



Glia: Non-neural Players in Orofacial Pain

The upsurge of pain research over the last 2 decades has provided important new insights into the cellular, molecular, and integrative neural processes in pain and its management. However, there has also been a gradual awareness of a novel set of non-neural mechanisms intimately involved in pain, particularly chronic pain. Some of these mechanisms were reviewed in the plenary presentation given by Linda Watkins (University of Colorado) at the annual meeting of the American Academy of Orofacial Pain, which was held in Philadelphia in April this year. I wish to highlight further the importance of these non-neural mechanisms and what they may mean for orofacial pain.

As pointed out in this journal in 2004,¹ the predominant focus of neuroscience research related to pain has been on the role of neurons; however, non-neural cells called glia outnumber neurons by approximately 10 to 1 in the central nervous system (CNS). There are 3 main types of glia (astrocytes, microglia, and oligodendrocytes), and the view that glia serve primarily a supportive role in neuronal cell function, protecting and aiding the repair and regeneration of damaged neurons, has radically changed in recent years. It is becoming clear that while glia may not directly transmit pain signals in the CNS, they may modulate nociceptive transmission by releasing a variety of substances that they synthesize and thereby contribute to the pathophysiological processes underlying pain associated with nerve injury or inflammation of peripheral tissues. Their peripheral “cousins,” satellite cells adjacent to peripheral nerve fibers and primary afferent neurons, may contribute to some peripheral nociceptive mechanisms.

In the case of the role in pain of glia in the CNS, microglia and astrocytes appear to be the key non-neuronal elements. Not only do they release a host of substances that can influence the excitability of neurons involved in nociceptive transmission in the CNS—for example, so-called proinflammatory cytokines (such as tumor necrosis factor- α and interleukin-1 (IL-1)), prostaglandins, adenosine triphosphate (ATP), excitatory amino acids (such as glutamate) and nitric oxide—but also they themselves have receptors and ion channels sensitive to neurotransmitters and neuromodulators such as ATP, glutamate, substance P, nitric oxide, proteins (such as fractalkine), pathogens, and products of

other non-neural cells.^{1,2} Microglia, in particular, monitor the CNS environment for pathogens and debris and thus participate in the immune system responses to infection and sickness as well as in neural modulation. The astrocytes encapsulate synapses and can respond to synaptically released neurotransmitters and neuromodulators by releasing substances into the synapse and thereby influencing the function of neurons. Thus, glia in pain-related regions of the CNS, such as the spinal dorsal horn and trigeminal brainstem subnucleus caudalis (also termed the medullary dorsal horn), can be activated by nociceptive afferent inputs evoked in inflammatory and nerve-injury conditions and so modulate nociceptive transmission. Furthermore, they may also be recruited by other non-neural cells in the CNS (eg, fibroblasts, endothelial cells) that release proinflammatory cytokines and thereby represent integral components of “sickness responses” as well as pain.² In addition, some drugs administered to alleviate pain (eg, morphine) may activate glia; thus, glia may counteract the pain suppression intended with such drug treatments. Also of interest is that while disruption of glial cell function or blockade of the actions of glial-derived substances in animal models of inflammatory or neuropathic pain can markedly interfere with the hyperalgesia and allodynia that characterize many chronic pain states, several spinal studies have reported that such manipulations do not affect thermal or mechanical pain thresholds.² This suggests that glia may not play a significant role in normal pain processing but rather are involved in exaggerated pain states.

Do glia have a role in orofacial pain conditions? A growing body of evidence is beginning to indicate that they do. There are reports in trigeminal pain models that microglial activation occurs after facial injury and that glial inhibition can ameliorate inflammatory or nerve injury-induced allodynia.^{3–6} Furthermore, the cellular and molecular mechanisms underlying these pain behavioral consequences of glia inhibition are starting to be unraveled in trigeminal brainstem studies. Central sensitization is an N-methyl-D-aspartate (NMDA) receptor-dependent process; it is considered a major CNS mechanism underlying hyperalgesia and allodynia. Xie et al⁷ and Chiang et al⁸ have recently provided the first documentation in either the spinal or trigeminal nociceptive systems that central sensi-

zation (induced by inflammatory irritant application to the rat molar pulp) in functionally identified dorsal horn nociceptive neurons can be abolished by application to the caudal brainstem of inhibitors that suppress astrocytic metabolic processes or release of modulatory substances from astrocytes. In contrast, they found that the normal nociceptive responses in the neurons were unaffected, supporting findings published in the spinal literature that glia play an important role in exaggerated pain states but not in normal pain processing. Moreover, Guo et al⁶ have recently provided evidence in their rat model of chronic masseter muscle inflammatory hyperalgesia that the nociceptive afferent input to the CNS in this model leads to the induction of cytokines and other chemical mediators in caudalis glia that augment central sensitization and lead to enhanced orofacial pain. Their data especially implicate the cytokine IL-1 released from astrocytes and NMDA receptors in caudalis neurons and indicate that glia and cytokines may interact with neurons in this inflammatory model of hyperalgesia.

The recent focus on glial mechanisms in pain, including the evidence for their involvement in trigeminal inflammatory and neuropathic pain models, has shed new light on the processes involved in conditions manifesting pain hypersensitivity, and further studies promise to provide additional insights into how the immune system can interact with the nociceptive system and thereby influence pain expression in acute and chronic pain and various types of sicknesses. Further studies of glial-neuronal interactions and the underlying processes hold out promise from another aspect. The information provided will also be fundamental in identifying new targets that may lead to better outcomes in analgesic therapies. Such therapies may help prevent the initiation of inflammatory or neuropathic pain associated with orofacial tissues as well as promote the relief of such pain, possibly without compromising normal nociceptive processing per se. Since almost all centrally acting therapies for pathological pain have been developed explicitly to target neurons, shifting the focus of drug therapies to include modulation of glial function would provide a novel approach to control pain.



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