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Gliopathy Ensures Persistent Inflammation and Chronic Pain after Spinal Cord Injury

Claire E. Hulsebosch, Ph.D. [Director, Mission Connect, Chair in Neurological Recovery, Vice-Chair and Professor]

Neuroscience and Cell Biology, 301 University Blvd. Rt. 1043, University of Texas Medical Branch, Galveston, Texas 77555-1043, phone: 409-772-2939, FAX: 409-772-3222

Claire E. Hulsebosch: cehulseb@utmb.edu

Abstract

Research focused on improving recovery of function, including the reduction of central neuropathic pain (CNP) after spinal cord injury (SCI) is essential. After SCI, regional neuropathic pain syndromes above, at and below the level of spinal injury develop and are thought to have different mechanisms, but may share common dysfunctional glial mechanisms. Detloff et al, 2008 describes events in the lumbar region of the spinal cord after a midthoracic SCI injury, the so called “below-level” pain and compares the findings to peripheral nerve lesion findings. This commentary briefly reviews glial contributions and intracellular signaling mechanisms, both neuronal and glial, that provide the substrate for CNP after SCI, including the persistent glial production of factors that can maintain sensitization of dorsal horn neurons in segments remote from the spinal injury; ie. dorsal horn hyperexcitability to formerly non noxious stimuli that become noxious after SCI resulting in allodynia. The term “gliopathy” is proposed to describe the dysfunctional and maladaptive response of glial cells, specifically astrocytes and microglia, to neural injury that is initiated by the sudden injury induced increase in extracellular concentrations of glutamate and concomitant production of several proinflammatory molecules. It is important to understand the roles that different glia play in “gliopathy,” a condition that appears to persist after SCI. Furthermore, targeted treatment of gliopathy will attenuate mechanical allodynia in both central and peripheral neuropathic pain syndromes.

Commentary

Research focused on improving recovery of function, including the reduction of central neuropathic pain (CNP) after spinal cord injury (SCI), is essential. The CNP syndromes or dysesthesias (disturbing somatic sensations that may not be painful) can be divided into two broad categories: 1) spontaneous pain – which occurs independently of peripheral stimuli, is persistent, waxes and wanes intermittently, and is described as numbness, burning, cutting, piercing or electric-like (Davidoff and Roth, 1991); 2) peripherally evoked pain – which occurs in response to either normally nonnoxious or noxious stimuli. The article in *Experimental Neurology* by Detloff et al., 2008 uses a rodent SCI model to address possible mechanisms that underlie neuropathic pain after SCI, a life long “secondary” symptom

Requested Commentary of Detloff, et al., Remote activation of microglia and pro-inflammatory cytokines predict the onset and severity of below-level neuropathic pain after spinal cord injury in rats, *Exp. Neurol.* (2008).

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suffered by the majority of people with SCI (Hulsebosch, 2005). The Detloff article describes events in the lumbar region of the spinal cord after a midthoracic SCI injury, so called “below-level” pain and compares the findings to peripheral nerve lesion findings. To put the article in context, following SCI, people develop different regional syndromes. Siddall and colleagues (2002) defined three regional categories of pain that result from SCI: 1) above-level pain which occurs at dermatomes cranial to the injury site and occurs in areas where normal sensation persists following injury, 2) at-level pain which occurs in dermatomes near the spinal injury, develops shortly after SCI, and is often characterized as either stabbing pain or a stimulus independent type that is accompanied by allodynia (“girdle” or allodynia at the level of the sensory loss, Tasker and Dostrovsky, 1989), and 3) below-level pain which is localized to dermatomes distal to the injury site, develops more gradually than does at-level pain, and is often classified as a stimulus independent burning continuous pain (Sjolund, 2002; Vierck Jr et al., 2000). The current thinking is that the differential regional “pain syndromes” arise from differing mechanisms. However, we propose that there may be some common mechanisms which include abnormal glial functioning or “gliopathy” that ensure a persistent and chronic pain state.

The authors in the present article use evoked somatosensory tests to determine hindlimb mechanical allodynia (increased “pain-like” sensitivity in which formally nonnoxious stimuli becomes noxious) in a model of below level pain and report that increased microglia activation, as inferred by increased OX-42 immunoreaction product, correlated with increased “pain-like” behavior. Furthermore, activation of an intracellular signaling molecule, p38, is reported to be principally in neurons in the lumbar spinal cord. By contrast, our lab reports increased phosphorylation of p38 (p-p38, which is the activated form) in both microglia, astrocytes and neurons (see Crown et al., 2008) in regions immediately rostral to the spinal lesion (model of at level pain). Specifically, p38 MAP kinases are serine threonine kinases that are activated by several upstream kinases in response to inflammation. In turn, p-p38 plays a key role in monocyte/macrophage inflammatory responses and inhibition of p-p38 is associated with reduction in iNOS, TNF α , IL-1 β , COX-2 and iNOS, all proinflammatory mediators known to be involved in neuropathic pain. Cellular localization of activated p38 is involved in neuronal and glial cell death, days after SCI (Crown et al., 2006), and is involved in persistent activation of both microglial and astrocytes (Zhuang et al., 2005; Svensson et al., 2005a,b; Hua et al., 2005) and in dorsal horn hyperexcitability (Crown et al., 2008), presumably by different pathways but possibly may share the same pathways in which the results are concentration dependent. In the latter case for example, p-p38 downstream activation of the transcription factor CREB can lead to feed forward phosphorylation of the NMDA receptors leading either to maintained hyperexcitability or neuronal death if sufficient numbers of NMDA are activated. It should be noted that there are two isoforms (p38 α in neurons, p38 β in microglial) so that selection of antibodies will determine cellular localization and may provide the reason for differential findings between laboratories.

We hypothesize that activation of the transcription factor CREB and ERK1/2 and p38 MAP kinase pathways play pivotal roles in persistent inflammation in the induction (which involves GABA neuronal death) and the maintenance phases of CNP after SCI (Crown et al., 2006,2008). Several studies support the important roles of these factors in peripheral neuropathic models (Milligan et al., 2003; Jin et al., 2003; Tsuda, et al., 2004; Svensson, et al., 2005a,b). Furthermore, we hypothesize that the increased expression of p-p38, p-ERK and p-CREB over time after SCI is in different cell populations, and in different cellular compartments reflecting either their role in apoptosis early after SCI (Zhuang et al., 2005) or their continued role in inflammation and/or persistent hyperexcitability (Crown et al., 2008). As a side note, certain MAP kinases, ERK, JNK and p38, are well known to be involved in cell apoptosis, and likely contribute to the early apoptotic events contributing to CNP after

SCI, specifically demyelination of descending inhibitory circuits via oligoapoptosis (Finnerup, et al., 2003a,b,c; Beattie, et al., 2002) and loss of GABA cells (Rafati et al., 2008), both being mechanisms that contribute to the induction of chronic neuropathic pain via loss of inhibitory tone on somatosensory circuits (Finnerup, et al., 2003a,b,c; Gwak et al., 2008). The point is that the same molecules can have very different results depending on concentrations and temporal expression in a disease process (cell death vs. continued activation of intracellular signaling) that contributes to permanent neuronal hyperexcitability and resultant CNP.

In Detloff et al., 2008, the authors describe no significant increase in GFAP protein in the lumbar region, but increased GFAP mRNA in SCI groups compared to naïve. The increased GFAP is classically used as a “marker” of astrocytic activation which is known to occur after SCI and is also referred to as “reactive” astrocytes; although the significance of the increase GFAP is unknown. It is important to point out that Nesic et al., 2005 demonstrate significant GFAP protein increases from 4 hours up to 9 months after SCI in regions adjacent to the lesion (Fig.10a) and in lumbar and cervical regions (Fig.9a). Detloff et al., 2008 also conclude that an increase in proinflammatory cytokines correlated with the severity of below level chronic pain, although the source of the proinflammatory cytokines is unknown. The conceptual basis that increased severity of SCI corresponds to increased neuropathic pain was well described in previous manuscripts (Liu et al., 1997; Yezierski et al., 1998; Hao et al., 1991; Xu et al., 1992; Christensen and Hulsebosch, 1997) which indicate that the larger the lesion, the greater the area of allodynia. These observations were related to inflammation in a subsequent publication (DeLeo and Yezierski, 2001). Thus, given that inflammation follows CNS lesion, and greater lesions produce more inflammation, then the authors' conclusion is not too surprising, but it is important to have the correlation between proinflammatory cytokine levels and mechanical allodynia rigorously tested.

It is interesting to note that the mechanisms of the differential regional pain all appear to have early and permanent activation of both microglia and astrocytes in common (for below-level: Hains and Waxman, 2006, Gwak et al., 2008; for at level-Crown et al., 2008; for above level-Nesic et al., 2005). Perhaps the best of these studies is by Gwak et al., 2008. This study reports the use of the phosphodiesterase inhibitor, propentofylline (PPF), which modulates both microglial and astrocytic activation (Tawfik, et al., 2007) given early after midthoracic SCI (Gwak et al., 2008). After midthoracic SCI, hindlimb mechanical allodynia occurs, that persists for the life of the subjects, accompanied by significant increases in GFAP and OX-42 immunoreaction product in the lumbar dorsal horn and significant development and persistence of dorsal horn neuron hyperexcitability, all which occur several segments remote from the SCI region. PPF administration for 7 days after SCI results in decreased changes in the lumbar cord that include decreased mechanical allodynia, decreased GFAP and OX-42 expression, and decreased glial (both astrocytic and microglia) soma hypertrophy (also a classical marker for activation), as well as decreased neuronal hyperexcitability, a fundamental substrate of central neuropathic pain (Hulsebosch, 2005 review). Thus, the conclusion is that inhibition of glia activation, both astrocytic and microglia, will improve chronic and persistent pain syndromes in remote segments below the level of lesion after SCI and in other central neuropathies. However, it is recognized that the mechanisms of astrocytic and microglial contributions to CNP are likely to be different.

In more recent work examining p38 activation, in astrocytes, microglia and dorsal horn neurons just rostral to the level of SCI, Crown et al., 2008 report that inhibiting the enzymatic activity of p38 MAPK reverses mechanical allodynia and decreases hyperexcitability in dorsal horn neurons. In addition, there is a SCI induced increase in GFAP and OX-42 protein expression which is attenuated by blocking activation of p38

MAPK. Thus, the conclusion is that glia activation, both astrocytic and microglia, have important roles in development and maintenance of persistent pain syndromes after SCI and other central neuropathies in regional neuropathic pain syndromes; and blocking specific intracellular signaling pathways can functionally alter the glia activation response. Genetic differences (Mills et al., 2001) and age at time of injury (Gwak et al., 2004) certainly play roles in neuropathic pain and genetic differences certainly play a role in cellular inflammatory responses (Popovich et al., 1997) and may explain differences between studies. However, irrespective of differences, the specific roles that glia populations play after SCI in central neuropathic pain are important to investigate.

To review, in the CNS there are two general types of macroglial cells: oligodendrocytes and astrocytes. Oligodendrocytes are the myelinating cells in the CNS, providing multiple and different axonal nodes (Schwann cells are the myelinating cells in the PNS). Thus, loss of oligodendrocytes after SCI or their dysfunction causes changes in conduction parameters not unlike demyelinating diseases. Astrocytes are classically thought to play roles in potassium, glutamate and other transmitter regulation and homeostasis in the extracellular and synaptic spaces through uptake mechanisms. Specialized astrocytes also play roles in the blood brain barrier and in neuronal nutritive functions (ex. satellite cells of dorsal root ganglion neurons). Microglia are classically thought to be principally phagocytes that are able to be mobilized after injury, infection, disease and in seizures. When activated, glia cells are known to hypertrophy, increase production of cell specific “markers” (GFAP for astrocytes and OX-42 for microglia and other macrophages) and produce proinflammatory cytokines, reactive oxygen species (ROS), ATP, excitatory amino acids, and nitric oxide (NO) (Johnstone et al., 1999; Martin, 1992; Piani et al., 1992; Shafer and Murphy, 1997; Tanaka et al., 1994); all of which are powerful candidates for mediating pain following neural injury and are known to produce neuronal hyperexcitability in dorsal horn neurons, a necessary substrate for neuropathic pain. Additionally, it is important to note that chronically activated astrocytes lead to permanent blood spinal cord barrier breakdown that ensure continued immune cell infiltration and feed forward continued activation of both astrocytes and microglia (Nesic et al., 2005).

In the mammalian system, we propose that normal glial function becomes abnormal and dysfunctional after CNS injury. The dysfunctional glial state contributes to conditions that initiate and ensure persistence of neuropathic pain. While the concept of glia-neuronal and neuronal-glia interactions were described in invertebrate systems several decades ago (see Lasek et al., 1974; Villegas, 1972); the conceptual basis of dysfunctional glial cells contributing to neuropathic pain is relatively new (Crown et al., 2008; Detloff, et al., 2008; DeLeo et al., 2006; Gwak et al., 2008; Nesic et al., 2005; Romero-Sandoval, et al., 2008; Milligan et al., 2008).

We propose the term “gliopathy” to describe the dysfunctional and maladaptive response of glial cells to neural injury. We hypothesize that the initiation of gliopathy after neural injury, is the sudden increase in the extracellular concentration of glutamate after peripheral nerve injury (Rooney et al., 2007) and after SCI (McAdoo, et al., 1999) that in some cases is 37 fold higher than resting concentrations and results in excitotoxicity (Xu et al., 2008) and glutamate receptor mediated sensitization of both neuronal and glial populations (Hulsebosch, 2005). With respect to the role of glutamate receptors in the dorsal horn excitability, we have published data that all three receptors are involved in CNP after SCI (Bennett et al., 2000; Mills et al., 2002; Hulsebosch, 2003). We know that NMDA receptor activation participates in the upregulation of several proinflammatory molecules (Nesic et al., 2002) and that proinflammatory cytokines exacerbate the glutamate mediated excitotoxicity after SCI (Hermann, et al., 2001). We hypothesize that one of the cellular sources for cytokine production immediately and for the first few days after SCI are from

the dysfunctional glial cells (of course infiltrating cells are key contributors of proinflammatory cytokines and other sensitizing agents in early SCI (Fleming et al., 2006) and late in SCI (Nesic et al., 2005). Furthermore, we hypothesize that persistent and permanent glia dysfunction occurs in regions near as well as very remote from the spinal lesion and into the brain and that the dysfunctional glial cells continue to secrete proinflammatory cytokines and other sensitizing agents in both an autocrine and paracrine manner, creating persistent glial inflammation and continual sensitization of dorsal horn neurons.

It is obvious that the initial glutamate and proinflammatory cytokine increases that occur over the first few hours after SCI are not going to be useful therapeutic targets since most patients present to the emergency rooms 3 hours or later after injury. However, we propose the importance of understanding the roles that different glia play in “gliopathy,” a condition that appears to persist after SCI, and that the targeted treatment of gliopathy will attenuate mechanical allodynia in both central and peripheral neuropathic pain syndromes.

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