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Spinal glia and chronic pain

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Abstract

Therapeutic management of chronic pain has not been widely successful owing to a lack of understanding of factors that initiate and maintain the chronic pain condition. Efforts to delineate the mechanisms underlying pain long have focused on neuronal elements of pain pathways, and both opiate- and non–opiate-based therapeutics are thought largely to target neurons. Abnormal neuronal activity at the level of spinal cord "pain centers" in the dorsal horn leads to hypersensitivity or a hyperalgesic response subsequent to the initial painful stimulus. Only recently has the experimental literature implicated nonneuronal elements in pain because of the realization that glial-derived signaling molecules can contribute to and modulate pain signaling in the spinal cord. Most notably, glial proinflammatory mediators within the dorsal horn of the spinal cord appear to contribute to self-perpetuating pain. Chronic pain is modeled experimentally through a variety of manipulations of sensory nerves including cutting, crushing, resection, and ligation. The cellular and molecular responses in the spinal cord due to these manipulations often reveal activation of 2 types of glia: microglia and astrocytes. The activation states of both microglia and astrocytes are complex and may be driven by underlying chronic neuropathology and/or a chronically "primed" condition that accounts for their contribution to chronic pain. Recent evidence even suggests that opioid tolerance and withdrawal hyperalgesia may be initiated and maintained via actions of microglia and astroglia. Together, these recent findings suggest that glia will serve as novel therapeutic targets for the treatment of chronic pain. To fully exploit glia as novel therapeutic targets will require a greater understanding of glial biology, as well as the identification of agents able to control the glial reactions involved in chronic pain, without interfering with beneficial glial functions.

1. The problem

Even today, a large number of people suffer from chronic pain at a significant cost to society and the individual [1]. The inadequacy of the available therapies to treat chronic pain frustrates both patient and physician. Normally, pain is brief and serves a protective role by alerting the individual to possible tissue destruction; and it initiates an immediate withdrawal response. Under many different circumstances, pain becomes pathologic and chronic; chronic pain can occur following tissue injury, central and peripheral nerve damage, disease, stroke, infection, or chemical irritation. Often, the initiating event is not considered severe enough to provoke chronic pain. The common factor in all of these circumstances is the persistence of the pain after the initiating event or injury has apparently subsided. The instigating events associated with chronic pain can vary greatly in location, "type," and magnitude [2]. Patients with chronic pain describe a large variety of sensations (eg, burning, pressure, stinging, etc), and this has led to multiple descriptive categories (eg, neuropathic, complex-regional, inflammatory); yet such classification strategies have not resulted in a greater understanding of the genesis of chronic pain or its treatment. The pathogenic mechanism(s) of chronic pain is not well understood; therefore, there is a need to reexamine our current thinking concerning the cellular events that instigate or process pain, as well as the factors that cause and modulate pain signaling. Recently, spinal glia have emerged as active participants in chronic pain; and as such, drugs affecting these cellular targets may offer new hope for chronic pain sufferers.

This short review will focus on the role of spinal glia in chronic pain. *Chronic pain* will be defined broadly as pain

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that persists in the absence of tissue damage. Many excellent reviews cover this topic in more detail [3-9]. Here we will emphasize facets of glial involvement in chronic pain that have yet to be well defined but that hold promise for providing avenues for therapeutic intervention in man. We will briefly review the concept of "glial activation" relative to chronic pain, including the complexity of glial responses, and the potential role of glial "priming" to explain the maintenance of the chronic pain state. Although recent preclinical findings, as well as human case reports, point to avenues for development of novel therapeutics, knowledge gaps in our understanding of chronic pain remain and must be filled if basic findings are to be effectively translated into clinical benefits.

2. Pain signaling can be modulated by glia at the level of the spinal cord

Pain long has been viewed from a "neurocentric" perspective because of the knowledge of spinal neuronal circuitry that mediates "normal" pain signaling and more recent knowledge that these same spinal pain pathways (Fig. 1) become sensitized/hyperactivated during chronic pain [3,4,8]. The traditional view of nociceptive signaling received via receptors throughout the periphery and the transmission of these signals through the dorsal root ganglion and spinal dorsal root up to higher centers now is seen as too simplistic. Spinal glia are believed to actively participate in these pain signaling pathways, especially at the level of the dorsal horn of the spinal cord. The burst of neuronal pain fiber signaling that occurs in the dorsal horn in association with acute pain from peripheral nerve damage or inflammation now is widely believed to be maintained in chronic pain due to factors emanating from activated glia. A clearer understanding of the roles of spinal glia in chronic pain will be essential for developing new analgesic therapies.

3. Glial cell types and pain

Much of the literature on pain and glia refers to *glia* as a unitary cell type. Of course, this label just reflects our lack of knowledge of the role(s) of glial subtypes in pain. There are 3 major types of glial cells in the central nervous system (CNS): oligodendroglia, microglia, and astrocytes. Based on molecular, cellular, and functional evidence, it is unequivocal that all glial cells are known to be active players in nervous system function and not simply supportive "glue" among the various neuronal cell types. Of the variety of neuron-glia interactions identified, microglia have received the greatest attention in recent years as mediators or modulators of pain owing to their known propensity to elaborate proinflammatory cytokines and chemokines, that is, immune signaling molecules related to inflammation at the sites of injury [10,11], and, more recently, as factors known to facilitate pain signaling within spinal pain centers [3,4]. Astrocytes, by comparison, have received less attention as players in pain processing despite the fact that, like microglia, they too elaborate and receive signaling from

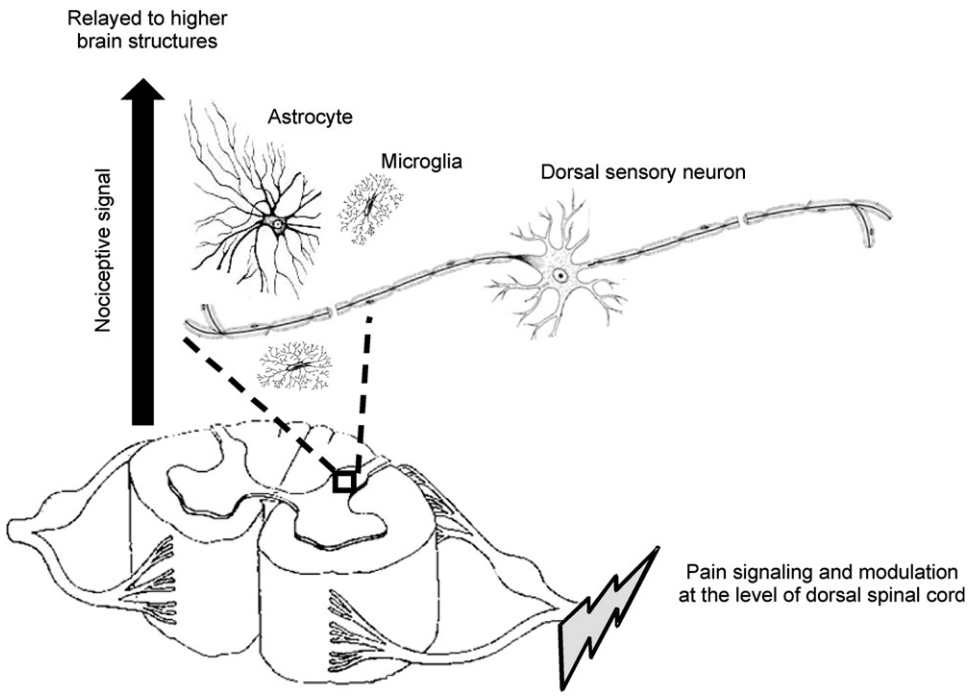

Fig. 1. Cartoon representation of pain signaling via sensory neuronal input through the dorsal horn of the spinal cord. Microglia and astrocytes within this dorsal horn pain relay center are now known to modulate pain signals transmitted to the brain.

proinflammatory molecules [12,13]. Indeed, almost 20 years ago, astrocytes were shown to enter an activated state in the spinal cord in response to ligation of the sciatic nerve [14]. One difficulty in assigning relative roles for glial subtypes in pain processing is the lack of in vivo evidence for specificity of glial cell-type involvement in various models of experimental pain, much less in humans with chronic pain. Nevertheless, a mounting body of evidence from chronic pain studies in animals suggests roles for both microglia and astrocytes in pain processing [3-9].

Evidence for the relative roles of microglia vs astrocytes in chronic pain tends to favor the former over the latter. In large measure, this is due to the presumed release of pain signaling molecules (eg, interleukin-1β, interleukin-6, tumor necrosis factor–α) by activated microglia and their suppression by presumed inhibitors of microglial activation, using a number of drugs and a variety of animal models of experimental pain. Although not as well documented, attenuation of astrocyte activation with the few inhibitors available has been shown to attenuate experimental pain in some models (eg, nerve ligation) [15]. Despite efforts to define "the" specific glial cell type that contributes to chronic pain, it is important not to do so for many reasons. For example, contemporary neuroscience is in its infancy with respect to establishing subtypes of microglia or astroglia [13]; therefore, it is premature to assign selective roles to microglia and astroglia in chronic pain states. Moreover, because neuron-glia interactions are important for the maintenance of the central nervous system in health as well as disease [13,16,17], and glial-glial interactions also exist [18], it is likely that these complex interactions also contribute to glial roles in maintenance of a chronic pain. Finally, it is important not to overlook nonglial immune contributors such as neurotrophils/macrophages as players in the chronic pain state [5,6]. As can be gleaned from the fact that clinical trials have yet to be launched for glial inhibitors known to be effective in experimental pain (clinicaltrials.gov), we are some distance from translating the findings from animal data into clinically useful applications.

4. Spinal glial activation associated with chronic pain has yet to be defined

In the emerging body of literature that associates glia with chronic pain, *glial activation* often is the term used to generically describe the status of "glia" with respect to initiation and/or maintenance of chronic pain [19]. But what does it mean when glia are "activated" in association with chronic pain? Indices of glial activation derive mostly from our knowledge of "markers" of microglial and astroglial responses to CNS injury [7,11-13,20]. As the resident immune surveillance cells of the CNS, microglial reactions to injury long have been defined by cell-surface glycoproteins linked to immune detection [20,21]. Lectin staining also has been widely used to characterize microglial morphology after damage within the CNS as well as microglial responses to motor neuron damage resulting from damage outside the CNS. The broad repertoire of microglial "marker" changes observed in the facial motor nucleus of the CNS after peripheral damage to the facial neuron serves as examples (albeit related to motor neuron damage rather than sensory neuron damage associated with pain transmission) [20,21] of the need to carefully define differences among the various experimental models of pain as they relate to spinal microglial responses.

The more recent trend has been to overlook the potential role of dorsal horn neuron pathology and redirect attention to the cytokines and chemokines that are presumed to be elaborated by microglia in response to the various pain models (more often than not, without a characterization of damage to sensory neuron terminals within the dorsal horn of the spine). Indeed, just the enhanced expression of these cytokines now serves to define glial activation related to chronic pain [5,6]. The same constellation of cytokine/chemokine expression patterns also defines the condition known as *neuroinflammation*, that is, expression of inflammatory mediators in the CNS in response to a variety of diseases/injuries/conditions (including pain) [3]. Indeed, the evidence is strong for an involvement of neuroinflammatory mediators in pain because their local application facilitates pain transmission in the spinal cord and their inhibition with presumed microglial inhibitors reduces pain signaling [3,5,6,9].

It is important to not lose sight of the fact that glial activation is not always associated with a "bad" outcome but, rather, may be restorative in nature in the context of many exposures and perhaps disease states as well [13,22]. One such example relative to pain signaling is the "sickness behavior" associated with systemic infections and, experimentally, with the administration of the gram-negative bacterial cell wall toxin, lipopolysaccharide (LPS). Microglia are activated by LPS in the spinal cord along with higher centers [23]; but this response usually resolves and is not associated with neuropathology, astroglial activation, or chronic pain. Thus, the microglial activation response to LPS represents the expected "acute phase" physiologic reaction to infection (ie, sickness behavior), one associated with microglial activation and elaboration of proinflammatory cytokines, but not with chronic pain. Acute administration of anti-inflammatory agents and inhibitors of glial activation can dampen LPS-induced neuroinflammation; but such effects would offer little prospect for preventing the development of chronic pain, the origin of which has not been linked to an acute bout of sickness behavior subsequent to infection. Indeed, clinical trials of anti-inflammatory agents for pain provide evidence for relief from acute inflammatory pain but not for chronic pain (clinicaltrials.gov).

Astrocytic activation in association with brain injury and disease long has been defined by enhanced expression of the astrocyte intermediate filament protein glial fibrillary acidic protein [24]. As noted above, enhanced expression of glial fibrillary acidic protein in the dorsal horn of the spinal cord

was one of the first associations of glial activation in a chronic pain model [14]. Although more recent attention has been directed to a role of microglia in pain because of presumed linkage of proinflammatory mediators with this cell type, but not astrocytes, astrocytes now have been shown to elaborate and receive signals from proinflammatory cytokines as well [13,25]. Given the demonstrated lack of specific glial cell type roles in most chronic pain models, much less in man, there is cause for a renewed attention to astrocytic involvement in pain states [25]. Of note is the fact that in injury, disease, and pain models, microglial responses often are early and transient events, whereas astrocytic activation follows microglia activation and persists for a longer period. These latter observations have been put forth as evidence for a role of astrocytes in persistent pain [25].

Although descriptions of glial activation and pain provide information on the association of molecular entities with chronic pain, they do not reveal the origins of glial activation in the genesis and, most importantly, in the persistence of pain. Nevertheless, drawing on lessons learned from neuropathology, we know that greater damage to the neuropil leads to greater levels and often a greater duration of glial response to a given insult [2]. Moreover, ongoing neural (neuronal or glial) damage leads to continuous glial activation, a relevant clinical example being the massive and continuous astroglial response associated with Alzheimer disease [26]. These known relationships between glial activation and the degree and duration of underlying neural injury are consistent with numerous observations from experimental pain models. Thus, the more chronic and the more severe injuries are to dorsal root neurons the greater the glial activation in the dorsal horn [2]. The possibility exists that chronic pain in a clinical setting may be related to ongoing damage to dorsal root fibers despite the absence of the initiating event; that is, ongoing subtle neuropathology may underlie chronic pain. Given the now widespread availability of sensitive neuronal degeneration stains [27,28], the various animal models of pain should now be evaluated for the temporal sequence of degeneration responses that may occur in the dorsal horn, that is, subtle degenerative events that may underlie chronic glial activation and its associated pain.

5. Microglial priming and chronic pain

Above we addressed the importance of ruling out chronic peripheral neuron damage as a source of chronic pain related to glial activation at spinal pain relay centers; this brings us to the second and most widely held view of chronic pain: a persistent sensitization/facilitation of pain signaling in the absence of ongoing structural pathology. What signaling mechanisms exist to maintain a chronic state of pain, and how can we abort the dysfunction that causes chronic pain? Lessons again can be learned from recent literature on neurodegeneration and the role of the immune system [29]. Here, we are referring to the concept of microglial priming [29,30], whereby a variety of systemic insults lead to exacerbated neuroinflammatory responses associated with microglial activation [29]. Aging; stress; glucocorticoids; and, notably, opiates can serve as stimuli for microglial priming [31-33], that is, the same factors that contribute to glial sensitization in chronic pain [34]. Although the molecular stimulus for microglial priming remains unknown, once microglia are "primed," the continued elaboration of injury-related signals between microglia and neurons provides the mechanism for the primed condition to become self propelling and, therefore, lead to a persistent contribution of microglia to neural damage [30]. The potential for microglial priming to be persistent and self-perpetuating implicates it as a basis for understanding and treating chronic pain states. Nowhere is this now more evident than in the realization that opiates can serve as sensitizing ("priming") agents for enhancing pain signaling.

6. Glia and opioid actions

Repeated exposure to opioids often reduces their analgesic potency (ie, tolerance) and at the same time causes changes in spinal cord glia similar to those observed in various animal models of chronic pain. These similarities have led to the idea that activation of spinal glia is crucial in both chronic pain and opioid tolerance [35]. Opiates remain the treatment of choice for chronic pain, but their protracted use can result in a loss of effectiveness and the need for dose escalation as tolerance develops. Long-term use of opioids also can result in the development of hyperalgesia, an exaggerated response to a painful stimulus or the interpretation of a usually benign stimulus, like touch, as painful. In the clinic, it is difficult at best to differentiate reports of increased pain due to hyperalgesia with those related to a reduction in analgesic efficacy, as pain assessment in patients customarily relies on self-evaluation rather than objective measures. However, animal studies have confirmed that repeated exposure to opioids results in both tolerance and hyperalgesia [36,37]. The adaptive changes involved in producing opioid tolerance and analgesia are likely conferred at multiple levels of the neuraxis. Moreover, these alterations are now believed to involve glial participation, as a focus on neuronal elements has not provided a complete mechanistic explanation for either tolerance or hyperalgesia. Recent work exploring glia, pain, and pain therapeutics reveals roles for spinal glia in the reduced efficacy of opioids used in pain treatment. Both spinal astrocytes and microglia appear to participate in the reduction in analgesic efficacy found with protracted treatment with opioids, although they do not impact the initial pain-reducing effects of opioids [5,6].

As noted above, both microglial and astrocyte "activation" are believed to contribute to the initiation and maintenance of chronic pain; more contemporary work assigns a role for the activation of these cells in opioid tolerance and hyperalgesia as well. Experimentally, long-term administration of opioids

results in tolerance accompanied by both micro- and astroglial activation. Blocking this activation, for example, with the metabolic inhibitor fluorocitrate, reduces or blocks tolerance development as well as hyperalgesia [38]. When activated glia release proinflammatory substances (eg, cytokines like interleukin-1 and tumor necrosis factor–α), neuronal excitability is enhanced, an outcome known to result in enhanced pain sensitivity and to reduce the effectiveness of opioids. If given early, minocycline, a tetracycline analogue that inhibits neuroinflammation, blocks both microglial and astroglial activation; and tolerance does not develop. Interestingly, once tolerance is well established, minocycline does not block astrocyte activation even though microglial activation is blocked, suggesting that microglia may be responsible for initiation of tolerance and hyperalgesia, whereas astroglia are responsible for maintaining both of them [39].

7. Conclusions

Chronic pain remains a clinical problem owing, in no small measure, to a lack of understanding of the mechanisms responsible for its genesis and maintenance. Despite years of investigation and concerted efforts aimed at developing effective therapeutics, there remain few effective treatment options for those suffering from chronic pain. This lack of progress may be partly due to the emphasis on neuronal elements of the pain circuit. Thus, the observed links between the actions of spinal cord glia, the effectiveness of opioids, and the chronic pain state are important from both a clinical and experimental perspective, as they serve to highlight the previously unsuspected function of these nonneuronal cells in both analgesia and pain. Furthermore, these findings suggest that a greater understanding of glial biology will allow for the development of therapies centered on the control of glial rather than neuronal function. Contemporary imaging techniques (eg, positron emission tomography ligands specific for glia), as well as genomic and proteomic approaches [40], will lead to a greater understanding of glial function. Knowing how to control glial function will lead to better control of chronic pain, both through the development of therapies acting through glial modification, as well as by increasing the analgesic effectiveness of current therapeutic agents.

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