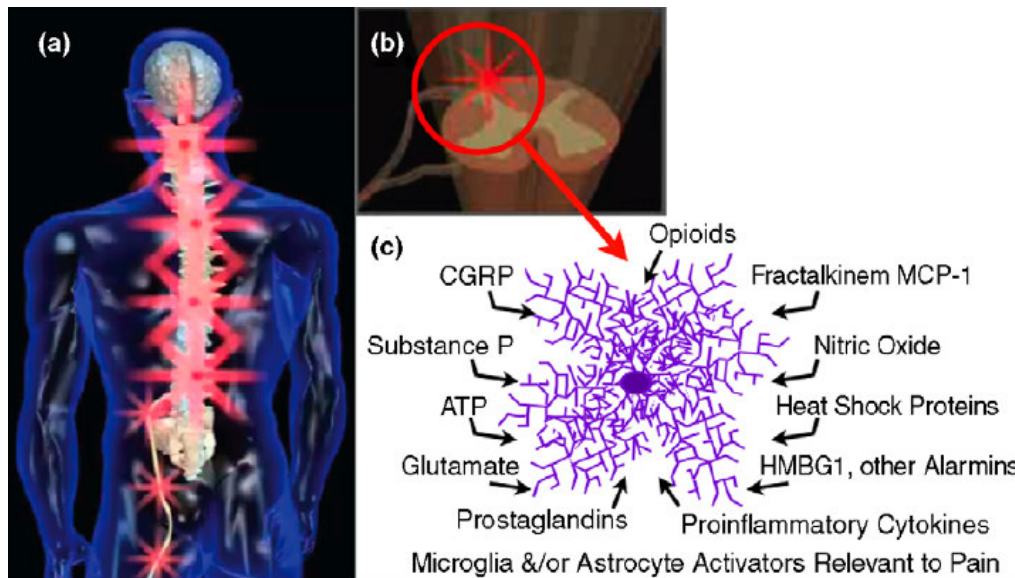
**Listening and Talking to Neurons:
Clinical Implications of Glial Dysregulation of Pain and Opioid Actions**

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Concepts of chronic pain and opioid actions have evolved in recent years. Among the most important developments has been the recognition that proinflammatory activation of glia—microglia and astrocytes—in the central nervous system (CNS) can be beneficial or harmful, depending on the conditions under which activation occurs. Glial activation is beneficial when it helps to resolve CNS immune challenges and facilitate neuroprotection. In chronic pain states and during opioid exposure, however, activated glia are proinflammatory, and they enhance pain and contribute to opioid tolerance, dependence, reward, and respiratory depression.¹⁻⁴

Astrocytes, developmentally derived from the neuroectoderm, are the most abundant glial cell type in the CNS.² In addition to their neuron-supportive functions, astrocytes also directly alter neuronal communication because they completely encapsulate synapses and are in close contact with neuronal somas.⁵ Resident microglia are bone marrow-derived hematopoietic cells that invade the CNS during embryonic development and are never replenished.² Resident microglia are known to survey the CNS and to proliferate rapidly on activation, exerting both inflammatory and anti-inflammatory effects.⁶

Recognition that activation of microglia and astrocytes is critical to pain enhancement is based on evidence from cell culture, anatomy, and in vivo studies.^{1,7} Cell culture studies provided the first evidence that spinal cord glia are responsive to pain-related neurotransmitters when they showed that the spinal cord is one of the few CNS sites where substance P activates astrocytes. Anatomy studies characterized the process of glial activation—(a) peripheral nerve injury triggers spinal amplification; in the spinal cord dorsal horn (b), glia and other immunocompetent cells amplify pain signals by releasing microglial and astrocyte activators (c)¹—and demonstrated that drugs used for neuropathic pain block glial activation.



In vivo studies, by inducing changes in physiology and behavior (eg, suppressing food and water intake), showed that many sickness responses, including enhanced pain, are created as a result of glial activation and proinflammatory cytokine release in the brain and spinal cord.

Several laboratories have reported activation of glia and release proinflammatory products in response to opioids.⁸⁻¹⁰ In vivo, opioid-induced glial activation has been inferred from morphine-induced upregulation of microglial and astrocytic activation markers [30,31] and release of proinflammatory cytokines and chemokines^{9,11-13}; enhanced morphine analgesia by glial activation inhibitors^{11,14,15} and proinflammatory cytokine blockers^{9,16}; and opioid-induced selective activation of microglial p38 MAPK and enhanced morphine analgesia by p38 MAPK inhibitors.¹⁷ In vitro studies have confirmed that opioids act directly on glia.^{14,18-20}

Opioids were once assumed to affect glia only through opioid receptors. But it is now known that the effects can occur via non-stereoselective activation of toll-like receptor 4 (TLR4), a glial receptor that also reverses neuropathic pain and mitigates opioid dependence and reward.¹ Moreover, a novel antagonism of TLR4 by (+)- and (-)- isomer opioid antagonists appears to potentiate antiallodynic and morphine analgesia. TLR4, one of multiple receptor-mediated activation pathways, facilitates glial activation and neuroexcitability under conditions of chronic pain and in response to opioids.¹

It appears that glia-targeting agents have begun to make an important transition from experimental compounds to approved medications. Robust evidence in rodent models^{21,22} has prompted the US Food and Drug Administration to clear ibudilast and propentofylline for Phase 2 clinical trials in neuropathic pain, with ibudilast also being cleared for evaluation as an opioid adjuvant. Ibudilast, a known TLR4 signaling inhibitor,¹ has been used for the treatment of asthma and post-stroke dizziness, and propentofylline has been tested in humans as far as Phase 3 trials for treating Alzheimer's disease.

Research has shown that glia are key contributors to pathological and chronic pain mechanisms, a discovery that may soon yield safe, effective medications that enhance the ability of opioids to relieve pain while reducing their risk of side effects and abuse. Given the high prevalence of chronic pain and the partial efficacy of currently available treatment options, new strategies to manipulate neuron-glia interactions in pain processing hold considerable promise.

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