

Mechanisms of Central Sensitization, Neuroimmunology & Injury Biomechanics in
Persistent Pain: Implications for Musculoskeletal Disorders

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ABSTRACT

This review will offer an overview of the mechanistic pathways of chronic pain associated with musculoskeletal disorders (MSDs). Traditional electrophysiological pain pathways of these injuries will be reviewed. In addition, recent research efforts in persistent pain have characterized a cascade of neuroimmunologic events in the central nervous system that manifests in pain behaviors and neurochemical nociceptive responses. Physiologic changes in the central nervous system will be covered as they pertain to the interplay of these two areas, and also as they focus on MSDs and injuries. One such injury leading to persistent pain is radiculopathy, which results from nerve root compression or impingement and leads to low back pain. This painful syndrome will be used as an example to provide a context for presenting immune mechanisms of chronic pain and their relationship to injury. Measures of injury biomechanics are presented in the context of the resulting pain responses, including behavioral sensitivity, local structural changes, and cellular and molecular changes in the CNS. Lastly, based on these findings and others, a discussion is provided highlighting areas of future work to help elucidate methods of injury diagnosis and development of therapeutic treatments.

Painful musculoskeletal disorders (MSDs) are a common problem in today's society, affecting an estimated one-third of the population. The societal costs, including litigation, work-lost, treatment and disability, for painful MSDs are staggering. For example, the cost of low back pain alone has been estimated to be between 40-50 billion dollars annually [20,21]. Until we gain a better understanding of the pathomechanisms in chronic pain and the injuries which cause them their effective prevention and treatment will remain somewhat elusive. It is the intent of this review to highlight traditional and emerging theories of pain transmission in the context of injury and MSDs. A brief discussion of the neurophysiology of pain highlights traditional concepts of injury and pain processing and more recent hypotheses of the central nervous system's (CNS) neuroimmunologic involvement in persistent pain. This discussion is followed by a presentation of biomechanical considerations for painful injuries and MSDs. Incorporating effects of injury parameters on mechanisms of persistent pain, text discusses implication of all of these for MSD. Lastly, a discussion of clinical implications of these findings and suggested areas of future work is offered. It is important to define, at the outset, relevant distinctions in terminology. "Pain" is a complex perception that is influenced by prior experience and by the context within which the noxious stimulus occurs; "nociception" is the physiologic response to tissue damage or prior tissue damage.

MECHANISMS OF PAIN: NEUROPHYSIOLOGY & NEUROIMMUNOLOGY

There are a host of physiologic mechanisms by which injuries lead to nociceptive responses, and ultimately pain. In persistent pain, CNS signals can result in a hypersensitivity or central sensitization response. In addition to the electrophysiologic changes leading to central sensitization, the CNS mounts a series of neuroimmune responses which may further contribute to sensitization

and persistent pain symptoms. The findings with regard to neuroimmunity are reviewed here to form a basis for discussing more recent views of persistent pain mechanisms.

Tissue Injury, Central Sensitization & Pain

Injury to a broad number of tissue components, including muscle, disc, and ligament, produces a variety of signals leading to pain perception. Neuroplasticity and subsequent CNS sensitization include altered function of chemical, electrophysiological, and pharmacological systems [3,13,15,41,44,50]. These are complicated and intricately involved with injury and changes in both the peripheral and central nervous systems (Figure 1).

An initial insult (injury- or inflammation-induced) activates local nociceptors (Figure 1). These A δ and C pain nerve fibers in turn become sensitized and have both lower thresholds for firing and increased firing rates when stimulated at levels similar to before injury [4]. In addition to altered electrical responses, injury initiates the synthesis and release of inflammatory mediators that act to induce inflammation and edema as part of the healing process. However, these healing activities also sensitize nociceptors and recruit new nociceptors to enhance pain [17,19]. Such chemical mediators include, but are not limited to, excitatory amino acids, nitric oxide, bradykinin, prostaglandins, histamine, and substance P [4,26]. Cytokines are also released in the periphery in association with tissue injury and inflammation. These proteins, in turn, contribute to the local inflammatory response, while further affecting electrophysiologic responses of pain and can establish a continuous feedback.

The injured primary afferents terminate in the dorsal horn of the spinal cord, where they communicate with spinal neurons via synaptic transmission. Many additional neurotransmitters (i.e. glutamate, NMDA, substance P) modulate postsynaptic responses, with further transmission to supraspinal sites via the ascending pathways [4]. Tissue damage (injury) generates an increased neuronal excitability in the spinal cord [50]; associated with this sensitization is a decreased

activation threshold, increased response magnitude, and increased recruitment of receptive fields [41]. The continuous input from nociceptive afferents can drive the spinal circuits, leading to central sensitization, and maintaining a chronic pain state [15]. These neuroplastic changes are accompanied by other electrophysiological manifestations that cause neurons to fire with increased frequency or even spontaneously [44]. In addition, spinal processing is further affected by descending inhibitory and facilitory pathways that provide additional modulation of spinal interneurons [40].

Persistent pain results from the sensitization of the central nervous system. While the exact mechanism by which the spinal cord becomes sensitized or in a “hyperexcitable” state currently remains somewhat unknown, many hypotheses have emerged. Here only highlights of these theories are provided as an overview. More extensive and detailed discussions can be found elsewhere in the literature [6,16,18,50]. Simply, low threshold A β afferents, which normally do not serve to transmit a pain response, become recruited to transmit spontaneous and movement-induced pain [16]. This central hyperexcitability is characterized by a “windup” response of repetitive C fiber stimulation, expanding receptive field areas, and spinal neurons taking on properties of wide dynamic range neurons [8]. Ultimately, A β fibers stimulate postsynaptic neurons to transmit pain, where these A β fibers previously had no effect, all leading to central sensitization. Nociceptive information is transmitted from the spinal cord to supraspinal sites, such as the thalamus and cerebral cortex by ascending pathways.

Neuroimmunologic Responses in the CNS

While central sensitization contributes to nociceptive mechanisms of persistent pain in the CNS, recent research has demonstrated the role of spinal neuroimmune responses as contributing to persistent pain [14]. A collection of researchers has documented CNS immune changes associated with persistent pain due to a host of painful syndromes, including radiculopathy, neuropathy,

diabetes, and HIV, among others [10,32,37,42,43,47]. Work by DeLeo has focused on the role of centrally produced proinflammatory cytokines, glial activation and leukocyte trafficking in a rodent pain model of L5 lumbar radiculopathy [7,23,33,36,47], lending support for these immunologic changes contributing to pain. From this body of work, a cascade of events in the CNS has been proposed following injury [13,14]: cells (glia, neurons) become activated and can produce and release cytokines which not only lead to their further activation, but also the release of pain mediators [10,11,42]. Glial or neuronal proinflammatory cytokines can sensitize peripheral nociceptive fields [25] and sensitize dorsal root ganglia [30]. Events that induce behavioral hypersensitivity also activate immune cells both centrally and in the periphery, mediating chronic pain [10,11,42]. Cytokines and growth factors have been strongly implicated in the generation of pathological pain states throughout the nervous system; in particular, proinflammatory cytokines, such as IL-1, IL-6 and TNF, are upregulated both locally and in the spinal cord in persistent pain [10,51]. Immune activation with cytokine production may indirectly induce the expression of many pain mediators such as glutamate, nitric oxide, and prostaglandins in the CNS, leading further to spinal sensitization. In conjunction with this neuroimmune activation, neuroinflammation occurs in which immune cells migrate from the periphery into the CNS in association with pain [13,14,33]. This infiltration may lead to further changes in the CNS and potentially to central sensitization. Infiltrating immune cells contribute to neuronal activation and algescic mediator release, further perpetuating the maintained excitability and sensitization in the CNS which leads to behavioral sensitivity and pain. The spinal immune response of nociception has many facets, forming a complicated cascade of events leading to pain.

BIOMECHANICAL CONSIDERATIONS FOR PAIN MECHANISMS & NEUROIMMUNITY

Electrophysiologic and neuroimmune responses of the CNS likely work together to affect pain for MSDs, with local biomechanics at the injury site modulating both such response cascades. Low back pain is an ideal representative syndrome to use as an illustrative example for discussing injury mechanisms and cellular response cascades of a chronic painful MSD in light of the previous section on mechanisms. In this discussion, injury conditions are presented as examples of how mechanical loading modulates nociception in low back pain, with particular emphasis on nerve root injury (radiculopathy).

Many animal studies report altered electrophysiologic and cellular function for graded cauda equina compression. Compression increases endoneurial pressure locally in the rat sciatic nerve and DRG in proportion to mechanical loading [27,34]. In addition, edema patterns and intensity are modulated by the nature of the mechanical insult [28,29,31,34]. Nerve root loading produces changes in electrical impulse propagation and conduction velocity [9,22,35] and repetitive neuronal firing in the dorsal horn of the spinal cord [22,52], which are all suggestive of sensitization leading to pain. Similarly, it has been shown that tensile loading of facet capsule ligaments produces altered neuronal firing indicative of injury and nociception and may be a causative mechanism of low back pain [2,5]. While this collective body of work suggests a mechanism of spinal cord plasticity and central sensitization for mechanical injuries, it is only inferential for understanding production and maintenance of pain.

Work using imaging techniques has quantified nerve root tissue deformation in a rodent model of painful lumbar radiculopathy [48,49] and examined this injury parameter in the context of pain (behavioral hypersensitivity). Local injury mechanics was found to modulate pain behaviors; a significant positive correlation exists in this pain model between behavioral sensitivity and the amount of tissue injury [48]. Most simply, the greater nerve root compression at injury, the worse

the clinical symptoms of behavioral sensitivity and pain. From this series of work, mechanical thresholds for pain behaviors were defined based on the amount of nerve root compression [46]. These mechanical parameters defining painful injuries provide added utility for clinicians in diagnosing painful injuries, directly linking the injury event to the likelihood of pain symptoms. Moreover, in the future, it will hopefully provide insight into predicting clinical outcomes for this class of injuries.

While defining the relationship between injury events and pain is necessary for understanding the clinical context of these pathologies, defining the relationship between injury and specific and relevant *nociceptive* responses is crucial for understanding the central mechanisms of persistent pain in MSD. Using RNase Protection Assays to detect spinal mRNA of a panel of cytokines (TNF α , IL-1 α/β , IL-6, IL-10), a statistically significant correlation was found between mRNA levels at postoperative day 7 and the degree of tissue deformation at injury [48]. This suggests a modulatory effect of injury magnitude on one aspect of spinal nociception. Using immunohistochemistry, spinal expression of the proinflammatory cytokine IL-1 β has previously been found to depend on nerve root compression intensity [23]; suggesting preservation of these changes at both the message and protein levels for the spinal cytokines involved in chronic low back pain responses. Consistent with the grading of behavioral responses and spinal cytokine expression according to injury severity [23,48,49], spinal microglial activation is more intense for greater nerve root deformation at injury [23,45]. Yet, astrocytic activation does not follow injury magnitude, highlighting that biomechanics at injury in lumbar radiculopathy models may differentially modulate some neuroimmune responses and not others (Figure 2).

IMPLICATIONS FOR MSD: PAIN MECHANISMS & INJURY BIOMECHANICS

It is recognized that spinal injuries are by no means the only chronically painful MSDs. As such, it should be noted that many of the theories described above may assist with developing a more broad understanding in the context of other painful MSDs, such as carpal tunnel syndrome. While magnitude, rate and duration of loading all modulate electrical signaling patterns (amplitude, frequency) and local tissue changes (edema, pressure), and the neuroimmune cascade for painful radiculopathy, their effects for other painful syndromes may be similar. Continued integration of multidisciplinary approaches applied to a broader class of MSDs will help define nociceptive responses in these disorders.

In the typical response of an acutely painful episode, the balance of injury, repair and healing is achieved and the cascade of electrophysiologic and chemical events resolves following inflammation and injury. However, for persistent pain, the local, spinal and even supraspinal, responses are undoubtedly altered from that described above. Based on the discussion presented in the previous sections regarding persistent pain, a comprehensive picture is emerging for nerve root injury and CNS responses of nociception: spinal cytokine upregulation, microglial and astrocytic activation, cellular adhesion molecule upregulation, and immune cell infiltration into the spinal cord [13,14,36,39,42]. These aspects of neuroimmune activation induce the expression and release of pain mediators (substance P, glutamate, nitric oxide) and also lead to neuronal hypersensitivity. In this context it is important to consider novel methods for preventing and treating painful injuries. Clinical emphasis has largely been focused on local interventions at the injury site. However, the previous discussion points to the spinal cord physiology as having equal, if not stronger, contribution for maintenance of pain. Continued understanding of spinal and supraspinal mechanisms and mediation of central sensitization can hopefully provide valuable contributions to this understanding.

IMPLICATIONS FOR MSD: APPLICATIONS & FUTURE RESEARCH

Emerging out of this discussion, it becomes clear that there are a number of areas of research focuses which remain to be investigated for painful MSD (Table 1). From the broad coverage presented above, it can be appreciated that many aspects of injury, physiology and cellular mechanisms contribute to chronic pain in MSDs. In this context, then, it is possible to synthesize these findings to discuss preventing these injuries and treating and managing them. As continued biomechanical research is performed to determine conditions under which tissue injury occurs and initiates physiologic responses, it becomes clear that findings can help guide preventive strategies to protect some of these structures from undergoing kinematically and kinetically risky situations. In addition, the cellular findings presented above highlight the need for defining the relationship of an injury event, its physiologic responses, and *their relationship to behavioral manifestations of pain symptoms*.

As the understanding of the mechanisms of persistent pain expands, increased research is being focused on development of effective treatment modalities. A broad variety of approaches exist for offering pain relief: joint blocks, TENS, manipulation, pharmacology, and many others [13]. However, the exact mechanisms of injury often remain elusive, making it extremely challenging to act at the structural site of injury for therapy. Pharmacologic treatment options offer a promising approach for manipulating those aspects of the CNS response which contribute to chronic nociception. For example, global immunosuppressants have been shown to ameliorate pain behaviors in both neuropathic and radiculopathy rodent pain models [47]. Likewise, manipulation of specific spinal cytokines to alter sensory processing and other select agents have been effective in reducing allodynia in a variety of pain models [1,12,24,37,38,47]. Pharmacologic antagonists to and inhibitors of particular proinflammatory cytokines and other algesic mediators (IL-1, TNF, COX-2)

have shown effectiveness in animal pain models for attenuating both behavioral hypersensitivity and elements of the CNS neuroimmune cascade [1,12,24,37,47]. Indeed, combinations of some of these agents may have promise for effectiveness in reducing pain. As continued research identifies the specific physiologic pathways (both electrophysiologic and immunologic) which are responsible for chronic pain, it will become more feasible and even more tractable to target specific sites along these pathways for selectively manipulating and modulating a persistent pain response. With continued integrative efforts, progress will be made in this area.

It is the hope that this review has provided a summary of current thinking in pain mechanisms with a particular emphasis on how these mechanisms relate to injury and MSD. Likewise, it was the intent to illuminate interesting new work within the study of pain, highlighting the complications and intricacies of its nature. Lastly, through this presentation, areas of future work have been indicated. It is only through continual efforts that meaningful advances will be made in preventing and treating painful musculoskeletal disorders.

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TABLE 1. Suggested Future Work for Painful MSD:
Specific Areas of Investigation

1. Mechanisms for Anatomic Injury & Definition of Nociceptive Responses

- Identify anatomic structures at risk for injury
- Understand physiologic meaning of “injury” for these structures
- Identify injury factors which dominate pain
 - PREVENTION of painful injuries
 - DIAGNOSTIC tools & measures for prediction of management

2. Development of Effective Treatments & Managements

- Pain symptom attenuation
- Pharmacological treatments targeted at spinal changes
 - TREATMENT for chronic pain
 - MANAGEMENT strategies for pain

FIGURE LEGENDS

Figure 1. This schematic illustrates physiologic mechanisms of pain following an injury in the periphery. Nociceptive responses are complicated and involve a host of changes both locally in the central nervous system. While the schematic depicts a simple linear cascade (from left to right) of events following injury which lead to pain perception, these events are quite dynamic in nature and involve aspects of electrophysiology, immunology and an interplay between both.

Figure 2. There is a wide array of physiologic responses which occur following a mechanical injury such as that resulting from MSD. Changes occur both at the site of injury and in the spinal cord and CNS. However, the degree to which these alterations occur is variable and dependent on both the nature of the injury and the type of response. For example, while it has been determined that spinal cytokine mRNA follows patterns of tissue deformation, the spinal astrocytic responses do not, suggesting a complicated and differential immune response for mechanical loading of tissue. While a detailed understanding of the relationship between the physiologic aspects of these responses is emerging, the role of biomechanics in pain onset and maintenance remains uncharacterized. It will be imperative to determine the relationship between mechanical injury and the nociceptive physiologic responses detailed in this flow chart (and others) for management of this class of injuries.